



Reproduction and Perinatology Update

A publication of the D.H. Barron Reproductive and Perinatal Biology Research Program and the Center for Perinatal Outcomes Research

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Work In Progress Meetings

Kirk Conrad, Dept. of Physiology & Functional Genomics

Work in Progress Conference convenes one or two times each month. The purpose is to present new data and ideas, in order to solicit feedback from one's peers, educate trainees, and find common ground for new grant applications.

We meet at the New Deal Café (3443 W University Ave, behind Mildreds) from 4 to 5 PM on one or two Fridays each month. Beverages and hors d'oeuvres are provided!

In fact, we often finish closer to 6 PM, because there is so much excitement, interest and fun!

Presentations should be really informal especially with NEW IDEAS and any data to back them up. New data are not necessary but new ideas are. There is powerpoint and screen available, but it is encouraged to use it sparingly. There is also a white board with markers.

Trainees are invited to attend and to present their ideas, in order to



engage them more actively.

We want spontaneity and interruptions; presenters can expect wild and off-the-wall questions and comments from PIs and trainees.

We try to schedule WIPs to mix up the presentations according to lab interests, e.g., we won't get 3 placental (WIP) conferences in a row.

Let me know of anyone else you can think of who should be in Club WIP. and relaxed—hard to beat.

Below is the schedule for the Spring semester. Please let me know date(s) at which you would like to present:

January 15
February 26
March 25
April 15



First Stages of Life Necklace
on sale at Etsy.com

Faculty, Student, Postdoc and Alumni News

Contribute IDC to Support Our Program

Our reproductive biology effort is supported by the Center for Perinatal Outcomes Research. This is a source of funds that are generated by indirect costs from us - up to 7.5% of IDC that otherwise goes to the Deans Office can be designated to the Center. These funds are used to invite speakers to campus, organize retreats and are used as a source of seed grants. Please consider designating some of your IDC to the Center

Identify Our Program on Your Next Paper

Please consider including the D.H. Barron Reproductive and Perinatal Biology Research Program as one of your affiliations

Johanny Perez Baez started work towards the PhD degree in veterinary medicine under the direction of Klíbs Galvão. Funded by a College of Veterinary Medicine scholarship, Baez will be working on the association of dry matter intake prepartum with immune function and diseases postpartum.

Rodolfo Daetz, a MS student in Large Animal Clinical Sciences under the direction of Klíbs Galvão, was recognized by the International Center for outstanding achievements in academics and service. Daetz is working on the use of chitosan microparticles, an alternative antibiotic, on the prevention of metritis in dairy cows. He completed the MS degree in veterinary science in December, 2015.

Eduardo de Souza Ribeiro, who completed his PhD in the Animal Molecular and Cellular Biology (AMCB) graduate program under the supervision of



Screenshot of Thatcher Interview for World Dairy Expo

Jose Santos in summer 2015, has taken a faculty position at the Dept. of Animal Biosciences, University of Guelph

In January, **Laila Awad Ibrahim** will begin a MS degree in AMCB under the direct of John Bromfield (Animal Sciences). Ibrahim has MS and MSc degrees from University of Garyounis in Libya.

Amy Skiebel joined the laboratories of Geoff Dahl and Jimena Laporta in Animal Sciences as a postdoctoral scientist. She obtained the PhD from Auburn University in 2012. Most recently, she completed a postdoc at Harvard.

Alice Rhoton-Vlasak (Ob/Gyn) received a 2015 Golden Apple Outstanding Teaching Award from the Golden

Apple Foundation.

William Thatcher (Animal Sciences) was recognized by Virtus Nutrition at the 2015 World Dairy Expo in Madison, WI for his role in achieving breakthroughs in use of fatty acid feeding to enhance reproductive function of dairy cow. An interview with Thatcher about the discovery process of making the link between fatty acids and reproductive function in cattle is available at <https://www.youtube.com/watch?v=CEu479HVI2M>

Charles Wood (Physiology & Functional Genomics) was elected President-Elect of the Association of Chairs of Departments of Physiology.

