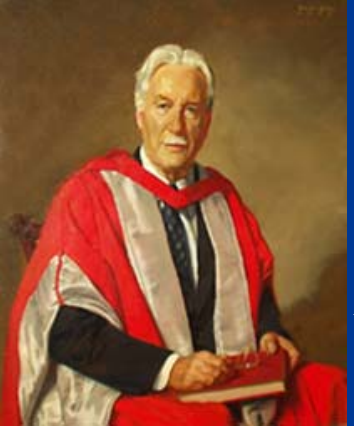
Vol. 3 No.1 Fall, 2016



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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UNIVERSITY of FLORIDA

DoHad Pioneer to Visit UF to Present Thatcher Lecture

Dr. Tom P. Fleming will visit UF September 19-23 to present the 6th Thatcher Lecture organized by the Dept. of Animal Sciences. The lecture will be held Sept. 20 at 4:00 PM in the Auditorium of the Cancer and Genetics Research Complex (CGRC). The lecture will be preceded by a reception at 3:30 PM in the CGRC atrium.

Fleming's group is interested in how the environment of the preimplantation embryo influences the developmental program of the embryo and fetus to modify long-term potential into adulthood. His work indicates maternal diet (in vivo), maternal sickness (in vivo) or IVF-related culture conditions (in vitro) around the time of conception may modify developmental potential with important implications for adult health and disease risk affecting cardiovascular and metabolic physiology, behaviour, and immune reactivity.

Dr. Fleming is Professor of Developmental Biology in the Centre for Biological Sciences at the University of Southampton, UK. He graduated in Zoology from University of Wales (1972), obtained his PhD from University of London (1979), was a postdoc at University of Keele until 1981 and then Senior Research Associate at Cambridge University before moving to Southampton in 1988.

Fleming has been Editor-in-Chief of *Reproduction*, is a Council member and Treasurer of the Society of Reproduction and Fertility (SRF) and sits on various grant committees and advisory boards including advisor to NICHD. He was awarded an Honorary RCOG Fellow (Royal College of Obstetrics and Gynaecology) *ad eundem* in 2013 and the Marshall Medal from SRF also in 2013.

The Thatcher Lecture Series was developed by friends, colleagues,

and family of Bill Thatcher on the occasion of his retirement in 2005.

The Lecture Series is supported in part from the Thatcher Lecture Endowment managed by the SHARE Office of the Univ. of Florida/IFAS.

Past recipients of the Thatcher Lecture include Robert Collier of the Univ. of Arizona, Vasantha Padmanabhan of the Univ. of Michigan, Sandra Rodriquez Zas of the Univ. of Illinois, Jonathan Tilly of Northeastern University, and Wansheng Liu of Pennsylvania State University.

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

Faculty, Student, Postdoc and Alumni News

The following people began doctoral programs in the Animal Molecular and Cellular Biology Graduate Program (AMCB) in Fall 2016: **Eliab Estrada** (Mexico), working in Peter Hansen's laboratory, and **Achilles Vieira Neto** and **Roney Zimpel**, both from Brazil and beginning programs in the laboratory of José Santos. **Vieira Neto** was also the recipient of the Graduate Student of the Year Award from the Animal Sciences Graduate Student Association in May.

Joonseok Cho, a doctoral student of Naohiro Terada in Pathology, received two awards in April – the College of Medicine 41st Medical Guild Student Competition Silver Award and first place in the Florida Statewide Graduate Research Symposium.

Gregory M. Christman, Professor of Ob/Gyn, was an invited plenary speaker at the 4th International Congress of Gynaecology and Obstetrics (ICGO-2016) in Barcelona, Spain in May. The lecture was on gene therapy in reproductive medicine.

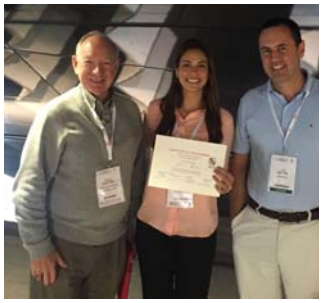
Eduardo de Souza Ribeiro, who completed his PhD in the AMCB graduate program under the supervision of **Jose Santos** in summer 2015, was honored twice in 2016. His dissertation was selected as the Dissertation of the Year by the College of Agric. & Life Sciences and the UF Chapter of Sigma Xi awarded him the Graduate Research Award at its annual banquet in March.

