HIGHLIGHTS FROM THE DIRECTOR

With the end of 2016 swiftly approaching, I am reminded of the dedication and momentum Center for Reproductive Medicine (CRM) members bring to our key mission areas of education, mentorship, innovation, collaboration, and community outreach. As we transition into 2017, it is essential that we continue to work towards this common mission by strengthening our community, and sharing our passion to address shifts in medicine, science, and health care. Taking on this cross-disciplinary approach will better position our involvement in delivering advanced patient care and educational resources, and establishing stronger local and global community ties.

This fall marked our third annual Reproductive Health Research Day (RHRD). Over 120 faculty, staff, trainees, and students from all over the Texas Medical Center attended this all-day scientific meeting to catch glimpses of research evolving in the reproductive field. We had two wonderful Keynote Speakers, including Peter Hotez, M.D., Ph.D., Dean for the National School of Tropical Medicine at Baylor College of Medicine, and Gail Cornwall, Ph.D., Professor of Cell Biology and Biochemistry at Texas Tech University Health Sciences Center.

Throughout the day, the common theme I heard amongst attendees was how much they were learning. The meeting is a great way to bring people together who have a unique knowledge of reproductive medicine, and come from an array of backgrounds, but who share a common interest to address the issues facing our patients and community. Watch the video documenting highlights and interviews from the meeting at youtu.be/KgtrhvEv4PI.

“I was impressed by the diversity of the speakers, but even more so by the energy and passion they have for their science. I think it’s important to come to a research day such as the one hosted today by Baylor, in that for me, it is a real exciting thing to share my science with other scientists, and learn from them, as I did today.”

– Dr. Gail Cornwall, 2016 RHRD Keynote Speaker

This issue of the CRM newsletter recaps our annual meeting, special seminars, and strides being made in endometrial research. Additionally, William Gibbons, M.D., who began his career as a medical student at Baylor College of Medicine, and now serves as Director of Reproductive Endocrinology and Infertility at Texas Children’s Hospital, gives us his thoughts as a Baylor alumni. As we bid 2016 a fond farewell, I wish all of you a safe and wonderful holiday season.

DORRIE
Among the leading conditions adversely affecting women’s reproductive health, it is not commonly appreciated that the neglected tropical diseases (NTDs) are among the most important. NTDs are chronic and debilitating parasitic (and related) infections, such as schistosomiasis, hookworm infection, Chagas disease, Zika virus infection, and leishmaniasis. New findings indicate the NTDs exert a staggering impact on reproductive health. For example, female genital schistosomiasis is one of the most common gynecologic conditions on the African continent where it is also promotes horizontal transmission of HIV/AIDS.
Amyloids are proteins that self-aggregate and form highly ordered cross-β-sheet fibrils that play a causative role in neurodegenerative disease and type II diabetes. Accumulating evidence, however, has established that some proteins self-assemble into amyloid fibrils that carry out biological roles in the absence of pathology and are known as functional amyloids. Although the mechanism(s) by which functional amyloids avoid pathology is not clear, presumably they form under controlled cellular conditions that minimize exposure of the cell to intermediate amyloid forms that can be cytotoxic.

We have determined that an amyloid matrix is an integral part of the mouse epididymal lumen and is composed of multiple members of the cystatin family of cysteine protease inhibitors including cystatin C and four members of the CRES (cystatin-related epididymal spermatogenic) family, a reproductive subgroup of cystatins. Using mouse models we determined that alterations in the amyloid matrix, either by the presence of a mutant, highly amyloidogenic cystatin C or by the loss of CRES, were associated with pathologies in the epididymis including infertility. Together, our studies suggest the amyloid matrix is an integral part of the epididymal lumen and necessary for the functional maturation and protection of spermatozoa; and that, if perturbed, can become pathological.

