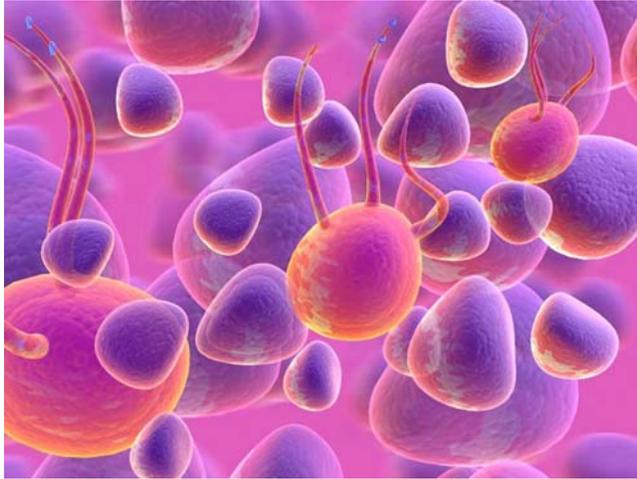


FROM CELLS *to* SOCIETY



Joint Research Symposium
Friday, April 4, 2008
University of Wisconsin - Madison
The Pyle Center



UNIVERSITY OF WISCONSIN
**Center for Women's
Health Research**

a National Center of Excellence in Women's Health

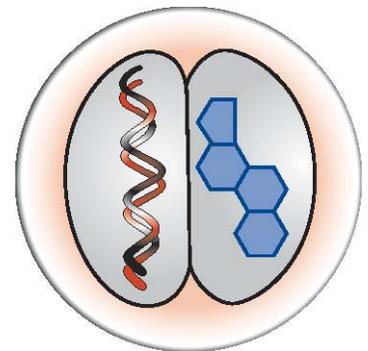


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Schedule

- 8:00 - 1:30 **Registration, Poster Set-up**
- 8:00 - 9:00 **Continental Breakfast**
- 9:00 - 9:10 **Welcome and Introductions**
- 9:10 - 10:10 **From Cells to Society Keynote Speaker**
"Thinking outside the system (box) for recognition"
Dr. Florence Haseltine, Director, Center for Population Research
National Institute of Child Health and Human Development
- 10:10 - 10:30 **Morning Break**
- 10:30 - 12:00 **Featured Student Abstracts**
- 10:40 *"Effect of suppression of FSH with a GnRH antagonist (Acyline) before and during follicle deviation in the mare"*
Celina Checurea, Parrish Lab, ERP Program
- 11:00 *"Ovarian tumor mucin MUC16 protects the cancer cells from NK cell attack"*
Jennifer Gubbels, Patankar Lab, ERP Program
- 11:20 *"Shear Stress Modulation of Endothelial Nitric Oxide Synthase (eNOS) Phosphorylation Responses in Follicular, Luteal and Pregnant Derived Ovine Uterine Artery Endothelial Cells (UAEC)"*
Christopher Huls, Magness Lab, ERP Program
- 11:40 *"Using an Adenoviral Approach to Investigate Pregnancy Specific Changes in Ca²⁺ Signaling in UAEC"*
Derek Boeldt, Bird Lab, ERP Program
- 12:15 - 1:15 **Lunch Break, Poster Sessions**
12:15 - 12:45 **Poster Session I** - Odd Numbered Abstracts
12:45 - 1:15 **Poster Session II** - Even Numbered Abstracts
- 1:30 - 2:30 **Scientific Keynote Speaker**
"Interpreting mixed messages from the fetal heart"
Dr. Kent Thornburg, Director, Heart Research Center
Oregon Health Sciences University
- 2:30 - 2:45 **Afternoon Break**
- 2:45 - 3:15 **Invited Faculty Speaker**
"Ptf1 a guided endocrine differentiation from embryonic stem cells"
Dr. Jon Odorico, Associate Professor, School of Medicine and Public Health
University of Wisconsin - Madison
- 3:15 - 3:45 **Clinical Sciences Speaker**
"Eliminating bias in scientific review"
Dr. Molly Carnes, Director, UW Center for Women's Health Research
University of Wisconsin - Madison
- 3:45 - 4:00 **Closing Remarks**

Keynote Speaker: Florence P. Haseltine, PhD., MD



Dr. Haseltine is currently the Director of the Center for Population Research (CPR) at the National Institute of Child Health and Human Development (NICHD). At NICHD she has led a large and comprehensive program of research in the reproductive sciences, contraceptives, reproductive products and procedures and has helped to develop a program to train obstetrician-gynecologists in basic research.

A board certified obstetrician and gynecologist and an expert in reproductive endocrinology, she has helped to set the research agenda for the coming decade. Currently she is working on the basis of gender differences and what these differences teach us about the system and the disease process.

Dr. Haseltine received her undergraduate training at University of California at Berkeley, a doctorate in biophysics from the Massachusetts Institute of Technology and a medical degree from the Albert Einstein College of Medicine. Following her internship at the University of Pennsylvania at Philadelphia and her residency at Boston Hospital for Women (Brigham and Women's Hospital), she served as assistant and associate professor in the Department of Ob/Gyn and Pediatrics at Yale University.

While at Yale University School of Medicine, she took a year of training at the School of Organization and Management in order to develop a proficiency in administration, policy, strategic planning and business development. She wrote computer programs for automating sperm counting and sold them to industry. She has served on the Scientific Advisory Board of Health Care Ventures, a venture capital group specializing in biotechnology.

The health of women and their advancement professionally are central issues for Dr. Haseltine. In 1990, she founded the Society for Women's Health Research and was its first president. This organization has brought the issue of research on women's health to the attention of high federal officials and prominent members of the media as well as placing it on the nation's priority research agenda. As the Society's founder she wrote mission statements, raised monies, established bylaws, and hired the original staff. Within three years the society was fiscally sound and now has a budget of over \$4,000,000 a year with over twenty full-time employees and at least four million in assets. She is also the founder of Haseltine Systems, a company devoted to easing travel for persons with disabilities.

Dr. Haseltine has co-edited, & reviewed numerous publications & books on a range of topics including reproductive biology, women's health, & proceedings of NIH-sponsored conferences related to the reproductive sciences & population issues. She was also the founding editor of the Journal of Women's Health. In addition, she has made many scientific, public, & media presentations across the country & internationally.

Dr. Haseltine was on the Board of Directors of the American Association for the Advancement of Science and the Society for Gynecologic Investigation. She is currently a board member of the American Women in Science and the Older Women's League. She has been recognized for her contributions in the field of women's health & reproductive science by election to the Institute of Medicine (IOM); a Weizmann Honored Scientist; a Kass Lecturer; a recipient of the American Woman's Medical Association Scientist Award; a recipient of The Kilby Laureates Award; a Health Hero honoree of the American Health For Women Magazine; a Prevention Magazine "Hall of Fame" honoree; Ladies' Home Journal "Champions of Women's Health" honoree; the Advocacy Award from Research!America for the Society for Women's Health Research; received the Barbara Eck Menning Founder's Award; recipient of the American Society for Reproductive Medicine (ASRM) Distinguished Service Award; a member of many professional societies; and the author of numerous publications.

Featured Student Abstracts

10:30-12:00

“Effect of suppression of FSH with a GnRH antagonist (Acyline) before and during follicle deviation in the mare” **Celina Checura**

“Ovarian tumor mucin MUC16 protects the cancer cells from NK cell attack” **Jennifer Gubbels**

“Shear Stress Modulation of Endothelial Nitric Oxide Synthase (eNOS) Phosphorylation Responses in Follicular, Luteal and Pregnant Derived Ovine Uterine Artery Endothelial Cells (UAEC)” **Christopher Huls**

“Using an Adenoviral Approach to Investigate Pregnancy Specific Changes in Ca²⁺ Signaling in UAEC” **Derek Boeldt**

Effect of suppression of FSH with a GnRH antagonist (Acyline) before and during follicle deviation in the mare.

C.M. Checura ^{1,2}, M.A. Beg ², E.L. Gastal ², M.O. Gastal ¹, M.C. Wiltbank ³, J.J. Parrish ⁴, O.J. Ginther ^{1,2}

¹Eutheria Foundation, Cross Plains, Wisconsin, USA. ²Pathobiological Sciences, University of Wisconsin-Madison, Madison, Wisconsin, USA. ³Department of Dairy Sciences, University of Wisconsin-Madison, Madison, Wisconsin, USA. ⁴Department of Animal Sciences, University of Wisconsin-Madison, Madison, Wisconsin, USA.

