



Faculty Research Summary V.1

Women's Health Research Division
Department of Obstetrics and Gynecology



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Joint Appointment Faculty – Other

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Generalists Division

Adams, Karen

Area(s) of Research/Scholarly Interest

Medical education, reproductive ethics, resident and physician professionalism

Current Grants and Contracts

None currently

Grants planned or in submission 2010

Strong Grant (CREOG supported grant for medical education research)

Key collaborators

Departmental Other members of the Education Division: Meg Oreilly, Charcie Clock
OHSU All members of the Graduate Medical Education (GME) community
Extramural

Most recent publications (last 5)

Adams KE. Mandatory parental notification: the importance of confidential reproductive services for adolescents. *Journal of the American Medical Women's Association*, Spring, 2004;58:87-89.

Adams KE. What's "normal": psychology, body image, and female genital mutilation. *Journal of the American Medical Women's Association*, Summer, 2004;58:168-170.

Adams KE, O'Reilly M, Romm J, James K. Effect of Balint training on resident professionalism. *Am J Obstet Gynecol*, Nov 2006; 195(5):1431-7.

Adams KE, Emmons S, Romm J. How resident unprofessional behavior is identified and managed: a program director survey. *Am J Obstet Gynecol*, June 2008; 198(6):692.

Adams KE, Allen R, Cain JM. Physician reentry: a concept whose time has come. *Obstet Gynecol*, May 2008; 111(5):1195-8.

Bednarek, Paula

Area(s) of Research/Scholarly Interest

Family Planning with specific interest in intrauterine contraception, long-acting contraceptive options, sterilization, menstrual suppression, post-abortion contraception, pain control in outpatient gynecologic procedures, training residents and medical students in family planning.

Grants and Contracts

Current:

Society of Family Planning. Pilot grant. "[The effect of nitroglycerin on the IUD insertion experience in nulliparous women.](#)" 2010-11.

Anonymous Foundation. Research funding, "Post-fellowship research funding" 2009-11.

Past:

Anonymous Foundation. Research funding, "Immediate versus delayed IUD insertion following suction aspiration between 5 and 12 weeks gestation: a randomized trial." 2006-09. Role: PI.

Key collaborators

Departmental

Jeffrey Jensen, MD, MPH

Mark Nichols, MD

Alison Edelman, MD, MPH

Family Planning Fellows

OHSU

None outside of OB/Gyn Dept

Extramural

Mitchell Creinin, MD (University of Pittsburgh)

Matthew Reeves, MD, MPH (CONRAD)

Carrie Cwiak, MD, MPH (Emory University)

Eve Espey, MD, MPH (University of New Mexico)

Bliss Kaneshiro, MD, MPH (University of Hawaii)

Michelle Isley, MD, MPH (University of Ohio)

Most recent publications (last 5)

1. Crawford JT, Edelman AB, Pereira L, **Bednarek P**, Buckmaster J. The effects of vasopressin injection on uterine artery blood flow during dilation and evacuation. *American Journal of Obstetrics and Gynecology*. 2007;196(5):e38-39.
2. Creinin MD, Schreiber CA, **Bednarek P**, Lintu H, Wagner M-S, Meyn LA. A randomized comparison of mifepristone and misoprostol administered simultaneously versus 24 hours apart for abortion. *Obstetrics and Gynecology*. 2007;109(4):885-94.
3. **Bednarek PH**, Nichols MD, Carlson N, Edelman AB, Creinin MD, Truitt S, Jensen JT. Effect

of “Observed Start” versus traditional “Sunday Start” on hormonal contraceptive continuation after medical abortion. *Contraception*. 2008;78(1):26-30.

4. Stanek AM, **Bednarek PH**, Nichols MD, Jensen JT, Edelman AB. Reported barriers to delayed intrauterine device placement post-abortion. *Contraception*. 2009;79(3):216-220.
5. **Bednarek PH**, Jensen JT. Safety, efficacy and patient acceptability of the contraceptive and non-contraceptive uses of the LNG-IUS. *International Journal of Women's Health*. 2009;1:45-58.