“Preovulatory Protein Restriction: Disrupted Amino Acid Kinetics and Mitochondrial Structure and Function in the Rat Oocyte”

Gestational exposures may program offspring to develop permanent changes in metabolism that increase the risk for adulthood diseases. Dietary protein restriction during pregnancy induces permanent changes in embryos and offspring. However, little is known about the effects of preovulatory dietary restriction on gamete structure and function, and maternal dietary intake critically supports the oocyte through maturation, fertilization, and until embryo genome activation.

We sought to investigate the effects of isocaloric preovulatory protein restriction on amino acid kinetics, antioxidant production, and mitochondrial ultrastructure and function in the rat cumulus oocyte complex. Preovulatory protein restriction appeared to decrease the oocyte’s ability to increase antioxidant precursor production. It may be inferred that the protein restricted oocyte is vulnerable to oxidative stress as it cannot increase antioxidant production. Further, protein restriction increased mitochondrial ultrastructural abnormalities within the cumulus oocyte complex, and oocyte mRNA expression of genes related to mitochondrial biogenesis was altered. Together, these data suggest that a proper preconception diet with adequate protein intake is essential for normal cumulus oocyte complex development.

“Exploring Novel Interactions in Cervical Cancer Etiology: Searching for a Better Screening Paradigm in the Molecular Era”

Cervical cancer kills nearly 300,000 women worldwide annually. Persistent infection with Human Papillomavirus (HPV) is a necessary cause of cervical cancer; however, other cofactors contribute to the malignant transformation. We found that several polymorphisms in XRCC4 are significantly associated with HPV DNA integration. Also exposure to hazardous air pollutants (HAPs) is associated with cervical dysplasia, possibly by facilitating viral integration. Further, women who were exposed to high levels of HAPs and carried adverse polymorphisms in the non-homologous end-joining DNA repair pathway were 3-times as likely to have cervical dysplasia.

Figure: Gene-environment interactions in the context of HPV may contribute to cervical dysplasia risk.
Cytomegalovirus (CMV) infection in pregnancy is a common occurrence, but a rarely addressed issue in reproductive health. Many women of child bearing age will have already had a CMV infection, and be serologically “immune,” with low risk of transmitting CMV to their fetus and newborn. However, almost half of women who are pregnant will have never had a CMV infection, and are vulnerable to a first or primary CMV infection during pregnancy, with potentially serious consequences to their fetus and newborn.

CMV infection in pregnancy may be transmitted to the fetus and produce outcomes in the newborn which range from a silent asymptomatic infection to hearing loss, vision loss, microcephaly, brain malformations, enlarged liver or spleen, and low platelets. Congenital CMV infection and disease can result in long-term sequelae in the infant and child, most commonly progressive hearing loss and neurodevelopmental disabilities.

There is not an injectable CMV vaccine licensed at this time. Prevention methods for CMV infection in pregnancy are currently through a “knowledge vaccine,” which includes CMV awareness and education for pregnant women. Many states now have CMV education laws in place and many public health agencies promote CMV education and awareness for pregnant women. Instructions on how to reduce their risk of catching CMV during pregnancy include precautions such as avoid sharing food or drink with anyone, especially toddlers, who often shed CMV in their saliva without symptoms; do not kiss young toddlers or children on or around the mouth or lips while pregnant to avoid contact with potential CMV in their saliva; and wash hands carefully after all diaper changes, and wiping noses and drool in children to avoid contact with CMV in urine or saliva.
“BMP Signaling Pathways in the Uterus and During Pregnancy”

Diana Monsivais, Ph.D.
Postdoctoral Associate, Lab of Dr. Martin M. Matzuk,
Department of Pathology and Immunology

Bone morphogenetic proteins (BMPs) are highly conserved molecules from the TGFβ superfamily that are implicated in developmental and pathological processes related to reproduction, such as infertility and preeclampsia. BMPs signal by binding to a heterodimeric receptor complex composed of a BMP type 1 receptor (ALK2, ALK3, ALK6) and a type 2 receptor complex (ACVR2A, ACVR2B, BMPR2). Studies using conditional inactivation of several members of the BMP pathway demonstrate its critical role during pregnancy, including implantation, decidualization, and placentation development.