A GnRH antagonist (Acyline) was used to study the role of FSH in early development of a follicular wave in 61 mares. In Experiment 1, a single dose of 3 mg/mare, compared to 0 and 1 mg, suppressed both the FSH and follicle responses to exogenous GnRH. In Experiment 2, high concentrations of FSH were induced by two successive ablations of all follicles ≥ 6 mm on Days 10 and 13 (Day 0 = ovulation). A single treatment with Acyline resulted in significantly greater suppression of plasma concentrations of FSH than a single treatment with charcoal-extracted follicular fluid (source of inhibin) or estradiol. Suppression of FSH was not significantly different between the group treated with Acyline alone and a group treated with a combination of Acyline, inhibin, and estradiol. In Experiment 3, all follicles were ablated on Day 10 to induce an FSH surge and a new follicular wave. Acyline treatment on Day 10 resulted in an immediate decrease in FSH without a significant effect on day of emergence of a new wave or growth of follicles from 7 to 11 mm on Days 11 to 13. Treatment on Day 15, a day before expected follicle deviation and after the peak of the wave-stimulating FSH surge, resulted in an immediate decrease in FSH and cessation of follicle growth. Results indicated that growth of follicles for about 2 days after wave emergence was independent of FSH. In contrast, during the decline in the wave-stimulating FSH surge and before follicle deviation, growth of follicles was dependent on FSH.

This abstract has been submitted for publication.

Ovarian tumor mucin MUC16 protects the cancer cells from NK cell attack

Jennifer A. A. Gubbels, Jennifer A. Belisle, Mildred Felder, Sarah Petrie, Joseph Connor, Manish S. Patankar

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Epithelial ovarian cancer (EOC) is the predominant malignancy of the ovary. The EOC cells overexpress MUC16, a glycoprotein with an average molecular weight of $3\text{-}5 \times 10^6$ Da. The tumor cells express MUC16 on their cell surface (csMUC16) and also shed this mucin (sMUC16). The sMUC16 binds to an inhibitory receptor and potently inhibits the cytotoxicity of human NK cells. sMUC16 also induces a significant downregulation of CD16 on the NK cells, a change that matches the increased proportion of CD16^{neg}/CD56^{br} NK cells observed in the peritoneal environment in which the EOC cells proliferate. These peritoneal NK cells likely function similar to the decidual NK cells and express proangiogenic factors that promote tumor growth. On the other hand, the csMUC16 prevents efficient recognition of the tumor cells. The csMUC16 expressing EOC cells form a decreased number of immune synapses with the NK cells in contrast to matching MUC16 knock-down tumor cells. Because of its extensive structure and negatively charged oligosaccharide chains the csMUC16 acts as a steric barrier to prevent adhesive interactions between the tumor and the NK cells. Thus the MUC16 is a major regulator of the function of by peritoneal NK cells in EOC patients.

Supported by the DOD (#W81XWH-04-1-0102) and the Ovarian Cancer Research Fund.

Shear Stress Modulation of Endothelial Nitric Oxide Synthase (eNOS) Phosphorylation Responses in Follicular, Luteal and Pregnant Derived Ovine Uterine Artery Endothelial Cells (UAEC)

Christopher K Huls, MD¹, Gladys E Lopez, BS¹, Dinesh M Shah, MD¹ and Ronald R Magness, PhD^{1,2,3}.

¹Depts of Obstetrics & Gynecology; ²Animal Sciences and ³Pediatrics, University of Wisconsin, Madison, WI, United States, 53715.

Compared to the Luteal (Lut) Phase, uterine blood flow is increased *in vivo* during the Follicular (Fol) Phase and more so during Pregnancy (Preg). Both of these are physiologic states of high estrogen and shear stress. Endothelial cells express eNOS and produce greater amounts of nitric oxide (NO) in response to elevations of shear stress. Phosphorylation of eNOS is a signaling marker of activation. We have recently validated Lut, Fol and Preg UAEC culture models for evaluating eNOS phosphorylation responses to shear stress and vascular

We **hypothesized** that UAECs derived from Fol and Preg sheep will show greater eNOS phosphorylation than Lut phase UAECs, and with more robust responses in the presence of Estrogen (E₂).

Methods: UAECs were cultured until 80% confluence, and then subjected to 0 (static control), 3 or 15 dynes/cm² for 48hrs in the absence or presence of E₂ (10nM). Western analysis was used to compare optical densities of Ser635-peNOS (peNOS) normalized to total-eNOS (mean ± SEM).

Results: In Lut UAEC peNOS was equally increased two fold by 3 and 15 dynes/cm² (from 1.26 ± 0.5 to 2.4 ± 0.008 and 2.56 ± 0.06, respectively). Compared to Lut UAECs, the static control Fol UAECs appeared to have higher peNOS levels (2.2 ± 1.5) and this was further increased 1.5-1.8 fold with 3 dynes/cm² (3.2 ± 0.8) and 15 dynes/cm² (3.9 ± 0.38). As seen with Fol UAECs, Preg UAEC static peNOS (1.8 ± 0.4) appeared higher than Lut UAEC, but unexpectedly, neither 3 nor 15 dynes/cm² significantly raised these levels of peNOS (1.76 ± 0.05 and 1.6 ± 0.04). Regardless of shear stress level, E₂ replacement in the culture media only increased the peNOS levels in the nonpregnant, but not the pregnant derived UAECs.

Conclusions: Increasing amounts of shear stress have a corresponding increase in the ratio of eNOS that is phosphorylated at Serine635 in Lut and Fol UAECs. Pregnant UAECs do not appear to increase the constitutive ratio of Serine635 phosphorylation of eNOS at either 3 or 15 dynes/cm². In contrast to our hypothesis, chronic treatment with E₂ for 48hrs did not augment the ratio of eNOS phosphorylation in pregnancy.

Using an Adenoviral Approach to Investigate Pregnancy Specific Changes in Ca²⁺ Signaling in UAEC

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Pregnancy is a time of greatly increased blood flow, through mechanisms of angiogenesis and vasodilation, to the uterus to meet the demands of the growing fetus. In diseased states, such as preeclampsia these needs are not properly met. This can result in intrauterine growth retardation (IUGR) and low birth weight, and therefore increased neonatal morbidity. We are focusing on control of vascular flow through endothelial cell production of the potent vasodilator nitric oxide (NO). It has previously been established that pregnant uterine artery endothelial cells in primary culture (P-UAEC) show greatly enhanced NO production in response to ATP by Arginine-Citruline conversion assay, despite the fact that endothelial nitric oxide synthase (eNOS) expression levels are at a common level with NP-UAEC at Passage 4. Endothelial nitric oxide synthase activity is affected by intracellular Ca²⁺ concentration ([Ca²⁺]_i). Increased [Ca²⁺]_i occurs as a biphasic (initial and sustained) response to ATP stimulation. The initial response is an emptying of ER stores into the cytosol, and corresponds to a single large peak immediately after ATP stimulation in real-time [Ca²⁺]_i imaging. The sustained phase is characterized by periodic [Ca²⁺]_i bursts (influx from extracellular sources) over a period of 30 minutes or more. P-UAEC differ from NP-UAEC by showing greater numbers of responding cells and increased bursts during the sustained phase. Previous students have implicated IP3R2 and TRPC3 as important mediators of the sustained phase, and therefore the greater P-UAEC response. We propose the use of adenoviral transduction as a means of gene delivery, to study the effects of various parts of this system, as well as increasing eNOS levels in order to make real-time NO imaging possible. Our initial experiments have validated that adenoviral treatment can be done at high efficiency in our cells. Furthermore, they have also shown that neither the adenovirus itself, nor reporter genes such as GFP alter Ca²⁺ response to ATP or our detection methods.

Poster Session

12:15 - 12:45: Session I

12:45 - 1:15: Session II

Lab Bratz Episode #54 - Poster Presentation



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Abstract I

Increased body weight, and enhanced insulin sensitivity and secretion, in infant female rhesus monkeys exposed to androgen excess during early gestation

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Typical of women with polycystic ovary syndrome (PCOS), adult prenatally androgenized (PA) female rhesus monkeys exhibit insulin resistance, diminished beta cell insulin response to glucose, abdominal adiposity and hyperlipidemia (1). It is unknown whether these metabolic defects exist at birth or develop later in life. To examine whether androgen excess during early pregnancy impairs infant glucose homeostasis, 9 gravid rhesus monkeys with female embryos (2) were given 15 mg TP once daily sc during 40-80 days gestation (term 165 [range \pm 10] days), while 5 dams of similar preconception age and weight received oil vehicle as controls. A greater ($P < 0.016$) progressive increase in body weight was observed in prenatally androgenized (PA) female infants compared to controls. PA infants increased their birthweight by $91.0 \pm 5.3\%$ (mean \pm SEM) by 60 days of postnatal age, whereas controls gained only $72.4 \pm 7.1\%$. PA female crown-rump and femur lengths, however, did not differ from controls. A frequently sampled intravenous glucose tolerance test with tolbutamide was performed at 45 days of postnatal age. Insulin sensitivity in PA infants (SI: $28.4 \pm 3.6 \times 10^{-4}$ min/uU/ml) was greater ($P < 0.02$) than in control animals ($12.2 \pm 4.8 \times 10^{-4}$ min/uU/ml), while PA infant basal insulin and glucose levels were normal. PA female disposition index ($6.9 \pm 1.6 \times 10^2$ /min) was elevated ($P < 0.03$) in comparison to that found in controls ($2.2 \pm 0.9 \times 10^2$ /min). Acute insulin response to glucose was similar in PA (26.0 ± 6.1 uU/ml) and control (24.8 ± 4.1 uU/ml) infants. Basal and post-glucose serum levels of total non-esterified fatty acids did not differ between infant groups. Therefore, infant PA monkeys demonstrate greater insulin sensitivity and insulin secretion (relative to insulin sensitivity) than control infants. The adult phenotype of diminished insulin sensitivity and insulin secretion appears to develop at a postnatal age beyond early infancy. Our findings suggest potentially complex developmental origins for metabolic dysfunction in our nonhuman primate model.