Bell, Moira

Area(s) of Research/Scholarly Interest

Current Grants and Contracts

Grants planned or in submission 2010

Key collaborators

Departmental

OHSU

Extramural

Most recent publications (last 5)

Berlin, Michelle

Area(s) of Research/Scholarly Interest

Women's health epidemiology

Screening and prevention services, particularly cancer screening and detection

Disease prevention and health promotion

Current Grants and Contracts

Oregon Clinical and Translational Research Institute (OCTRI); "The Oregon Health & Science University Human Investigations Program," NIH; Michelle Berlin, Course Director; Eric Orwoll PI; 7/1/2006 – 6/30/2011; 5% effort.

Evidence-Based Practice II: Faculty & Curriculum (Western States Chiropractic College); NIH; Michelle Berlin, PI (subcontract); 8/1/2009 – 6/30/2013; 10% effort.

Women with Disabilities Health Equity Coalition; Johnson & Johnson; Michelle Berlin, PI; 9/1/2009 – 12/31/2010.

Susan G. Komen for the Cure (Oregon & SW Washington); Michelle Berlin, PI. 4/1/2010-3/30/2011.

Grants planned or in submission 2010 -2011

- AHRQ (large conference) grant re: updating Women's Health Report Card

- Foundation grant(s) to support 2nd Oregon Women's Health Policy Summit

- Cervical dysplasia: further work re: p16 & Ki67 (with Pathology department) – NIH R01

Key collaborators

Departmental: Family Planning Group (DSMB for Paula Bednarek & Roseanne Botha); Jeanne-Marie Guise & others

OHSU: Knight Cancer Institute: OCTRI; Depts of Family Medicine, Internal

Medicine, Public Health & Preventive Medicine, Medical Informatics & Clinical Epidemiology;

Office of Rural Health; Oregon Office on Disabilities,

Kinsman Ethics Center; OHSU IRB

Extramural:

Local & Regional: Oregon Department of Human Services, Public Health Division, Office of Family Health [including the Maternal Child Health Section, the Immunization Section, the Women's Health Program and its Oregon Breast and Cervical Cancer Prevention (BCCP) Program, the Family Planning Program, the Adolescent Health Section, and Preconceptional Care Work Group] and Office of Disease Prevention and Epidemiology, Health Promotion & Chronic Disease Prevention; Multnomah County Health Department University of Western States Chiropractic College; March of Dimes; Susan G. Komen Race for the Cure of Oregon & Southwest Washington; American Cancer Society; Northwest Health Foundation

National & International: DHHS Office of Women's Health; NIH Office of Research on Women's Health; HRSA Office on Women's Health; FDA Office of Policy; American Congress of Obstetricians & Gynecologists; Kaiser Family Foundation (Women's Health Policy and Race, Ethnicity and Health Care); Ontario Women's Health Council

Most recent publications (last 5)

Rebbeck TR. Troxel AB. Norman S. Bunin GR. DeMichele A. Baumgarten M. Berlin M. Schinnar R. Strom BL. A Retrospective Case-Control Study of the Use of Hormone-Related Supplements and Association with Breast Cancer. International Journal of Cancer, 120(7):1523-1528, 2007.

Rebbeck TR. Troxel AB. Norman S. Bunin GR. DeMichele A. Baumgarten M. Berlin M. Schinnar R. Strom BL. Phytoestrogen-Containing Herbal Preparations and Breast Cancer Risk. *International Journal of Cancer*, 120(7):1523-8, 2007.