We recently showed that BMP signaling via ALK3 is necessary for female fertility and for inducing uterine receptivity and embryo attachment to the endometrium. We also showed that in the uterus, signaling via ALK3 induces uterine receptivity through the joint transcriptional activation of Klf15 by SMAD4 and progesterone receptor. Targeting these pathways in the endometrium of infertile women has the potential to improve reproductive outcomes in women seeking assisted reproductive technologies.
ON THE PATH TO ALTERNATIVE ENDOMETRIOSIS TREATMENTS
RESEARCH FROM THE LABS OF DRS. BERT O’MAŁLEY & SANG JUN HAN

Endometriosis is a painful and chronic disease affecting millions of women and girls worldwide, and in some cases, can lead to infertility. Within the Department of Molecular and Cellular Biology at Baylor College of Medicine, Drs. Bert O’Malley and Sang Jun Han are focused on unfolding the molecular etiology of endometriosis to help develop alternative treatment therapies for this disease.

As an estrogen-dependent pro-inflammatory disease, endometriosis is defined as the colonization and growth of endometrial tissues at anatomic sites outside the uterine cavity, primarily the pelvic peritoneum and ovaries. Up to 10% of reproductive-aged women worldwide chronically suffer from the symptoms of endometriosis.

The development of endometriosis is closely associated with the progression of a number of other women’s diseases because estrogen dominance and hyper-inflammatory signaling impact the physiology of peritoneal tissues. For example, the prevalence of endometriosis increases dramatically to 50% in women with infertility. Due to the severe chronic morbidity associated with this gynecological disorder, past studies have attempted to identify the distinguishing molecular features of endometriotic lesions, with the aim of developing more effective prognostic, diagnostic, and/or treatment strategies for the clinical management of this debilitating disease; a particular challenge is to ameliorate the progression of endometriosis associated infertility. Despite such efforts, many of the current clinical treatments are not effective in treating endometriosis and relieving its associated symptoms. Current conventional endometriosis treatments also are associated with many side effects.

To improve therapy efficiency and minimize these side effects, new and essential pathological pathways that are involved in endometriosis and endometriosis-associated endometrial dysfunction are needed.

Alterations in estrogen-mediated cellular signaling play an essential role in the pathogenesis of endometriosis. For example, in addition to elevated local levels of estradiol, increased ERβ levels are detected in endometriotic tissues as compared to normal endometrium. Our studies revealed that ERβ plays an essential role in the pathogenesis of endometriosis because a gain-of-ERβ function enhances the progression of endometriotic lesion and inhibition of enhanced ERβ activity by an ERβ-selective antagonist (such as 4-[2-Phenyl-5,7-bis(trifluoromethyl)pyrazolo[1,5-a]pyrimidin-3-yl]phenol; PHTPP) suppresses mouse ectopic lesion growth1.

ENDOMETRIOSIS RESEARCH | CONTINUED ON PAGE 8
As a mechanism to evade endogenous immune surveillance for cell survival, ERβ interacts with cellular apoptotic machinery in the cytoplasm to inhibit TNFα-induced apoptosis (Model). ERβ also interacts with components of the cytoplasmic inflammasome to increase interleukin-1β and thus enhance its cellular adhesion and proliferation properties (Model). Furthermore, this gain of ERβ function enhances epithelial-mesenchymal transition signaling, thereby increasing the invasion activity of endometriotic tissues for establishment of ectopic lesions.

Until now, a mechanistic role for Steroid Receptor Coactivators (SRCs) in endometriosis progression has not been discovered. However, we revealed that a novel 70-kDa proteolytic isoform of SRC-1 is highly elevated both in the endometriotic tissue of mice with surgically induced endometriosis and in endometriotic stromal cells biopsied from patients\(^2\). The activation of TNFα-induced Matrix MetalloProteinase-9 mediates formation of the 70-kDa SRC-1 C-terminal isoform in endometriotic mouse tissue.