(1) Abbott DH, et al. Hum Reprod Update, 2005;11:357

(2) Jimenez DF, Tarantal AF. J Med Primatol. 2003;32:315

Supported by NIH/NICHD P50 HD044405, NIH/NCRR RR000167, RR000169.

Abstract 2

The Effect of Erythropoietin and Iron Supplementation on Brain Growth

Sharon E. Blohowiak¹, Joy J. Winzerling² and Pamela J. Kling¹

UW Department of Pediatrics and Meriter Hospital and ²University of Arizona Department of Nutrition

Background: During infancy, iron deficiency detrimentally affects the growth and development of major organs. Red blood cell production is the primary and essential use of available iron, while use and storage in tissue is secondary when iron delivery is impaired. The period of time as a fetus and young infant is critical for brain development, with iron deficiency causing disturbed growth and long-term cognitive delays. The growth factor, erythropoietin (Epo) stimulates red cell production and is clinically used to treat anemia. Erythropoietin increases iron utilization in red cells. Epo exerts different effects if given enterally vs. parenterally, and may be a neurotrophic factor in CNS injury. Our goal was to determine if Epo, administered under the condition of iron sufficiency, could stimulate brain growth or iron incorporation in brain. Our hypothesis is that Epo, given enterally or parentally, would improve brain growth and iron content.

Methods: We treated newborn Sprague-Dawley rats during the postnatal period, P4-12, when the rats were damfed (iron sufficient, IS) or fed iron-deficient artificial milk via gastronomy (iron deficient, ID). Epo was administered enterally or parentally (subcutaneously) at 425 U/kg/day (E/Epo, P/Epo) and compared to control. Iron was supplemented at 6 mg/kg/day in all groups (+Fe). At sacrifice (P12), we collected body weight and brain weight, as well as brain iron content using atomic absorption. We measured blood and marrow hematology parameters.

Results: Across the groups, body weights were similar, supporting similar iron needs for growth. IS rats given P/Epo+Fe had higher hemoglobin ($p<0.0001$), red blood cell ($p<0.002$) and lower myeloid/erythroid ratios ($p<0.002$) versus control IS+Fe or IS E/Epo+Fe. Standardized brain weight ($p<0.03$) and brain iron content ($p<0.03$) improved with P/Epo, compared to IS+Fe or IS E/Epo+Fe. Brain weight and iron content were lower in all ID groups ($p<0.05$), compared to IS+Fe. In ID groups, there evidence for slightly increased erythropoiesis in P/Epo (M:E ratios fell, $p<0.02$, but similar hemoglobin). However, brain weights and brain iron content in ID E/Epo and P/Epo groups were unaltered, compared to ID+Fe.

Conclusions: With sufficient iron availability, P/Epo, but not E/Epo stimulated brain growth and improved brain iron delivery. Despite the abnormally smaller brain size and iron content in ID, compared to control IS+Fe, Epo did not improve brain growth or iron delivery, confirming previous work showing tissue iron delivery is sacrificed for red blood cell production in conditions of limited iron delivery.

Abstract 3

Dietary Effects of Growth and Obesity in Cytochrome P4501b1 Knock-out Mice

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²Molecular and Cellular Pharmacology, University of Wisconsin, Madison, Wisconsin

Cytochrome P450, family I, subfamily b, polypeptide I (Cyp1b1) is a nonspecific monooxygenase whose substrates include estradiol, Vitamin A, polycyclic aromatic hydrocarbons (flavonoids, benzo[*a*]pyrene, DMBA) and possibly fatty acid oxidation products. Cyp1b1 is expressed in many endocrine tissues, (adipocytes, adrenal, ovary, mammary, and uterus). Although Cyp1b1 expression is temporally and spatially regulated in early development (quail, mice and zebra fish), Cyp1b1^{-/-} mice appear normal but share eye defects found in Cyp1b1-deficient humans. Mice deficient in Cyp1b1 are resistant to a high fat diet (HFD) induced obesity response post weaning, which this obesity prevention is lost in an ob/ob^{-/-} background. The deficiency of Cyp1b1 in C57B6 mice was believed to suppress the obesity response to a HFD during gestation, producing offspring that weigh less than a maternal chow diet exposed pup. A maternal HFD in the Cyp1b1^{-/-} background produced a litter of pups that weighed less than pups exposed to a chow diet during gestation. Unfortunately upon expanding the experiment, it revealed that the maternal HFD enhanced the obesity response in Cyp1b1^{-/-} offspring, rendering them heavier than the offspring exposed to a chow diet during gestation. The increase in male weight was not significant but in the females it proved to be significant (male p-value 0.0996, female p-value 0.0017). This initial jump in weight however did not enhance their obesity through maturation. These HFD gestational exposed pups weekly weight gain corrected itself, allowing the chow diet exposed pups weight to catch up after each were on the HFD for ~2.5 weeks. There was no difference in gene expression for the Cyp1b1 knockout mice between the two maternal diets. The mice were subsequently compared to a wild-type (WT) control put on either a low fat diet (LFD) of 10% kcal from fat or the HFD of 60% kcal from fat for 11 weeks. Cyp1b1 deficiency greatly enhanced recruitment of macrophage to adipose tissue, which can enhance lipolysis while gene expression changes in liver indicate enhanced fatty acid oxidation. These findings suggest that the Cyp1b1^{-/-} promotes energy expenditure and fat pad clearance as the key processes preventing obesity. Due to these results along with other extenuating circumstances, influenced a change in my experimental focus to studying the effects of a maternal Vitamin A deficient diet and the impact on the offspring. This future study aims to elucidate the contributions of Cyp1b1 in the retinoic acid driven development of embryos.

Abstract 4

Natural killer cell cytokine production in response to rhesus monkey classical and nonclassical MHC class I molecules

Jessica G. Drenzek, Svetlana V. Dambaeva, and Thaddeus G. Golos.

Wisconsin National Primate Research Center, Department of Comparative Biosciences, School of Veterinary Medicine, University of Wisconsin-Madison, Madison, WI 53715, USA

During pregnancy, a delicate Th1/Th2 cytokine balance is thought to support implantation success. In the endometrium at the implantation site, antigen specific T and B lymphocytes are nearly absent, while non-antigen specific NK cells are numerous and highly specialized. In humans, trophoblasts are characterized by expression of the nonclassical MHC class I molecule HLA-G and no expression of classical HLA-A or HLA-B. HLA-G at the maternal-fetal interface is thought to interact with NK cells to promote pregnancy success. In the rhesus monkey (*Macaca mulatta*), Mamu-AG was shown to be the functional homolog of HLA-G. The hypothesis is that natural killer cell cytokine production is modulated by the presence of Mamu-AG during pregnancy. To test this hypothesis, NK cells were isolated from rhesus monkey peripheral blood and first trimester decidua and co-cultured with MHC class I null 721.221 B-lymphoblastoma cells or with 721.221 cells transfected with Mamu-AG or classical MHC class I molecules, Mamu-A*01, Mamu-A*04, Mamu-B*01, or Mamu-B*03. Supernatants were collected at 24 h and 48 h. The supernatants were assayed using a multiplex Nonhuman Primate Th1/Th2 Cytokine Cytometric Bead Array. The results indicate that upon interaction with Mamu-AG, Mamu-A*01, Mamu-B*01, and Mamu-B*03, there was an increase in IFN-g in co-cultures with peripheral NK cells while TNF production by NK cells was reduced in co-cultures with Mamu-AG. In co-cultures with decidual NK cells, Mamu-AG stimulated IFN-g and IL-6 production and suppressed TNF. In conclusion, these results demonstrate that rhesus monkey peripheral and decidual NK cells express receptors that recognize Mamu-AG and suggest that the Mamu-AG receptor is differentially coupled to NK cell signaling pathways, in comparison with classical KIR receptor(s).