Research Highlight 1 - Membrane-Localized Estrogen Receptor 1 Is Required for Normal Male Reproductive Development and Function

Manju Nanjappa, Theresa I. Medrano and Paul S. Cooke, Dept. of Physiological Sciences

Estrogen receptor 1 (ESR1; also known as ER α) is the major regulator of 17 β -estradiol (E2) effects on reproduction. Male mice in which *Esr1* was knocked out (*Esr1*KO) are infertile and have provided the first demonstration of an essential role of E2/ESR1 regulation in male reproduction. Infertility in these mice resulted from epididymal abnormalities and by inhibited efferent ductule epithelial fluid resorption resulting in backpressure that damages seminiferous epithelium and eventually eliminates sperm production.

Although ESR1 is predominately cytoplasmic and nuclear, approximately 5% of ESR1 is located in cell membranes. In mice, membrane localization of newly synthesized ESR1 is obligatorily dependent on palmitoylation of ESR1 at

cysteine 451. This was recently exploited by our collaborator Dr. Ellis Levin from University of California-Irvine, who developed transgenic mice where alanine was substituted for cysteine 451 in ESR1. Resulting mice (nuclear-only estrogen receptor; NOER) expressed nuclear ESR1 (nESR1), but membrane localization was eliminated by lack of ESR1 palmitoylation.

Despite extensive research in this area, it has not been clear exactly what roles membrane ESR1 (mESR1) plays in reproductive and

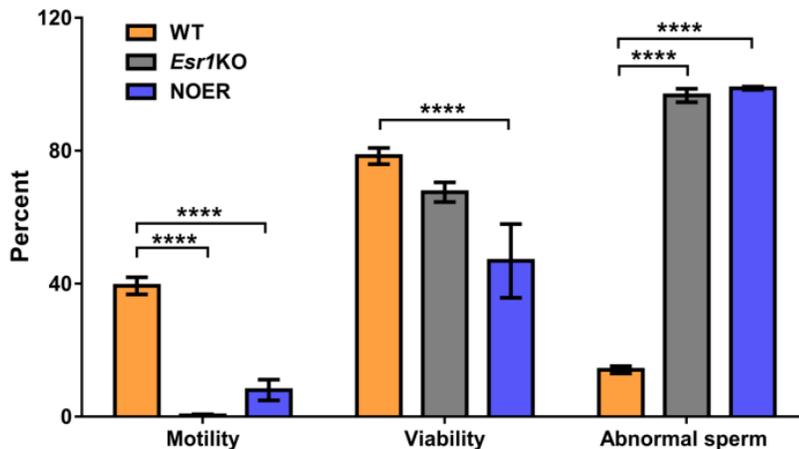


Figure 1. Loss of membrane estrogen receptor 1 in 8-month-old male nuclear-only estrogen receptor (NOER) mice leads to significant decreases in caudal epididymal sperm motility and viability, and increases sperm abnormalities compared to age-matched wild-type (WT) mice. Importantly, the NOER abnormalities are comparable to those in 4-month-old estrogen receptor 1 knock out (*Esr1*KO) male mice. ****P<0.0001.

NOER males compared to wild-type (WT) controls (Fig. 1). NOER mice had decreased epididymal sperm viability, although this decrease was less than for motility (Fig. 1). In addition, >95% of NOER sperm had abnormalities, including coiled heads, absent heads and folded tails (Fig. 1); this was comparable to what has been reported previously in *Esr1*KO males. The NOER mice had dilated rete testes, decreased efferent ductule epithelial height and an increased incidence of seminiferous tubule abnormalities compared to WT controls. At 8 months of age, NOER males had a 62% reduction in daily sperm production. Critically, young NOER males were initially subfertile, but became totally infertile with advancing age. These results suggest that membrane-initiated E2/ESR1 signaling is required for normal sperm production, sperm motility and viability, male reproductive function and fertility and emphasize the role of mESR1 in normal E2 signaling in males. Exactly how mESR1 facilitates normal E2 signaling in both males and females is presently unknown, but is a topic of ongoing investigation in the lab. This work was done in collaboration between our laboratory and those of Rex A. Hess at the University of Illinois and Ellis R. Levin from the University of California-Irvine.