Along with ERβ, the endometriotic 70-kDa SRC-1 Isoform prevents TNF-α-mediated apoptosis in human endometrial epithelial cells and causes epithelial-mesenchymal transition and invasion of human endometrial cells that are hallmarks of progressive endometriosis (Model).

Thus, we propose that targeting the SRC-1 isoform/ERβ functional axis could be a potential strategy to increase both specificity and efficiency of endometriosis therapies.

Reference:

Carolina Jorgez, Ph.D.
Assistant Professor, Department of Urology

Despite advances in molecular diagnostics, the etiology of most male infertility cases remains unknown or undiagnosed. Copy number variants (CNVs) resulting in gene dosage changes have emerged as one of the causes of male fertility. We identified a microdeletion at chromosome 3p21.31 in 4 infertile men. Validation and analysis by qPCR of a total of 172 infertile men identified 7 subjects lacking both copies of this genomic region, and 6 other with microduplications in the same region. These events were not observed in any of the 207 fertile controls. According to data in the UCSC genome browser, this genomic region contains the gene, PRSS50.

In the reference genome, the deleted region does not contain genes, but is flanked by the PRSS50, PRSS46, PRSS45, and PRSS42. From these four serine proteases family members, only PRSS50 is expressed in the germ cells. Prss50 is expressed in mouse spermatocytes starting at post-natal day 14 and in the midpiece of the spermatozoa. Because Prss50 could play a role in the initialization and progression of meiosis, we generated Prss50-null mice.

Figure 1: PRSS50-deficient spermatozoa have multiple tail defects ranging from two-spermatozoa heads conjoined by a single tail, spermatozoa with 2 or more tails, or spermatozoa with duplicate midpieces.

During the Society for the Study for Reproduction (SSR) 2016 Annual Meeting in July, Dr. Carolina Jorgez presented her current research efforts in studying the etiology of male infertility, to further understand the causes of infertility.

CRM MEMBER ACTIVITIES IN THE REPRODUCTIVE FIELD

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CONGRATULATIONS to Meade Haller on receiving her Ph.D.! (Image: Meade with advisor, Dr. Dolores J. Lamb)

DISSERTATION DEFENSE
NOV. 3, 2016

“Identifying Copy Variant Genes Responsible for Congenital Genitourinary Defects”

Meade Elspeth Haller, Ph.D.
Department of Molecular and Cellular Biology

Meade Haller’s thesis project focused on identifying genomic hotspots where aberrations in the genome are highly associated with genitourinary birth defects such as renal agenesis and hydronephrosis. She identified two such loci and used expression screening and literature review to narrow down each multi-genic region to a single candidate gene.

Murine deletion models of each candidate gene were then generated to show the extent to which each gene’s aberration contributed to the genitourinary birth defects associated with the human syndrome. Interestingly, the genes that were modeled turned out to control not just genitourinary development, but also ocular and heart development.

Together these findings have clarified important single-gene targets within multi-genic syndromic loci that can be used to generate in utero therapies in the future.
PRSS50 deficiency in mice had no apparent effect on germ cell development in the testis, but instead led to defective maturation of epididymal spermatozoa. Compared to control mice, mice lacking Prss50 produce three times more spermatozoa that unfortunately, have reduced sperm-fertilizing ability due to a significant increase of spermatozoa abnormalities (78%).

PRSS50-deficient spermatozoa have multiple tail defects ranging from two-spermatozoa heads conjoined by a single tail, spermatozoa with 2 or more tails, or spermatozoa with duplicate midpieces (Figure 1). These defects are also observed at the ultrastructural level in which 25% of the spermatozoa have multiple flagella covered by the same plasma membrane. The tail defects cause a 3-fold decrease in spermatozoa motility. These results suggested that Prss50 could be involved in microtubule dynamics and flagellum organization that are required for spermatozoa motility. Gene-dosage changes flanking the PRSS gene cluster on 3p21.31 may represent a previously unrecognized cause of male infertility.