Abstract 5

Effect of Acetyl-L-Carnitine on the Viability of Ovarian Cancer Cells in Vitro in the Presence of Taxane and Platinum Chemotherapies

David B. Engle, MD, Jennifer A. A. Gubbels, BS, Paul R. Hutson, PharmD, David M. Kushner, MD, Manish S. Patankar, PhD

University of Wisconsin Paul P. Carbone Comprehensive Cancer Center, Madison, WI

Objectives: Peripheral neuropathy in patients receiving chemotherapy with platinum analogs and taxanes occur with an incidence of 15-25%. These effects can be permanent and often require either a dose reduction or a change in chemotherapy drug. Acetyl-L-carnitine (ALCAR) is an ester of L-carnitine, an endogenous compound, has a critical function in mitochondrial transport of fatty acids. ALCAR has been shown to treat multi-factorial peripheral neuropathy in humans as well to prevent paclitaxel induced neuropathy in rats (Grandis, 1998; Flatters 2006). To this date, it is not known whether the administration of ALCAR to cancer patients would affect treatment outcomes. The goal of this in vitro study was to: 1) examine the effects of ALCAR on ovarian cancer cells, 2) determine if ALCAR affected the cytotoxicity of standard chemotherapy on ovarian cancer cells.

Methods: An equal number of OVCAR-3, ovarian cancer cell line (ATCC), were divided between 2 treatment arms. One arm, in addition to standard media, was treated with 10uM ALCAR. The second arm was media only. The cells in both arms were then exposed to paclitaxel (1.4nM), carboplatin (22.2uM), or combination paclitaxel/carboplatin at a drug concentration shown to inhibit 50% growth (IC_{50}) (Smith, 2005). The cells were incubated for 72 hours. The cells were then harvested and flow cytometry was performed. Propidium iodide was used to differentiate live from dead cells. The live cell population was gated, and after 10,000 live events were recorded the value between live and dead cells was evaluated. Chi-square test was used to evaluate statistical difference.

Results: Comparing paclitaxel vs. paclitaxel + ALCAR, 13.1% and 13.6 % of the population was dead respectively ($p=1.0$). In the carboplatin vs. carboplatin + ALCAR group there were 10.7% and 13 % dead cells respectively ($p=0.83$). Finally, in the paclitaxel + carboplatin without and with ALCAR there were 12.1% and 17.3 % dead cells ($p=0.42$).

Conclusions: Peripheral neuropathy is a common problem facing many chemotherapy patients. The presence of ALCAR did not affect either the effectiveness of the chemotherapy agent or the viability of cancer cells in any of the 3 chemotherapy regimes. ALCAR may be safe to use in combination with chemotherapy drugs to prevent peripheral neuropathy.

Abstract 6

Co-culture effects on trophoblast differentiation from human embryonic stem cells

Maria Giakoumopoulos^{1,2*}, Leah Siegfried^{1,2*}, Mark Garthwaite^{1,2}, Thaddeus Golos^{1,2}

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* These authors contributed to this work equally

Objective: Our laboratory has recently shown that when human embryonic stem cells (hESC) are allowed to differentiate under specific conditions in culture, they will differentiate into trophoblasts and secrete high levels of placental hormones. We therefore propose a three-dimensional, co-culture system to achieve the goal of utilizing various effector cell types to drive differentiation.

Methods: We used GFP-expressing HI human embryonic stem cells (HIEGFP hESC) in combination with red Cell Tracker-labeled human term placental fibroblasts (TPF) and chorionic villus sampling fibroblasts (CVS) to form embryoid bodies (EBs). These EBs were kept in culture, in suspension for 30 days with media collection and replenishing done daily on half the media.

Results: Levels of human chorionic gonadotropin (hCG) in combination (TPF/HIEGFP) EBs in suspension increased 3-fold by day 20, peaked by day 25 (244.5 ng/ml) and dropped again by day 30, compared with hESC-only EBs, that maintained a low level of secretion (<19.1 ng/ml). CVS/HIEGFP combination EBs increased earlier at day 15, dropped by day 20 and then peaked at day 30. Immunohistochemistry of both combination EB types confirmed trophoblast differentiation by cytokeratin and hCG staining.

Conclusions: Effector cells can facilitate trophoblast differentiation through cell to cell contact with hESC within aggregated EBs. Furthermore, the three-dimensional suspension environment fosters a greater hCG secretion than is seen in hESC-only EBs.

This work was supported by NIH grants HD046919 and HD038843.

Abstract 7

Effects of a uterine restriction model on fetal kidney development in sheep.

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Introduction: Fetal influences may alter organ development of offspring, such as kidneys. A deficiency of kidney filtering units, nephrons, may ultimately result in hypertension as an adult. New nephrons develop until approximately 125 days gestation in sheep. A novel model of uterine size restriction and altered placental hemodynamics could be a tool to evaluate effects on the fetal organ maturation. We **hypothesized** that uterine restriction will disturb kidney nephron development in the sheep fetus. **Methods:** Before pregnancy, a unilateral horn of the uterus was tied off in mixed-breed sheep (unilateral restriction) and compared to non-instrumented controls. The sheep were bred and pregnancy timed. The fetuses continued during pregnancy, delivered at 120 or 130 days gestation (term 145). Because relative kidney size differs between singleton and twin gestations, only twin gestations were studied. Fetal and kidney weights were determined. Renal tissues were fixed, and sections stained by H&E and Gomori trichrome for collagen. Histology was evaluated microscopically. **Results:** Weights from control and unilateral restriction fetuses were equal and appropriately-sized for gestation, based on published Magness laboratory norms (Am J Physiol 1996; 272: H1730). The kidney weight/kg fetal weight was lower in unilateral lambs, $p < 0.0001$. Histology showed disturbed nephron development and increased collagen staining. **Conclusions:** Kidney development was disturbed suggesting smaller kidneys and fibrosis in offspring kidneys after the unilateral uterine restriction model. More studies are planned to examine potential mechanisms involved.

Abstract 8

Synergy between PKA and PKC Stimulation of StAR Expression: Evidence for Distinct Nuclear Pathways Controlled by Acetylation/De-acetylation

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Previous work has shown that mouse StAR transcription in MA10 cells is stimulated synergistically by activation of PKC and PKA pathways (1). Other work has implicated histone acetylation as a key regulatory mechanism for StAR in granulosa cells (2) and MA10 cells (3). Chromatin immunoprecipitation (ChIP) has shown that histone acetylation is enhanced by PKA stimulation of StAR along with binding of specific regulatory factors (4). Histone deacetylases (HDACs) inhibit StAR by binding to a sin3 complex in the proximal promoter. Star transcription is mediated by cooperation between SF1 and several CREB half-sites, API, C/EBP β , API, GATA4, and SREBP in the immediate proximal promoter. ChIP analyses of Pol II binding to the StAR promoter parallel early increases in nuclear transcripts and the later mRNA responses. We show the synergy between PMA and Br-cAMP in two types of adrenal cell, a novel primary culture generated from temperature –sensitive large T antigen mice and early passage Y-1 cells. Low concentrations of Br-cAMP and PMA synergize to provide maximum transcriptional activation of StAR, while retaining mechanisms of the PMA-initiated process. We find that StAR expression is sensitive to HDAC inhibition in both adrenal and MA10 cells but in opposite ways depending on the mode of stimulation. We demonstrate that HDAC inhibitors (trichostatin A, butyrate, VPA) block stimulation of StAR expression in Y-1 cells by Br-cA, but not by PMA. By contrast, two other inhibitors, UO126, a MEK kinase inhibitor, and LMB, an inhibitor of CRM, a component of the export process selectively inhibit PMA stimulation of StAR, as well as the synergistic stimulation. We show that protein acetylation plays very different roles in the PKA and PKC stimulated processes. Recruitment of C/EBP β was increased by Br-cA exclusively at proximal sites, in parallel with Pol II increases, and was suppressed by TSA, in parallel with the effect on transcription. Recruitment of C/EBP β was increased less by PMA and was much less sensitive to TSA. We are testing the hypothesis that Br-cAMP and PMA initiate distinct processes of SF-1 activation during StAR transcription and whether Br-cAMP enhances this PMA-initiated process.