Anna Denicol, who completed the PhD in the AMCB in 2014 and did a postdoc at Northeastern Univ. in the Jonathan Tilly laboratory, has taken a position as assistant professor of endocrinology in the Dept. of Animal Science at Univ. of California-Davis.

Natalie Fredette, a postdoctoral scientist in the Terada laboratory, was awarded the best poster in group at the Office of Postdoctoral Affairs 2016 postdoc research symposium in April.

Sofia Ortega, a doctoral student in the AMCB in Peter Hansen's laboratory, was runner-up for the Graduate Student Research Competition of the International Embryo Technology Society (IETS) Foundation in Louisville KY at the annual conference of the IETS in January.

Malgorzata Pozor was promoted recently to Clinical Associate Professor in the Dept. of Large Animal Clinical Sciences. She was also the invited plenary speaker at the 7th International Symposium on Stallion Reproduction in Champaign, IL, in August where she addressed the topic of application of various techniques in localizing retained testes in horses before cryptorchidectomy.



Leticia D.P. Sinedino, shown above with William Thatcher and José Santos, was the winner of the student paper competition at the 18th International Congress of Animal Reproduction in Tours, France in June. She is a doctoral student in the AMCB in Santos's laboratory.

Paula Tribulo, a doctoral student in the AMCB in the Hansen lab, received a grant-in-aid of research from Sigma Xi (Scientific Honor Society), to support research on bovine embryology.

Di Xia, an undergraduate student of Naohiro Terada, received the University Scholars Program Award.

Research Highlight - What Are The Long Term Consequences of Infection on fertility?

Sossi Iacovides, Laila Ibrahim, Rachel Piersanti and John Bromfield, Dept. of Animal Sciences

Bacterial infections of the female reproductive tract are common in both women and dairy cows. In women it is estimated that sexually transmitted infection causes infertility in 24,000 women per year. Comparatively the incidence of infertility in dairy cattle is 40% higher in animals that have suffered a uterine infection. These uterine infections cause infertility in both species, but the specific mechanisms resulting in a failure to conceive remains unclear. It is probable that the uterus itself, oviduct and hypothalamus-pituitary axis are all potential offsite targets of infection and components of subsequent infertility (Fig 1). However, emerging evidence suggest that the infection impacts ovarian health, and that ovarian problems are important causes of the infertility associated with uterine infection. Pathogen-associated molecules such as lipopolysaccharide (LPS, endotoxin) which initiate inflammation are concentrated in the follicular fluid of dairy cows with uterine infection, and ovarian function is disrupted resulting in extended luteal phases, reduced follicle growth and reduced sex hormone production. We have recently been able to demonstrate that both human and bovine cells of the ovarian follicle exhibit characteristics of an innate immune response to specific pathogen associated factors by increasing the production of inflammatory mediators like IL1B and IL6, and chemokines like IL8 (Fig. 2A). Interestingly when we mature bovine oocytes in an environment where these bacterial components (or resultant inflammatory mediators) are present oocytes show a reduced meiotic competence (Fig. 2B). Furthermore, exposure of bovine ovarian explants to pathogen-associated molecules accelerates activation of the primordial follicle reserve. An almost identical response is seen in mice exposed to LPS, suggesting that infection may deplete the total number of follicles available in the ovary and reduce overall long-term fertility. We are implementing

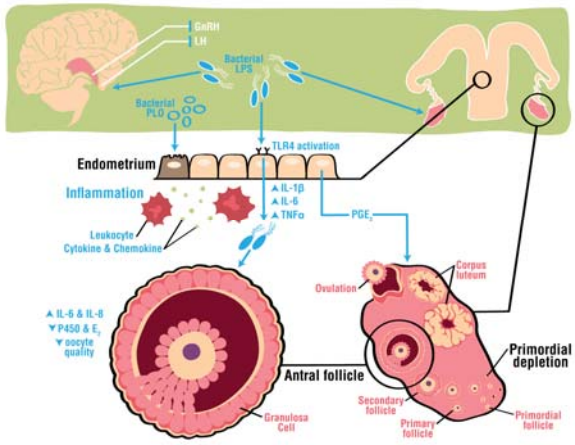


Figure 1. Schematic representation of uterine infection and impacts on the reproductive tract. This figure represents the all-encompassing effects of uterine bacterial infection on neuroendocrine signaling, uterine health and ovarian function. Brain; GnRH and LH production are reduced. Endometrium; bacterial LPS initiates an inflammatory response via TLR4 activation increasing secretion of inflammatory mediators. Ovary; the primordial follicle reserve is depleted, follicle growth is retarded and luteal phase prolonged. Ovarian granulosa cells respond to bacterial LPS increasing inflammatory mediators, reducing estradiol, and perturbing oocyte competence.