Schedule Spring Seminar Series

Reproductive & Perinatal Biology Seminar

Wednesday 4:00-5:00 PM

D.H. Barron Conference Room Medical Sciences Building M-304

sponsored by the D. H. Barron Reproductive & Perinatal Biology Research Program
and the Center for Perinatal Outcomes Research

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| January 27: | Chris Vulpe, PhD <i>Perinatal iron deficiency and hair loss in mice: a potential role for the androgen receptor</i> Professor, Physiological Sciences, College of Veterinary Medicine, University of Florida | March 2: | NO MEETING: Spring Break |
| February 3: | Connie Mulligan, PhD <i>The effect of maternal stress on newborn birth outcome and DNA methylation</i> Professor and Associate Chair, Anthropology, College of Liberal Arts and Sciences, University of Florida | March 9: | Paul Cooke, PhD <i>Membrane-Localized Estrogen Receptor 1 Is Required for Normal Male and Female Reproductive Development and Function in Mice</i> Professor and Chair, Physiological Sciences, College of Veterinary Medicine, University of Florida |
| February 10: | Abdel Alli, PhD <i>Exosomes as novel biomarkers and therapeutics</i> Assistant Professor, Physiology & Functional Genomics, College of Medicine, University of Florida | March 16: | NO MEETING: SRI |
| February 17: | Miguel Zarate <i>Hypoxia-Induced Fetal Brain Inflammation: Is it all about the oxygen?</i> PhD Student, Physiology & Functional Genomics, College of Medicine, University of Florida | March 23: | Joe Neu, MD <i>Factors Affecting the Fetal and Neonatal Microbiome</i> Professor, Pediatrics, College of Medicine, University of Florida |
| February 24: | Mary Brown, PhD & Linda Hayward, PhD <i>Nicotine and Infection: Dual Threats Impacting Prenatal and Postnatal Outcomes</i> Professor, Infectious Diseases & Pathology & Associate Professor, Physiological Sciences, College of Veterinary Medicine, University of Florida | March 30: | Thomas P. Yang, PhD <i>Epigenetic Effects of Prenatal Ethanol Exposure: DNA Methylation Profiling in a Mouse Model for Fetal Alcohol Syndrome</i> Professor, Biochemistry & Molecular Biology, College of Medicine, and Director, Center for Epigenetics, University of Florida |
| | | April 6: | Jackie Walejko <i>Global Metabolomics of the Placenta over 24 hours</i> PhD Student, Biochemistry & Molecular Biology, College of Medicine, University of Florida |

Recent Contracts and Grants

Bayer. A randomized, parallel-group, double-blind, placebo-controlled, multi-center phase II study to assess the efficacy and safety of different doses of BAY 1002670 in subjects with uterine fibroids over 3 months. A Rhoton-Vlasak (subinvestigator). 2014-2015, \$176,585.

Phibro Animal Health. Effect of OmniGen-AF and heat stress on mammary remodeling during the dry period and subsequent productive performance and immune status” GE Dahl, J Laporta. 2015-2018. 2015-2018, \$130,299.

TherapeuticsMD. A phase 3, double-blind, placebo-controlled, randomized, multi-center trial to evaluate the safety and efficacy of HR TX-004HR in postmenopausal women with moderate to severe symptoms of vulvar and vaginal atrophy. A Rhoton-Vlasak (subinvestigator). 2014-2015, \$42,560.

US Agency for International Development. Feed the Future Innovation Lab for Livestock Systems. A Adesogan, G Dahl, G Roberts, S McKune, G Kiker, J Hernandez. 2015-2020, AID-OAA-L-15-00003, \$19,000,000.

Selected Publications

Bentley PA, Wall EH, Dahl GE, McFadden TB. Responses of the mammary transcriptome of dairy cows to altered photoperiod during late gestation. *Physiol Genomics* 2015;47:488-99.

Benzaquen M, Galvão KN, Coleman AE, Santos JE, Goff JP, Risco CA. Effect of oral mineral and energy supplementation on blood mineral concentrations, energetic and inflammatory profile, and milk yield in dairy cows affected with dystocia. *Vet J* 2015;204:186-91.