Abstract 9

Further evidence for the role of G-protein coupled receptor 30 (GPR30) in rapid action of estrogen in primate LHRH neurons

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Previously, we have reported that the rapid action of estrogen (E_2) in luteinizing hormone releasing hormone (LHRH) neurons in primates is, in part, mediated by GPR30. 1) The E_2 -induced changes in $[Ca^{2+}]_i$ oscillations and LHRH release were not blocked by the pure ER antagonist ICI 182,780, in both primate LHRH neurons and GTI-7 cells, 2) the E_2 -induced LHRH release was blocked by an activated form, but not an inactivated form, of pertussis toxin in primate LHRH neurons, and 3) GPR30 was expressed in both LHRH neurons and GTI-7 cells. In the present study we further investigated the role of GPR30 in mediating rapid action of E_2 in primate LHRH neurons as well as in GTI-7 cells. First, knockdown of GPR30 in primate LHRH neurons by transfection with siRNA for human GPR30 completely blocked the E_2 -induced changes in $[Ca^{2+}]_i$ oscillations, whereas transfection with control siRNA did not interfere with the E_2 -induced changes in $[Ca^{2+}]_i$ oscillations. Similarly, the E_2 -induced changes in $[Ca^{2+}]_i$ oscillations were blocked by transfection with siRNA for mouse GPR30, but not by control siRNA in GTI-7 cells. The siRNA effect was specific, as a significant reduction in GPR30 protein was observed following siRNA transfection, when compared to that of control siRNA transfection in GTI-7 neurons. Second, GI, a specific GPR30 agonist, induced rapid increases in both $[Ca^{2+}]_i$ oscillations and LHRH release in primate LHRH neurons and GTI-7 cells, which were similar to those observed with E_2 in these neurons. Collectively, the results are consistent with a hypothesis that GPR30, in part, mediates the rapid E_2 action in LHRH neurons.

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Transcriptional Responses in Bovine Liver following Treatment with Estradiol and Progesterone

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The steroid hormones, estradiol (E2) and progesterone (P4) regulate reproductive function and gene expression in a broad range of tissues. Previous studies have reported antagonism as well as synergistic interactions between by P4 and E2. To better understand these interactions and possible mechanisms involved, we employed global gene expression analysis to evaluate the effects of E2, P4, and co-treatment (E2+P4) on bovine liver. **Methods:** A 4X4 Latin Square design was used with ovariectomized Holstein cows randomly assigned to 4 treatment groups (n=4), 1) No hormone supplementation, 2) E2 treatment (ear implant delivering physiological E2 concentrations), 3) P4 treatment (2 intravaginal progesterone-releasing devices producing ~3.5 ng/ml), and 4) E2+P4. After 14 d of treatment, liver biopsies were collected and frozen, allowing 28 d interval between periods. Gene expression in the liver biopsies was monitored using Affymetrix bovine-specific arrays (Bovine GeneChip Genome Array) representing 23,000 transcripts. Signal values on perfect-match and mismatch probes of each transcript were combined into expression indexes using the MAS5.0 algorithm, and the Quantile procedure was used to normalize the data. The MIXED procedure of SAS was used to test for the main effects of E2, P4 and E2+P4 interaction. **Results:** Treatment with E2 caused differential expression of 2841 transcripts of which 1208 was upregulated and 1633 downregulated. Also, E2-induced upregulation was inhibited by P4 for 87 (7.2%) of these transcripts, whereas E2-induced downregulation was inhibited by P4 for 203 transcript (12.4%). In contrast, treatment with P4 caused significant differential expression of 2512 transcripts of which 1100 were upregulated and 1415 downregulated. In addition, P4-induced upregulation or downregulation was reversed by E2 in 61 and 193 transcripts, respectively. Most of the transcripts were upregulated by both P4 and E2 (683 transcripts) or downregulated by both E2 and P4 (759 transcripts). Furthermore, synergistic effects were observed for some genes in combined E2+P4 treatment (193 [13.6%] of downregulated transcripts; 61 [5.5%] of upregulated transcripts). **Conclusions:** Treatment for 14d with E2, P4, or E2+P4 caused differential expression of a large number of transcripts, with a remarkable amount (>50 %) of overlap in the regulation of these genes by the steroid hormones. In addition, antagonistic or synergistic effect was observed for some genes in co-treatment experiments. Some genes regulated by E2 and P4 had their expression reverted by the opposite hormone.

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Effects of iron deficiency and enteral erythropoietin on transferrin receptor concentration in newborn rat duodenum

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Background: The availability of iron is critical in cell proliferation necessary for infant growth. Duodenal intestinal epithelium absorbs milk-borne iron, delivering it to enterohepatic circulation. Once inside, the epithelial cell exports iron-transferrin complexes via the transferrin receptor (TfR) to be transported via the bloodstream to liver. Hepatic iron directly regulates intestinal iron absorption by negative feedback. Erythropoietin (Epo), found in human milk, stimulates erythropoiesis, but its role in iron absorption is unclear. Our aim was to understand whether Epo increases duodenal iron transport in iron-deficient anemic (IDA) newborn rats. First, we hypothesized that duodenal TfR expression would be higher in dam fed or IDA rats fed enteral Epo, compared to control. **Methods:** We studied newborn Sprague-Dawley rats from postnatal day 4-12, damfed or iron-deficient artificial milk via gastrostomy (IDA). Enteral Epo was administered as 425 U/kg/d (Dam+Epo, IDA+Epo). H&E and Prussian blue iron analysis was performed on duodenum and liver. Immunohistochemistry for TfR was performed on duodenum, and color expression quantitated. Body or liver iron content was measured. Images were analyzed digitally by Spot and Metamorph Software. **Results:** Although body iron content was 30% lower in IDA group ($p < 0.005$), weights were similar. Duodenal weights were greater in IDA and IDA+Epo than either Dam or Dam+Epo ($p < 0.05$). Epo treatment did not alter weights. No Prussian blue staining of duodenum was observed, supporting no hemosiderin/storage iron buildup in enterocytes. TfR density was slightly higher in IDA, compared to DF ($p = 0.05$), but was the same for the other groups. Liver iron content ($\mu\text{g/g}$ rat wt) was greater in IDA and IDA+Epo than Dam or Dam+Epo, $p < 0.0005$, but liver Prussian blue staining was markedly lower in IDA and IDA+Epo, compared to Dam or Dam+Epo ($p < 0.0001$). Liver weights were greater in IDA and IDA+Epo than either Dam or Dam+Epo ($p < 0.05$). Epo did not alter liver weights. **Conclusions:** These data support increased TfR density with iron deficiency, but no appreciable effect with Epo. Because duodenal weights differed in iron sufficient vs. deficient rats, and Epo is known to increase villus surface area, we should examine TfR expression more quantitatively by immunoblot and/or expressing TfR for measured villus surface area. Because Prussian blue results do not account for our finding of heavier livers and greater liver iron in IDA, we will examine whether hemoglobin iron is responsible for the discrepancy in total iron content, as iron deficiency could stimulate hepatic erythropoiesis or hepatic vascular dilation.

Abstract 12

Identification of small molecules from human embryonic stem cells using metabolomics

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Neural tube defects affect 1 in 1,000 live births. In spite of that, there are few sentinel biomarkers for early diagnosis of neurodevelopmental disorders. This study sought to identify biochemical pathways and potential biomarkers that are altered by valproate, a known disruptor of human neural development. We hypothesized that small molecules could be measured from undifferentiated hES cells and hES cell-derived neural precursors (hNPs) using metabolomics and that these compounds are altered in response to known disruptors of human development. Biochemical pathways of human development are likely active in human embryonic stem (hES) cells and derivatives, since they recapitulate organogenesis in vitro. The effects of biochemical pathways of valproate-injury on human neurogenesis are determined by modulation of target pathways (detected by metabolomics) followed by differentiation of hES cells into neural precursors and serotonergic neurons. Metabolomics employs either nuclear magnetic resonance (NMR) or mass spectrometry (MS) to identify the abundance of small molecules (metabolites) present in a biological sample. These small molecules may serve as candidate biomarkers of pharmacological efficacy or toxicity. Metabolite profiling was performed in hES cells and hNPs after exposure to valproate. Kynurenine, an intermediate in tryptophan metabolism, and other small molecules in glutamate metabolism were significantly upregulated in response to valproate. Thus, for the first time, we have been able to measure and identify small molecules secreted from hES cells and cells derived from hES cells. The hES cell metabolome may thus serve as a source of candidate biomarkers to predict or measure pharmacological efficacy or toxic response.