Recap:
American Society for Reproductive Medicine
2016 Scientific Congress & Expo
October 15 – 19, 2016
Salt Lake City, Utah

Scaling New Heights in Reproductive Medicine

72nd annual meeting

6 posters presented by CRM members:

Distress and Early Decisional Conflict and Satisfaction in Women Considering Fertility Preservation Prior to Cancer Treatment
• Andrea Bradford, Ph.D.

Preservation Decision Aid for Young Women with Cancer
• Veena Mathur, M.S.

The Down Expression of NPAS2 Predicts Low Testosterone Levels Due to Decreased Expression of StAR
• Amin Herati, M.D.

NEL1 and CTDSPL: Novel Genetic Factors Predisposing to Peyronie’s and Dupuytren’s Diseases
• Alexander Pastuszak, M.D., Ph.D.

Validation of the Estradiol Assay by Use of Mass Spectrometry and Follicular Volume AND Optimization of Estradiol Assay for Use During Ovarian Stimulation for In vitro Fertilization
• Mary Peavey, M.D.

2 oral abstracts by CRM members:

More Than a Flagellar Protein: IFT140 is a Male Infertility Candidate Gene that may Modulate Cell Signaling
• Amin Herati, M.D.

Preovulatory Protein Restriction (PPR): Disrupted Amino Acid (AA) Kinetics and Mitochondrial Structure and Function in the Rat Oocyte
• Amy Schutt, M.D.
Dr. William Gibbons is a nationally-renowned physician, specializing in Reproductive Endocrinology and Infertility (REI). Beginning his medical career as a student at Baylor College of Medicine, Dr. Gibbons went on to complete both his Residency in OB/GYN and Fellowship in REI at Baylor. Below, Dr. Gibbons describes his admirable accomplishments in research and patient care, along with a memorable moment, reflecting his advice to those starting off their careers in medicine and science.

Q| How did your Fellowship training and research at Baylor prepare you for your career?
A| My research here, during my Fellowship in reproductive medicine, was with Dr. Roy Smith in the Department of Molecular and Cellular Biology. Dr. Smith came from Vanderbilt University with Dr. Bert O’Malley. My research involved evaluating estrogen receptors, and how different aspects of estrogen preparation affected estrogen receptors within the uterus. My exposure to the very dynamic and active department of cell biology was very helpful to me, since it was an exciting time in cell biology, from the standpoint of evaluating how receptor functions worked. This experience helped provide an intellectual stimulus to some of the things that I subsequently did.

My first job, after I finished my Fellowship, was at the University of Southern California (USC). I was hired there not only because of my clinical expertise, but also because of my research expertise. At that time, they were beginning to evaluate and look at the role of estrogen receptors in different aspects of reproductive medicine. For a while if you came to The USC Los Angeles County (LAC) Medical Center and were diagnosed with breast cancer, my lab performed the breast biopsy analysis to determine whether the breast tumor had estrogen receptor. I would say that my Fellowship training, and my research with Dr. Roy Smith, of which Dorrie Lamb was also trained with Dr. Smith (that was when I first met Dorrie), was important to my success at USC.

Q| What are some of your contributions to reproductive medicine?
A| I got in on the ground floor of assisted reproductive technology (ART)—producing one of the first children in America from assisted reproduction, and I’ve watched this area, in both clinical and research medicine grow.

With Dr. Richard Marrs at USC, we launched the second successful (after the Jones Institute – Eastern Virginia Medical School) IVF program in America. Within that program, the third U.S. IVF baby was born just five months after the first. I returned to Baylor, and started the BCM IVF program, and became the Division Director of Reproductive Endocrinology and Infertility (REI). In 1990, I transitioned to Chair of the Department of OB/GYN at the Eastern Virginia Medical School (EVMS), and subsequently became the Medical Director of the Jones Institute IVF program.