Biel NM, Santostefano KE, DiVita BB, El Rouby N, Carrasquillas S, Simmons C, Nakanishi M, Cooper-DeHoff RM, Johnson JA, Terada N. Vascular smooth muscle cells from hypertensive patient-derived induced pluripotent stem cells to advance hypertension pharmacogenomics. *Stem Cells Transl Med* 2015;4:1380-90.

Cho J, Seo J, Lim CH, Yang L, Shiratsuchi T, Lee M, Chowdhury R, Kasahara H, Kim JS, Oh SP, Lee YJ, Terada N. Mitochondrial ATP transporter Ant2 depletion impairs erythropoiesis and B lymphopoiesis. *Cell Death Differ* 2015; 22:1437-50.

Dikmen S, Wang XZ, Ortega MS, Cole JB, Null DJ, Hansen PJ. Single nucleotide polymorphisms associated with thermoregulation in lactating dairy cows exposed to heat stress. *J Anim Breed Genet.* 2015; 132:409-19.

Gaievski FR, Lamb GC, Weiss RR, Bertol MAF, Sequi MS, Abreu ACMR, Kozicki LE. Gonadotropin releasing hormone (GnRH) and equine chorionic gonadotropin (eCG) improve the pregnancy rate on protocols for timed-artificial insemination in beef cattle. *Vet. E Zootec* 2015; 22:471-80.

Kannampuzha-Francis J, Denicol AC, Loureiro B, Kaniyamattam K, Ortega MS, Hansen PJ. Exposure to colony stimulating factor 2 during preimplantation development increases postnatal growth in cattle. *Mol Reprod Dev* 2015;82:892-7.

Lima FS, Greco LF, Bisinotto RS, Ribeiro ES, Martinez NM, Thatcher WW, Santos JE, Reinhard MK, Galvão KN. Effects of intrauterine infusion of *Trueperella pyogenes* on endometrial mRNA expression of proinflammatory cytokines and luteolytic cascade genes and their association with luteal life span in dairy cows. *Theriogenology* 2015;84:1263-72.

Mercadante VR, Kozicki LE, Ciriaco FM, Henry DD, Dahlen CR, Crosswhite MR, Larson JE, Voelz BE, Patterson DJ, Perry GA, Funston RN, Steckler TL, Hill SL, Stevenson JS, Lamb GC. Effects of administration of prostaglandin F at initiation of the seven-day CO-Synch+controlled internal drug release ovulation synchronization protocol for suckled beef cows and replacement beef heifers. *J Anim Sci* 2015; 93:5204-13.

Shonka BN, Tao S, Dahl GE, Spurlock DM. Genetic regulation of prepartum dry matter intake in Holstein cows. *J Dairy Sci* 2015;98:8195-200.

Selected Publications (continued)

Silva TV, Lima FS, Thatcher WW, Santos JE. Synchronized ovulation for first insemination improves reproductive performance and reduces cost per pregnancy in dairy heifers. *J Dairy Sci* 2015;98:7810-22.

Williams RS, Doody KJ, Schattman GL, Adashi EY. Public reporting of assisted reproductive technology outcomes: past, present, and future. *Am J Obstet Gynecol.* 2015; 212:157-62.

Research Highlight 2 – Long-Term Impact of Incorporating Estrus Synchronization (ES) and Fixed-Time Artificial Insemination into a Beef Cattle Operation – A Case Study

G. Cliff Lamb, Vitor R.G. Mercadante, Darren Henry, Francine Ciriaco, Pedro L.P. Fontes, and Nicolas DiLorenzo, North Florida Research and Education Center, Marianna, Florida

Current research has focused on the development of methods that effectively synchronize estrous in postpartum beef cows and replacement beef heifers by decreasing the period of time over which estrous detection is required, thus facilitating the use of fixed-time AI (TAI). This new generation of estrus synchronization protocols uses two strategies which are key factors for implementation by producers because they: 1) minimize the number and frequency of handling cattle through a cattle-handling facility; and 2) eliminate detection of estrus by employing TAI. As a result, our laboratory led an effort to develop the 7-day CO-Synch + CIDR protocol, which is now used on greater than 53% of all the cows inseminated in the United States.