**Acid Sensitive Channel Inhibition Prevents Fetal Alcohol Spectrum Disorders
Cerebellar Injury**

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Ethanol is now considered the most common human teratogen. Educational campaigns have not succeeded in reducing the incidence of maternal drinking during pregnancy leading to a growing interest in the development of therapeutic prevention or mitigation strategies. Based on previous findings that maternal ethanol consumption reduces maternal and fetal pH, we hypothesized that a pH-sensitive pathway involving the newly identified TWIK-related acid sensitive potassium channels (TASK 1 and TASK 3) is implicated in ethanol-induced neuronal injury in the fetal cerebellum, a brain structure that is extremely sensitive to ethanol. We modeled a binge drinking pattern during brain growth spurt by intravenously infusing pregnant ewes with ethanol (to create peak blood ethanol concentrations of 258 ± 10 mg/dl) or saline. Quantitative stereological analysis demonstrated that ethanol resulted in a reduction in the total number of fetal cerebellar Purkinje cells, the most sensitive cell type to developmental ethanol exposure. Specific inhibition of Purkinje cell TASK 1 channels by manipulation of extracellular pH, to create the same degree and pattern of pH fall caused by ethanol treatment resulted in one half of the reduction in Purkinje cell number mediated by ethanol. However, ethanol-induced mild transient biologically insignificant decreases in fetal arterial partial pressure of oxygen did not have any exclusive effect on the Purkinje cells. Pharmacological blockade of TASK1 and TASK 3 channels expressed in the fetal sheep Purkinje and granule cells respectively, simultaneous with the ethanol infusions, effectively protected against fetal neuronal loss in the developing brain. We conclude that inhibition of the novel tandem two pore domain TASK channels shows a promising direction for limiting the damaging consequences of maternal drinking during pregnancy. Supported by NIAAA Grant AA10940 and by the NIH Pediatrics Initiatives (TAC).

Donor contribution has larger impact on HSP70.I expression than cumulus removal technique in bovine embryos

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The impact of embryo manipulation and donor contribution on level of expression of molecular markers was investigated in the bovine model. Transcript expression analysis was performed on Holstein 2-cell embryos 24 h after undergoing one of two cumulus removal techniques. Oocytes from each of 5 abattoir obtained Holstein ovaries were fertilized with semen of an individual Holstein bull, yielding families of 4, 5, 18, 25, and 28 zygotes. Cumulus cells from zygotes within each family were removed 24 h post-fertilization by either repetitive pipetting with a 135 μ m pipette or by manipulation in a microfluidic chamber with a 30 μ m aperture. Levels of the stress response transcript, HSP70.I, were used to evaluate cumulus removal technique in the 5 full sib families of developing embryos. Embryonic HSP70.I cDNA from differentially-treated full siblings was analyzed by qPCR and resultant C^T values were normalized to 18S rRNA, the reference gene, to account for potential differences in cDNA levels in each reaction. The data were analyzed by using the GLM Procedure in SAS, testing for treatment and family effects. HSP70.I did not differ between microfluidically-treated and pipetted embryos ($p=0.45$). However, comparison of HSP70.I expression across families was different ($p<0.001$). These results indicate that pooling of genetically unrelated embryos may skew transcript expression data and influence research conclusions. Additionally, the question of culture conditions on embryo vitality needs to be evaluated without donor health status or heredity being additional factors.

Effects of Iron Deficiency on Renal Development in Early Life

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Background: Iron is essential for fetal growth and normal renal development. Iron deficiency may disturb renal development, decreasing nephron numbers (oligonephropathy), a condition linked to adult hypertension. Nephrogenesis occurs until 36 weeks gestation in humans and postnatal day (P) 10 in rats. Because the impact of tissue iron deficiency on renal development in late gestation is unknown, we investigated kidney development in newborn rats. **Methods:** Three groups were studied: 1) dam fed (DF) controls, 2) iron-deficient newborn rats (IDA) fed low iron formula, and 3) IDA plus 6 mg/kg/d enteral iron (IDA+Fe). IDA rats were given iron-deficient formula from P4 to P12 by gastrostomy. Blood was analyzed for hemoglobin and zinc-protoporphyrin-to-hemoglobin ratio (ZnPP). Kidneys were weighed and tissue iron content was measured. Microscopic H&E stained renal sections were examined for glomerular density and glomerular surface area. **Results:** IDA rats were anemic with lower hemoglobin than DF (8.5 ± 0.3 vs. 9.3 ± 0.3 g/dL), $P < 0.0001$, and higher ZnPP than DF, $P < 0.0001$. Hemoglobin and ZnPP in IDA+Fe equaled DF. Kidney iron content was lower in IDA than DF rats (0.289 ± 0.032 vs. 0.598 ± 0.145 $\mu\text{g/g}$ rat wt), $P < 0.003$. Compared to IDA, iron content increased in IDA+Fe (0.486 ± 0.040 $\mu\text{g/g}$ rat wt), $P < 0.02$. Standardized kidney weights were 20% heavier in IDA vs DF, $P < 0.001$ and although trending lower in IDA+Fe, the fall was not significant. Average nephron density was reduced in IDA vs. DF (0.020 ± 0.001 vs. 0.027 ± 0.001 glomeruli/ mm^2 cortex), $P < 0.0001$. Nephron density in IDA+Fe rats showed an increase over IDA (0.024 ± 0.001 glomeruli/ mm^2 cortex), $P = 0.002$, but not full restoration to DF. The planar glomerular surface area was decreased in IDA rats compared to DF (4.7 ± 0.2 vs. 6.6 ± 0.3 μm^2 percent), $P < 0.0001$, with IDA+Fe trending intermediate. Glomerular volumes were lower in IDA+Fe, $p < 0.01$. Trichrome and reticulum stained kidney sections suggested tubulointerstitial fibrosis in IDA. **Conclusions:** Compared to DF, IDA rats exhibit a 26% reduction in nephron density, 20% smaller total glomerular area and a partial recovery with iron. This model supports a critical role for iron in nephrogenesis. Mechanisms involved in this developmental disturbance are unknown, but collagen staining and greater weight support studying genes regulating fibrosis. Future studies should also investigate whether iron deficiency during late nephrogenesis also translates into hypertension later in life.

Abstract 16

The Vital Situation: a moral link for social determinants of health

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A visual model is presented that emerged to respond to the needs of a community-based participatory research (CBPR) carried out with a Latino community in Wisconsin. The main finding of the study was that health was put at risk by Latinos' acculturation towards an individualistic and away from an intersubjective sense of self. As participants analyzed their own stories, a core concept of what is "good" at the time of decision making arose. Under stress, the stories showed that striving for this good demanded that people progressively close their moral sphere (who else's good was also considered part of their own), consolidating the individualistic self. The individualized situations were made scripts for a play where people were asked to improve the theatre scenes. Almost all the improvement suggested were re-expansions of the moral spheres, making people aware of their capacity to creatively reverse individualism. To design a prevention strategy, a unit of analysis called the Vital Situation is proposed based on the concepts of allostasis and dignity and activity setting theory. The potential of the model as a tool for CBPR is discussed.

Abstract 17

Differential effects of leptin on mammary duct and alveolar development

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Leptin was first discovered as the defective gene in the obese (Ob) mouse, while its receptor is defective in the diabetes (Db) mouse. While the original research indicated leptin is expressed in high levels in replete adipose tissue and acts on the hypothalamus to suppress food intake, subsequent research indicated that leptin and leptin receptor are expressed in a wide variety of tissues, and exert a variety of physiological actions. In the mammary gland, leptin and leptin receptor are expressed in the stromal and epithelial portions, and epithelial expression is developmentally regulated. Leptin expression in the mouse mammary gland is highest during mid to late pregnancy. Furthermore, expression of leptin receptor is increased in late pregnancy. Interestingly, the greatest increase in leptin receptor is in the short form of the receptor, whereas the long form (most often associated with intracellular signaling events) shows only a modest change. Ablation of leptin receptors leads to profound inhibition of mammary development. Transplantation of leptin receptor deficient epithelium into normal mice leads to normal duct development, but greatly reduced alveolar development. In contrast, transplanting normal epithelium into leptin receptor deficient stroma, followed by transplanting the chimeric gland into a normal mouse, resulted in essentially no duct development. These results suggested that leptin may act on the mammary stroma during mammary duct development to induce production of paracrine growth factors, but act directly on the epithelium to support alveolar development. Analysis of mRNA and protein expression induced by leptin in cultured mammary epithelial cells suggests that leptin induces a variety of proteins associated with intracellular trafficking of proteins and polarization, but not growth. In contrast, treatment of leptin deficient mammary stroma with leptin induced the production of paracrine growth factors, as assessed by the ability of conditioned media to increase epithelial cell growth. These results suggest that the role of leptin in mammary development varies with stage of development. Leptin acts on the mammary stroma to induce paracrine growth factors during duct growth, but acts directly on the developing alveoli to support alveolar differentiation.

Protein Phosphatase Modulation of FGF2- and VEGF-Induced MAPK3/1 and AKT1 Activation in Ovine Fetoplacental Artery Endothelial (OFPAE) Cells.