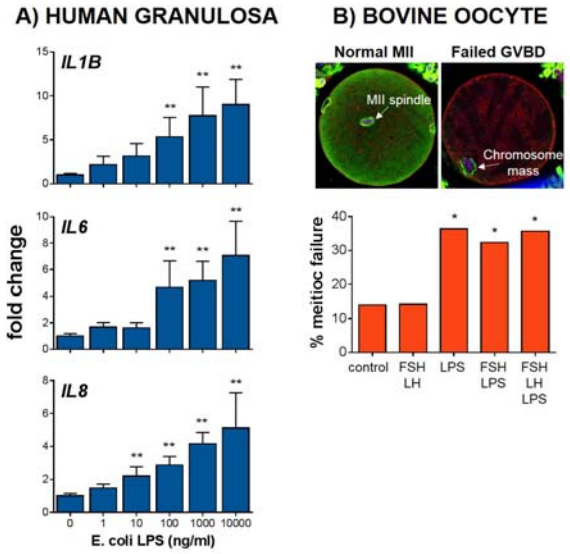
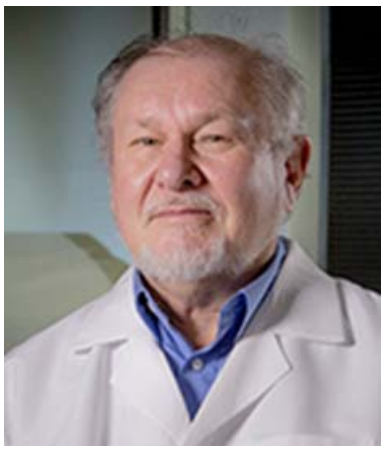


Figure 2. Impact of bacterial LPS on the follicle in humans and cows. A; human granulosa-luteal cells respond to LPS by increasing expression of inflammatory mediators in a dose dependent manner. B; meiotic competence of cow oocytes is reduced when matured in the presence of bacterial LPS. These data describe similar modes of action between the human and bovine in the ability of the ovary to act as an innate immune sensors and potentially impact fertility.

studies in the cow to tease apart the molecular and cellular mechanisms by which uterine infections impact fecundity of dairy cows by perturbing ovarian function, follicular quiescence, the follicular environment and ultimately oocyte competence. It is intriguing that molecular and cellular events pertaining to oocyte development, follicular growth and ovulation are akin to inflammatory events, yet the ovarian follicle contains no hematopoietic immune cells. This begs the question: If inflammatory-like processes used during normal ovarian physiology are altered by pathological events, is the normal development of female gametes perturbed? Answering this question could have potential impact on food and economic security of the dairy industry but also far reaching consequences on human health, pertaining to the reproductive lifespan of women and potential success of IVF patients. These programmatic ideas reveal a number of potential avenues where infection or inflammation in non-reproductive tissues or even gut dysbiosis could impact reproduction. Food for thought or are the Kangaroos loose in the top paddock?

Fall Warnick and Barron Lecturers



The Fall Warnick Lecture will be given by **Dr. Milo C. Wiltbank**, professor of endocrinology and reproductive physiology in the Department of Dairy Science, University of Wisconsin-Madison. Dr. Wiltbank received his BS (1980) and MS (1982) from Brigham Young University and the PhD (1987) from the University of Michigan, and a postdoc at Colorado State University for a postdoctoral fellowship. He has been at Wisconsin since 1991 where he studies the regulation of ovarian function in dairy cattle. Basic studies focus on the regulation of hormonal receptors in the corpus luteum and developing ovarian follicle. Applied studies focus on development of methods that allow timed artificial insemination and improve pregnancy rates in dairy cattle.

The Alvin C. Warnick Lecture Series was created by the Dept. of Animal Sciences to recognize the achievements of Dr. Alvin C. Warnick, one of the founders of the Reproductive and Perinatal Biology Group, Dr. Wiltbank's father, Dr. James N. Wiltbank, himself a pioneering reproductive physiologist, was a graduate student at the University of Wisconsin at the same time as Warnick.