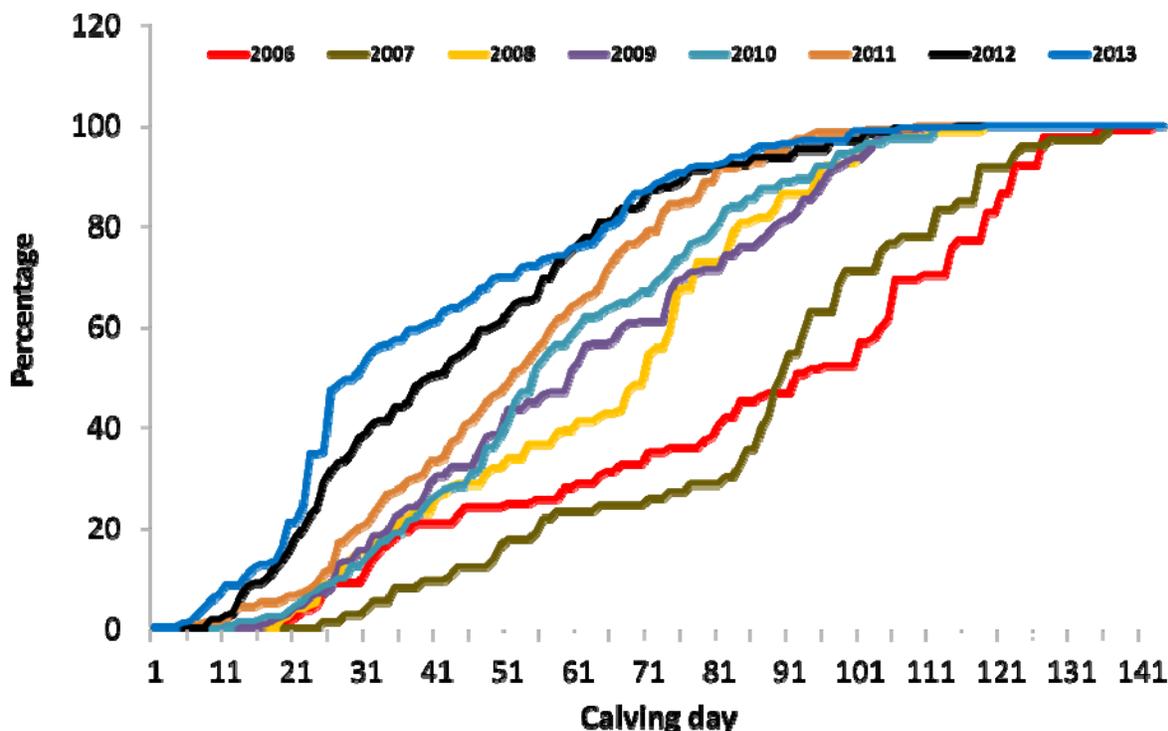


Figure 2. Cumulative calving by year for two years (2006 and 2007) prior to introducing ES and TAI and five years (2008 to 2013) after introducing TAI.

Research Highlight 2 (continued)

To determine the long-term impacts of ES and TAI, a case study was conducted at the University of Florida - North Florida Research and Education Center (NFREC) located in Marianna, FL. This case study was conducted during the spring 2008 to spring 2013 breeding seasons, in a cow/calf operation consisting of 300 cows. Prior to the 2008 the breeding season the herd was exposed to a 120 day breeding season. The goal was to reduce the breeding season to 70 days within 4 years. In addition to exposing every female to ES and TAI, strict rules were placed on criteria for retention in the herd: 1) replacement heifer must become pregnant during the first 25 days of the breeding season; 2) a cow must produce a live calf every year and calve without assistance or she was culled; 3) every cow must provide the resources for the genetic potential of the calves and each calf she produces must be genetically capable of performing; 4) every cow must maintain body condition score without requiring supplemental feeding; and 5) any cow with an undesirable temperament or disposition was culled. As a result, the breeding season was reduced from 120 to 70 days, with an increase in overall breeding season pregnancy rates from 83% to 93%. Survival analysis demonstrated a shift in calving distribution (Figure 2) such that the mean calving date from the first calf born each year was reduced from 80.9 days to 38.7 days. The net result is a more compact calving season that has increased the value of calves (in current dollars) by \$169 per calf or an annual increase in calf value for the 300 head operation of \$50,700 per year.