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Both FGF2 and VEGF are two key regulators of placental angiogenesis. Cellular responses to FGF2 and VEGF are involved a delicate balance between activations of protein kinases (i.e., MAPK3/1 and AKT1) and phosphatases (i.e., PPP2, also known as PP2A). PPP2 is capable of dephosphorylating MAPK3/1 (also termed as ERK1/2) and AKT1, thereby inactivating these kinases in some cell models. In OFPAE cells, we have reported that FGF2- and VEGF-stimulated OFPAE cell proliferation is mediated at least via the MAPK3/1 and AKT1. We have also observed that suppression of PPP2 catalytic subunit a (PPP2CA) expression by the siRNA did not significantly affect FGF2- and VEGF-stimulated OFPAE cell proliferation, whereas inhibiting ($p < 0.05$) FGF2-, but not VEGF-induced MAPK3/1 phosphorylation. In this study, we examined: 1) if suppression of PPP2CA expression by PPP2CA siRNA interference affected the FGF2- and VEGF-induced AKT1 phosphorylation and, 2) if protein tyrosine phosphatases (PTP) modulated FGF2-and VEGF-induced MAPK3/1 and AKT1 phosphorylation in PPP2CA siRNA transfected OFPAE cells using phenylarsine oxide (PAO), a broad spectrum PTP inhibitor. Both FGF2 and VEGF increased ($p < 0.05$) AKT1 phosphorylation in control (scrambled) siRNA transfected OFPAE cells. Suppression of PPP2CA expression inhibited ($p < 0.05$) FGF2-induced AKT1 phosphorylation, whereas enhancing ($p < 0.05$) VEGF-induced AKT1 phosphorylation. In PPP2CA siRNA transfected OFPAE cells, PAO (10 mM) greatly enhanced ($p < 0.05$) FGF2- and VEGF-induced MAPK3/1 and AKT1 phosphorylation in association with increased basal levels of MAPK3/1 and AKT1 phosphorylation. Thus, in OFPAE cells, suppression of PPP2CA differentially modulates FGF2- and VEGF-induced MAPK3/1 and AKT1 activation. Moreover, the inhibitory effect of PPP2CA suppression on FGF2-induced MAPK3/1 and AKT1 could be attributed partly to elevated PTP activity, which in turn dephosphoylates MAPK3/1 and AKT1 and/or their upstream tyrosine kinases.

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Phenotypic Expression of Decidual Natural Killer Cells

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The role and presence of decidual natural killer (dNK) cells at term in human gestations requires further study. Our objectives were to first determine the presence and phenotypic expression of dNK cells at term using noninvasive approaches. The second objective was to assess the relationship between the dNK cells and MUC16, a mucin expressed in the decidua.

STUDY DESIGN: All subjects signed an informed consent, and the study was approved by the Institutional Review Boards at the University of Wisconsin-Madison and Meriter Hospital. The women were recruited at the time of admission to Labor and Delivery. Placental samples were obtained upon delivery from full-term, uncomplicated pregnancies. The decidua was micro-dissected and digested. The mononuclear cells were isolated using Histopaque. The phenotypic expression of the cells was characterized by multi-color flow cytometry using an LSR-II.

RESULTS: NK cells are present in the deciduas at term. There are two subsets: CD56bright and CD56dim. The majority of these dNK cells are of the CD56bright phenotype. Both subsets of dNK cells were analyzed for the expression of CD158a, CD158b, CD158e, CD226, CD244, NKG2A, NKG2D, and NKp44. Both dNK subsets consistently express elevated levels of NKG2D. Expression of KIR (CD158a, CD158b, and CD158e) was variable across subsets. Decidual NK cells also carry MUC16 on their surface. MUC16 is present on the CD56dim cells.

CONCLUSION: In previous studies, we have demonstrated that MUC16 attenuates the cytolytic capacity of peripheral blood derived NK cells. The MUC16 is highly expressed by ovarian tumors, likely as a strategy to evade NK cell mediated responses. This method of suppression likely originates from the reproductive system where MUC16 and other factors are specifically produced in the decidua to protect the growing fetus from maternal immune responses.

Abstract 20

Pioglitazone decreases adiposity and increases food intake in a model of PCOS

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Polycystic ovary syndrome (PCOS), a common endocrine disorder affecting ~10% women in their reproductive years, is the leading cause of premature type 2 diabetes in young women. Prenatally androgenized (PA) rhesus monkeys express a phenotype similar to PCOS women. The objective of this study was to determine the effect of pioglitazone, an insulin sensitizer, on body composition and food intake in a group of PA monkeys compared to controls. Adult females (4 controls, 7 PA) were treated daily with placebo for 6-7 months, followed by at least 90 d of no treatment (to avoid seasonal oligomenorrhea), and then 6-7 months of daily treatment with pioglitazone (3mg/kg). Monkeys were fed a standard chow *ad libitum* throughout the study. Body composition was analyzed by DXA. Calorie intake was increased significantly during months 5 and 6 of pioglitazone treatment in both female groups. Total weight, total fat, and abdominal fat were greater in controls vs. PAs. PA females lost total fat on pioglitazone but not placebo. In conclusion, the body composition effects of pioglitazone differ depending on the presence or absence of a PCOS-like phenotype.

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Chronic Insulin Therapy Fails To Disrupt Ovulation In A Nonhuman Primate Model For Polycystic Ovary Syndrome (PCOS)

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As found in women with PCOS, hyperinsulinemia is associated with anovulation in prenatally androgenized (PA) female rhesus monkeys (1). Treatment with insulin sensitizers improves insulin sensitivity and stimulates ovulatory menstrual cycles in both PCOS women and PA monkeys (2). To ascertain whether experimentally induced hyperinsulinemia (basal serum levels >694 pmol/L) disrupts ovulation in PA monkeys, 5 PA and 4 control (C) females of equivalent age (PA: 20.7±0.7; C: 17.3±1.0 years; mean±SEM) and body mass index (PA: 36.5±0.9; C: 36.8±3.6 kg/m²) with normal menstrual cyclicity received daily sc injections of recombinant human insulin (Humulin U Ultralente, Eli Lilly, IN; PA: 7.8±1.7, C: 9.0±1.5 U/day) or diluent for 6 months. The mothers of PA females previously had received daily sc injections of 10 mg testosterone propionate for 15-35 days starting on gestation days 40-44 (term: 165 days). A cross-over experimental design was employed with treatment phases separated by at least 90 days. Blood was sampled three times weekly to determine ovulatory menstrual cycles (³² serum progesterone values ³¹ ng/ml within 15 days of menses) and all diagnostic testing was performed during days 1-5 of a menstrual cycle or 30-day anovulatory period. As expected, insulin treatment induced (p<0.04) a 5-8% reduction in fasting basal glucose levels compared to diluent treatment, but mean glucose values in each female group remained above 50th percentile values for normal adult monkeys. Contrary to expectations, however, insulin treatment diminished (p<0.03) follicular phase duration in PA females (insulin: 14.5±0.5, diluent: 21.9±2.2 days) and was without effect in C females (insulin: 12.1±1.4, diluent: 12.0±2.3 days). There was no insulin treatment effect on ovulatory menstrual cycle frequency or duration in either female group. In response to an im injection of 200 IU hCG after 4-5 months of each treatment phase, neither PA nor C females demonstrated hyperandrogenic responses while receiving daily insulin injections. A similar absence of insulin effects on serum LH and FSH levels was observed following an iv GnRH injection administered 5-6 months after onset of either treatment phase. Thus, experimentally induced hyperinsulinemia failed to disrupt ovulation in either PA or C female rhesus monkeys exhibiting menstrual cyclicity, raising questions as to its role in the ovulatory dysfunction observed in this nonhuman primate model for PCOS, and possibly in PCOS women.

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Keynote Speaker: Kent L. Thornburg, PhD.



Kent L. Thornburg, PhD, has been formally trained in developmental physiology, medical science, cardiovascular physiology and molecular biology. He is known internationally as an expert in cardiopulmonary physiology, placentology, and especially, developmental programming of the heart and the roots of adult-onset coronary artery disease. In 1994 he was chosen as the first director of Oregon Health and Science University's Heart Research Center. In 2001 he became the M. Lowell Edwards Chair in the Department of Medicine at Oregon Health & Science University. He now serves as Associate Chief of Cardiovascular Medicine and Director of Research. By invitation, he holds joint professorial appointments in 5 other departments: Physiology & Pharmacology, Biomedical Engineering, Anesthesiology & Peri-Operative Medicine, Obstetrics & Gynecology,

Medical Informatics and Clinical Epidemiology.