The Barron Lecture was instituted to recognize the contributions of the senior founder of the Reproductive and Perinatal Biology Group, Donald Henry Barron. This fall's lecturer, **Dr. David Albertini**, is an internationally recognized scientist and educator in the field of reproductive biology and medicine. He obtained his Ph.D. degree from Harvard University and is currently at the Center for Human Reproduction in New York City. Previously, he held The Hall Professorship of Molecular Medicine at the University of Kansas and was Director of the Center for Reproductive Sciences at the University of Kansas Medical Center. He also served at Tufts University School of Medicine as Chair of the Department of Anatomy and Cell Biology.

His major research contributions have been in the cell and developmental biology of mammalian reproduction, particularly in oogenesis, and the translation of basic science to improvements in oocyte and embryo quality in human assisted reproductive technologies. He has published over 150 peer-reviewed original research papers, over 50 chapters and reviews, and one book.

Schedule Fall 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

September 7: **Luiz Gustavo B. Siqueira**
Programming of fetal and postnatal phenotypes following in vitro fertilization in cattle
PhD Student, University of Florida Department of Animal Sciences / Embrapa, Brazil

September 28: **Josh Yarrow, MS, PhD**
Intracrine Mediated Regulation of Testosterone Metabolism in Bone, Muscle, and Fat: Basic Biology to Clinical Endeavors
Health Scientist, VA Medical Center & Assistant Scientist, University of Florida Department of Applied Physiology & Kinesiology

October 5: **Anthony R. Gregg, MD, MBA**
Translating Genomics into Prenatal Care
Professor and Chief, Division of Maternal-Fetal Medicine, Department of Obstetrics & Gynecology, University of Florida College of Medicine

October 12: **M. Sofia Ortega**
COQ9 - an example from the cow of a gene regulating mitochondrial function that plays an important role in reproduction
PhD Fellow, University of Florida Animal Molecular & Cellular Biology Program

October 19: **Kirk Conrad, MD**
Does suboptimal decidualization contribute to impaired placentation in preeclampsia?
Professor, Departments of Physiology & Functional Genomics and Obstetrics & Gynecology, University of Florida College of Medicine

October 26: **Milo Wiltbank, PhD (Warnick Lecture)**
Pivotal periods and prevention of pregnancy loss in dairy cattle and embryo recipients
Professor, Department of Dairy Science, University of Wisconsin

November 2: **Malcolm Maden, PhD**
The spiny mouse – the first regenerating mammal
Professor, Department of Biology & University of Florida Genetics Institute

November 9: **Maureen Keller-Wood, PhD**
Title to be announced
Professor & Chair, Department of Pharmacodynamics, University of Florida College of Pharmacy

November 16: **Michael Kladde, PhD**
Epigenetic Heterogeneity and the Emergence of Treatment-resistant Cancer Cells
Professor, Biochemistry and Molecular Biology, University of Florida Health Cancer Center & College of Medicine

November 30: **Todd Brusko, PhD**
Regulatory T cells in type 1 diabetes
Assistant Professor, Department of Pathology, University of Florida College of Medicine

December 7: **David Albertini, PhD (Barron Lecture)**
How regenerative medicine is changing the face of reproductive medicine
Director of Laboratories & Senior Scientist, Center for Human Reproduction, New York

Recent Contracts and Grants

Abbvie PrototocPharmaceuticals. A phase 3 study to evaluate the safety and efficacy of elagolix in premenopausal women with heavy menstrual bleeding associated with uterine fibroids. GM Christman (Site PI). Protocol M12-817. $400,000.

American Heart Association. A stem cell tactic to promote personalized medicine in hypertension. N Terada (PI). 6GRNT30980002. 2016-2018, $154,000.

NIH/NICHD. Uterine infection and infertility: how microbial infection of the reproductive tract causes ovarian dysfunction. JJ Bromfield (PI), JEP Santos, J Block, IM Sheldon, R01 HD084316. 2016-2021,

$1,600,000.**NIH/NIGMS.** A stem cell tactic to promote personalized medicine. N Terada (PI). R24 GM119977. 2016 - 2019, $1,312,846.

Selected Publications

Dodson W, Diamond M, Schlaff W, Casson P, Christman G, Barnhart K, Bates G, Usadi R, Lucidi R, Baker V, Zhang H, Eisenberg E, Coutifaris C, Dorkas A, Legro R. Benefit of delayed fertility therapy with preconception weight loss over immediate therapy in obese women with PCOS. J Clin Endocrinol Metab2016; 101:2658-2666.

Garcia M, Greco LF, Lock AL, Block E, Santos JE, Thatcher WW, Staples CR. Supplementation of essential fatty acids to Holstein calves during late uterine life and first month of life alters hepatic fatty acid profile and gene expression. J Dairy Sci 2016;99:7085-7101.