Death of Lou Guillette, Jr.

Dr. Louis J Guillette, professor of obstetrics and gynecology and director of the Marine Biomedicine and Environmental Sciences center at the Medical University of South Carolina, died on August 6, 2015, aged 60. Dr. Guillette was an internationally-recognized researcher and teacher who, while on the faculty in the Dept. of Biology at the University of Florida, was one of the first to develop the concept of endocrine disruption, from his work on the impact of toxic chemicals on alligators and other wildlife.

Dr. Guillette held an endowed chair in marine genomics from the South Carolina Centers of Economic Excellence and was a Howard Hughes Medical Institute professor. During his career, he was the recipient of many awards including the Heinz Award in 2011 for his contributions to the Environment. He also advocated for public action to reduce amounts of man-made endocrine-disrupting chemicals in the environment and testified about this issue to many governmental organizations including the US Congress. Tributes to Dr. Guillette have been published in the *Gainesville Sun*, *Orlando Sentinel*, and *Charleston Post and Courier*.

While at UF from 1985-2010, Lou was a member of the reproductive biology group. He was an inspiring teacher and involved large numbers of undergraduates in his research program. He was UF's Teacher/Scholar of the Year in 1998.

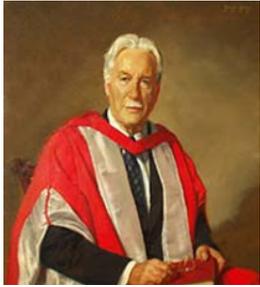
To commemorate his life, donations are being accepted to the Louis J. Guillette Jr. Graduate Student Travel Award via the North American Society for Comparative Endocrinology.



Lou Guillette with one of his research subjects.

The photograph is from Lou's website at

<https://www.musc.edu/mbes-lig>



**DH Barron Reproductive
& Perinatal Biology
Research Program**

University of Florida

**Repro & Perinatal
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Send items of interest to
P.J. Hansen at
Hansen@animal.ufl.edu

We're on the Web!
www.perinatal.ufl.edu

About the D.H. Barron Reproductive and Perinatal Biology Research Program

History: The Repro program was founded in 1969 by Donald Henry Barron, Fuller Bazer and others. Seminars have been held continuously since that time. Donald Henry Barron (1905-1993) came to UF as the J. Wayne Reitz Professor of Reproductive Biology after a career at Cambridge and Yale. His research in fetal physiology led to his being referred to as the Father of Scientific Obstetrics and the Father of Fetal-Placental Physiology. Known to his colleagues and students as "Dr. B.", his portrait is on the masthead. In 1969, Fuller Bazer, currently the O.D. Butler Chair in Animal Science at Texas A&M University, was an assistant professor in the Dept. of Animal Sciences. Since then, he has become one of the pioneers in understanding the nature of communication between the embryo and mother. Among the many recognitions he has received was the Wolf Prize in Agriculture in 2003.

Mission: To foster collaborative, multidisciplinary, and integrative approaches to basic and translational research that (i) improves the health of pregnant women and their babies, (ii) enhances the reproductive success of agriculturally important animals and wildlife, and (iii) prepares the next generation of scientists in these research disciplines.

Scope: Basic, translational and clinical research aimed at understanding (i) the biology of reproduction in humans and animals from fertilization to delivery and early postnatal development, and (ii) genetic, epigenetic or environmental influences that cause abnormal pregnancy outcomes, including those influences that predispose the mother and offspring to adult diseases.



Silver Cyrenian coin circa 485-475 BCE depicting the nymph Cyrene touching a stalk of silphium. The object behind her is the fruit of the silphium plant. Silphium, which probably went extinct by the time of Nero (1st century CE), grew along a narrow coastal region in modern Libya near the ancient Greek city of Cyrene. Resin produced from the plant was widely used as a contraceptive in the ancient Mediterranean world. The plant was so important to the Cyrenian economy that it appeared on most of their coins. The image is from <https://www.cngcoins.com/Article.aspx?ArticleID=313>