Dr. Thornburg is a fellow of the American Physiological Society (Cardiovascular). He has received some 25 teaching awards at OHSU and was elected Outstanding Scientist of the Year in 2000 by the Oregon Academy of Science. He has given a number of endowed lectures including the Archibold Byron Macallum Lecture at the University of Toronto. Dr. Thornburg has served on numerous study sections and advisory boards at the National Institutes of Health, the American Heart Association and other international bodies. He is presently the Section Head for the Commission on Development for the International Union of Physiological Sciences and he serves as an honorary member of the Society for the Natal Effects on Health in Adults in India. He has served as editor of the journal, *Placenta* and has sat on numerous editorial boards. He is presently a consulting editor for *Pediatric Research* and a member of the editorial board of the *American Journal of Physiology*.

The Thornburg laboratory studies embryonic and fetal heart development in several species including the role of wall shear stress, growth factors and signaling molecules in regulating gene expression patterns in the developing myocardium and coronary tree. Dr. Thornburg is the Principal Investigator of a basic Program Project Grant recently funded through year 15, *Maternofetal Signaling and Lifelong Consequences*. He also is the PI on clinical studies to determine the role of the pre-conception diet in regulating placental gene expression and fetal growth in rural women of Oregon.

INTERPRETING MIXED MESSAGES FROM THE FETAL HEART

Kent Thornburg, Nathan Sundgren, Sonnet Jonker, Samantha Louey, Natasha Chattergoon,
Perrie O'Tierney, Carley Shaut, George Giraud

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For nearly 20 years it has been known that low birthweight is a powerful risk factor for ischemic heart disease. However, few biological links between early life growth and later life cardiac disease have been established. We have investigated the elements of the intrauterine environment that regulate growth and development of cardiomyocytes and the coronary tree. The heart is particularly vulnerable at two stages of development: 1) early embryo looping and septation stages and 2) late fetal stages when cardiomyocyte numbers are being set. In the looping chicken embryo, systolic loading changes pan-gene expression profiles in the heart. In the sheep fetus, pressure loading stimulates increases in cardiomyocyte proliferation and more importantly, in cardiomyocyte “terminal differentiation”, the maturation stage when cardiomyocytes lose their ability to divide. In sheep this begins at 2/3rd gestation and spills over into early postnatal life. Cardiomyocytes become binucleated and cease cell cycle activity. At birth about 80% of all fetal cardiomyocytes are binucleated.

Growth factors also regulate cardiac development and are sensitive to the environment. Angiotensin II stimulates proliferation in the fetal sheep heart both *in vivo* and *in vitro*. Insulin-like growth factor-I is a powerful stimulant of cardiomyocyte proliferation in the near term fetus. Activation of both the mitogen activated protein kinase (MAPK) extracellular regulated kinase (ERK) pathway and the phosphoinositol-3 kinase (PI3K) phosphorylation cascade are simultaneously required for proliferative action. Cortisol generally suppresses proliferative growth of fetal organs. However, the heart is a notable exception. Cortisol stimulates cardiomyocyte growth when infused at subpressor doses into the vascular compartment of the fetus or into the coronary arteries. This provides the first evidence that cortisol can behave as a growth factor in the fetus. 3,5-tri-iodothyronine (T₃) is a powerful inhibitor of fetal cardiomyocyte growth *in vitro*. It appears that T₃ is responsible, in large part, for the suppression of heart cell division at term. This developmental role is different from its usual role in cardiac hypertrophy in the adult. The interesting point of this finding is that cortisol is the stimulus for the rise in T₃ that occurs near term. Thus cortisol stimulates 1) growth of the myocardium and 2) generation T₃, the hormone that is responsible for the cessation of proliferative growth. Atrial natriuretic peptide may work synergistically with T₃ in suppressing myocyte cell cycle.

In sheep fetuses that have placental insufficiency, heart growth is depressed. Both the rate of proliferation and the rate of cell maturation are decreased dramatically. The roles of each of the growth factors in regulating heart growth are unknown except that circulating levels of cortisol levels are increased.

Supported by NIH P01HD034430.

Jon S. Odorico, M.D.

Dr. Jon Odorico, MD is an Associate Professor of Surgery in the Division of Transplantation at the University of Wisconsin - Madison School of Medicine and Public Health. After receiving his medical degree from New York University in 1987 and completing his residency at the University of Pennsylvania Hospital in 1994, Dr. Odorico came to Madison as a Fellow in Transplant Surgery at the University of Wisconsin Hospital and Clinics.

Dr. Odorico's research focuses on stem cell biology and differentiation, with the goal of developing novel stem-cell based strategies for treating diabetes, pancreas transplantation, and islet cell transplantation. Directed differentiation of human embryonic stem cells towards pancreatic lineages offers a controllable culture model for studying islet ontogeny and the formation of insulin-producing beta cells. The immediate aims of his lab include: 1) inducing and studying neurogenin3-expressing islet progenitor cells from murine ES cells, 2) testing genetic selection transgene constructs as a means for selecting relatively homogeneous populations of pancreatic lineage cells from mouse and human ES cells, 3) selecting and testing the physiologic function of insulin -secreting ES cell progeny in vitro and in vivo, 4) investigating varieties of growth factors and culture conditions that increase the yield of mature and precursor islet progeny, 5) testing the effect of over-expression of key pancreatic transcription factor genes such as *ptfla* and *pax4* on differentiation of ES cells, 6) developing an in vitro clonogenic assay for insulin positive cell progeny, 7) testing *in vivo* conditions that promote terminal differentiation of ES cell - derived PDX1+ pancreatic precursors, and 8) studying the developmental potential of magnetic bead sorted Ep-CAM+ ESC-derived endoderm progenitors.

Dr. Odorico is certified by the American Board of Surgery and specializes in pancreatic, islet cell and multi-organ transplant. In 2004, Dr. Odorico became the first surgeon in Wisconsin to cure a patient's diabetes by islet cell transplantation, but currently organ donation is the only way to acquire islet cells and the limited supply restricts the number of patients that can be treated. His research could lead to a more abundant islet cell supply that is grown from stem cells. In addition to his active laboratory effort, Dr. Odorico has several clinical studies involving patients receiving pancreas or islet transplantation. Some of these studies in pancreas transplant recipients involve understanding the molecular fingerprint of pancreas allograft rejection by microarray analysis, understanding the expression of chemokines and their receptors during pancreas rejection, and developing better non-invasive methods of diagnosing rejection without need for a biopsy. Dr. Odorico is also principal investigator for the UW Islet Transplant Program clinical trial, which is studying the effects of insulin sensitizers, such as pioglitazone, on blood sugar control after islet transplantation.

Molly Carnes, M.D., M.S.

Dr. Carnes is a Professor in the Departments of Medicine, Psychiatry, and Industrial & Systems Engineering at the University of Wisconsin and Vice Chair for Faculty Development in the Department of Medicine. She directs the U.W. Center for Women's Health Research, three federally-funded training and career development programs in women's health and the NIH Multidisciplinary Clinical Research Career Development Program (Roadmap K12). Dr. Carnes is the founder and director of the Women's Health Program at the Wm. S. Middleton VA Hospital and co-founder and director of the Women in Science and Engineering Leadership Institute (WISELI) in the U.W. College of Engineering.

Dr. Carnes did her undergraduate work at the University of Michigan and received her M.D. from the State University of New York at Buffalo. She trained in Internal medicine and Geriatrics at the University of Wisconsin where she earned a Masters of Science Degree in Population Health.

In 1999, Dr. Carnes received the distinct honor of becoming the first Jean Manchester Biddick Professor of Women's Health Research. She is on the Board of Directors of the Wisconsin Women's Health Foundation. Dr. Carnes is a sought after guest speaker on the advancement of women in academic medicine, science and engineering and the recipient of numerous awards including the Association of American Medical Colleges (AAMC) 2004 Women in Medicine Leadership Development Award and the 2006 Joseph T. Freeman Award given to a prominent physician in the field of aging both in research and practice. Dr. Carnes was accepted as a Fellow in the 2006-2007 Class of the Executive Leadership in Academic Medicine (ELAM) and selected as a 2006 Fellow by the Wisconsin Academy of Arts and Sciences, Arts and Letters. Most recently, she was named the 2007 Helen Dickie Woman Physician of the Year by the American College of Physicians.

Abstract: Eliminating Bias in Scientific Review

Molly Carnes

As scientists, we like to think we are objective and without bias in evaluating data. Dr. Carnes will discuss how unconscious assumptions that we all have about groups of people can affect the way we evaluate individuals from that group and the work that they perform. While her talk will focus on research on gender, the principles are broadly applicable and should stimulate self-reflection.

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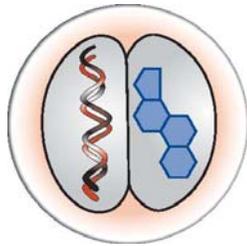
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