Q| Can you describe one or two fond memories you had from your time here at Baylor?
A| Some of the more memorable activities that occurred at that time were the now famous parties of cell biology on St. Patrick’s Day. I also had an opportunity, as a very minor player in a process, to be exposed to many of the true leaders in research of steroid action—from Baylor, as well as those that came from other parts of the country. Investigators who were doing some of the significant research in this area were coming through Baylor to lecture and collaborate, and I had the chance to be exposed to this talented work. Plus, Roy Smith’s lab was a very nurturing place.

WILLIAM GIBBONS, M.D.
Director of Reproductive Endocrinology and Infertility
Director of the Fellowship Program in Reproductive Endocrinology
Professor of OB/GYN, Baylor College of Medicine
Chief of Reproductive Medicine, Texas Children’s Hospital

BCM DISTINGUISHED ALUMNI WITH DR. GIBBONS | CONTINUED ON PAGE 12
There I teamed up with Dr. Gary Hodgen, who had moved from NIH to the Jones Institute, and started a pre-implantation genetic diagnosis (PGD) program—producing the first birth, in the world, of a child screened for Tay-Sachs disease. Other achievements include creating a classification of uterine anomalies (again work that stemmed from my Baylor Fellowship) that was adopted by the American Society of Reproductive Medicine (ASRM), and working with the FDA on clinical studies resulting in the approval of a new vaginal progesterone gel for use in the U.S. for ART.

Nationally, I have been President of both the Society of Reproductive Endocrinology and Infertility (SREI) and Society of Assisted Reproductive Technology (SART), and advanced from the ASRM Board to its President in 2010. I returned to Baylor in 2008, after stepping down as Chair of EVMS. I became the Division Director of REI, and with Dr. Cecilia Valdes restarted the REI Fellowship Program at Baylor. I will say that I have been fortunate to be in the right place at the right time.

Q| What advice do you have for a starting scientist or medical/science professional?
A| Let me share a memory. While I was at USC, Dr. E. Diczfalusy, a European, internationally known reproductive scientist, came there, as he was a mentor to some of the senior faculty in the Department of OB/GYN. They arranged for him to meet with some of the fledgling new assistant professors. He gave me good advice that I never could follow because he said to “focus.” Another thing he said was that those of us who are involved in clinical or more basic research are very fortunate, and that unlike the vast majority of the world’s population, we have the opportunity to try and critically study something. We have the ability to then perturb one nature of this phenomenon, and then look at the outcome. Then from there, try and learn more about the world around us. We are fortunate to have the capacity to communicate with each other in the “language of science” which crosses every written/spoken language. This allows us the flexibility, skill, and power to understand the world around us, and communicate with those of similar interests.

Q| Where would you like to see your research go into the future?
A| At this point, we are trying to expand our understanding of reproduction. While having facilities to look at the oocyte and early embryo, we are fortunate to have skilled scientists like Dr. Lamb who are looking into the very basic nature of and genetics of sperm function, and Dr. Joanne Richards who is working with our fellows to evaluate ovarian function. Baylor through collaboration with world-class scientists offers us a very special opportunity to focus on male and female reproduction, and determine how we can improve outcomes for infertile couples.

![BCM DISTINGUISHED ALUMNI WITH DR. GIBBONS](CONTINUED FROM PAGE 11)

UPCOMING EVENTS

CRM and MCB R&D Workshop Series

“Small RNAs and a Tale of New Birth”

Swathi Arur, Ph.D.
Associate Professor, Department of Genetics,
Division of Basic Science Research
Co-Director, Genes and Development
Graduate Program
The University of Texas
MD Anderson Cancer Center

Thursday, December 8, 2016
12 – 1 p.m.
DeBakey Building, Room M616

Mark your calendars for our remaining FY 2017 seminars taking place at Noon in DeBakey M616: Jan. 12, Feb. 9, March 9, and April 13

SAVE THE DATE:
CRM Quarterly Membership Meeting & New Year’s Reception

Thursday, January 12, 2017
4 - 6 p.m. (reception begins at 5 p.m.)
Alkek Building, Room N317

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