Hansen KR, He A, Styer AK, Wild RA, Butts SA, Engmann, L, Diamond MP, Legro RS, Coutifaris C, Alvero R, Robinson RD, Casson P, Christman GM, Huang H, Santoro N, Eisenberg E, Zhang H, for the NICHD Reproductive Medicine Network. Predictors of pregnancy and live-birth in couples with unexplained infertility following ovarian stimulation-intrauterine insemination. Fertil Steril 2016; 105:1575-1583.

Ibrahim LA, Kramer JM, Williams RS, Bromfield JJ. Human granulosa-luteal cells initiate an innate immune response to pathogen-associated molecules. Reproduction 2016; 152:261-270.

Mercadante VRG, Fontes PLP, Ciriaco FM, Henry DD, Moriel P, Ealy AD, Johnson SE, DiLorenzo N, Lamb GC. Effects of recombinant bovine somatotropin administration at breeding on cow, conceptus and subsequent offspring performance of beef cattle. J Anim Sci 2016; 94:2128-2138.

Ortega MS, Denicol AC, Cole JB, Null DJ, Hansen PJ. Use of single nucleotide polymorphisms in candidate genes associated with daughter pregnancy rate for prediction of genetic merit for reproduction in Holstein cows. Anim Genet 2016;47:288-297.

Ozawa M, Sakatani M, Dobbs KB, Kannampuzha-Francis J, Hansen PJ. Regulation of gene expression in the bovine blastocyst by colony stimulating factor 2. BMC Res Notes 2016;9:250.

Pozor M, Freeman D, Troedsson M, Brown M, Morton A, Smith A, McNaughten J. Anatomical variations in epididymal-testicular fusion in stallions and their possible clinical significance. Equine Vet J 2016;48:490-495.

Pozor M, Harnik A. Lateral branches of the testicular artery affect testicular shape in adult stallions. J Equine Vet Sci 2016;36:90-96.

Selected Publications (continued)

abnormalities in equine pregnancies generated by somatic cell nuclear transfer from one donor horse. Theriogenology 2016;86:1573-1582.

Rabaglino MB, Chang EI, Richards EM, James MO, Keller-Wood M, Wood CE. Genomic effect of triclosan on the fetal hypothalamus: evidence for altered neuropeptide regulation. Endocrinology 2016;157:2686-2697.

Ribeiro ES, Monteiro AP, Bisinotto RS, Lima FS, Greco LF, Ealy AD, Thatcher WW, Santos JE. Conceptus development and transcriptome at preimplantation stages in lactating dairy cows of distinct genetic groups and estrous cyclic statuses. J Dairy Sci 2016;99:4761-4777.

Stevenson JS, Lamb, GC. Contrasting effects of progesterone on fertility of dairy and beef cows. J Dairy Sci 2015; 99:5951-5964.

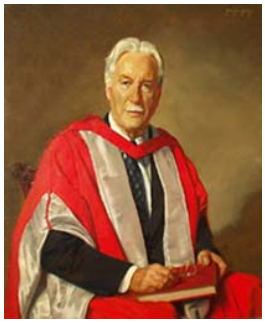
Organized by Kirk Conrad, the purpose of the Work in Progress Conference is to present new ideas and new data, in

Work in Progress Meetings

order to solicit feedback from one's peers, educate trainees, and find common ground for new NIH R01 and P01 applications. We meet at the New Deal Café from 4 to 6 PM on approximately one Friday each month. Beverages and hors d'oeuvres are provided! It is preferred that presentations should be really informal and spontaneous, with NEW IDEAS and data to back them up, if you have any (not necessary). PowerPoint and screen are available, but you are encouraged to use them sparingly. There is also a white board with markers.

The schedule for the fall semester is as follows
September 30 – TBA
November 4 – John Bengston
December 2 – Nicole Cacho

Scene from a recent WIP meeting featuring Charles Wood as speaker. Not shown are the tasty fries and thirst-quenching glasses of beer.



DH Barron Reproductive & Perinatal Biology Research Program

University of Florida

Repro & Perinatal Update is issued each August and January

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 lead 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.

Film poster for *Man with a Movie Camera* (Человек с киноаппаратом). The 1929 movie directed by Dziga Vertov featured the first video recording of a human birth. The movie can be viewed at http://benbeck.co.uk/firsts/2_The_Human_Subject/life_events.htm