DeMichele A. Troxel AB. Berlin J. Weber A. Bunin G. Turzo E. Schinnar R. Burgh D. Berlin M. Rubin S. Rebbeck T. Strom BL. Impact of Raloxifene or Tamoxifen Use on Endometrial Cancer Risk: A Population-Based Case-Control Study. *Journal of Clinical Oncology* 26 (25): 4151-4159 ,2008

Wisdom J. Michael Y. Ramsey K. Berlin M. Women's Health Policies Associated with Obesity, Diabetes, High Blood Pressure, and Smoking: A Follow-Up on the Women's Health Report Card. *Women & Health* 48 (1): 103-122, 2008.

Wisdom J. McGee M. Horner-Johnson W. Michael Y. Adams E. Berlin M. Health Disparities Between Women With and Without Disabilities: A Review of the Research. *Social Work in Public Health* 25 (3): 368 -386, 2010.

Edelman, Alison

Area(s) of Research/Scholarly Interest:

Obesity and contraception
Mechanisms for contraceptive failure
Novel forms of contraception
Breakthrough bleeding prevention on contraception
Menstrual suppression
Office procedures (abortion, IUD insertion) and pain control
International low resource settings and reproductive health

Current Grants and Contracts

Present

R01 HD 061582-01 NICHD 9/2009, "Improving Contraceptive Effectiveness in Obese Women".
\$100,000,000.

Principal Investigator: Alison Edelman MD

Society of Family Planning Large Funding Grant 2009. "A non-hormonal model for emergency contraception: a prostaglandin-endoperoxide synthase 2-specific inhibitor" (SFP3-7), \$119,958.

Principal Investigator: Alison Edelman MD

Society of Family Planning Funding 2007, "Combined oral contraceptives and body weight: do oral contraceptives cause weight gain – a primate model", \$120,000

Principal Investigator: Alison Edelman MD

Society of Family Planning Pilot Funding 2007, "Blood Loss at the Time of First Trimester Surgical Abortion in Anticoagulated Women", \$14,737.40

Principal Investigator: Bliss Kaneshiro MD

Completed

HD 01243-03 Women's Reproductive Health Research Fellow (NICHD K-12) 7/03-present
Fellowship provides salary support for research. Current project involves investigation of obesity and oral contraceptive efficacy (Cain, PI).

1 R03 HD 053611-01 Contraceptive efficacy and body weight: does obesity affect the risk of failure?
9/2006- 2008. \$100,000

Principal Investigator: Alison Edelman MD

Oregon Health & Science University's General Clinical Research Center (GCRC) Research Grant 2003, "Oral Contraceptive efficacy and body weight: does obesity affect the risk of contraceptive failure?",

Principal Investigator: Alison Edelman MD

Oregon Health & Science University's Center for Women's Health Grant 2004, "Oral Contraceptive efficacy and body weight: does obesity affect the risk of contraceptive failure?", \$15,000

Principal Investigator: Alison Edelman MD

Society of Family Planning Pilot Funding 2007, "An Alternative Model for Emergency

Contraception: Prostaglandin Inhibitor-induced Luteolysis", \$15,000
Principal Investigator: Alison Edelman MD

Society of Family Planning Funding 2007, "Paracervical Block with Combined Ketorolac and Lidocaine in First Trimester Surgical Abortion", \$83,740
Principal Investigator: Catherine Casino MD

Grants planned or in submission 2010

Resubmission of R01 grant for bariatric surgery and oral contraceptive pharmacokinetics (sub-investigator with John's Hopkins Anne Burke)

Possible grant extension versus new grant in Fall 2010 on pharmacogenomics: a potential mechanism for contraceptive failure

Grant submission Winter 2010 in collaboration with ONPRC regarding cox2 inhibitors as EC (preliminary data due fall 2010)

Key collaborators

Departmental: Jensen, Nichols, Leclair, Fellows

OHSU: Dick Stouffer (ONPRC), Jon Hennebold (ONPRC), Dennis Koop (PK Core), Ganesh Cherala (Pharm D OSU), Cheryl Maslen (Genetics)

Extramural: Frank Stanczyk (USC), Melissa Gilliam (UCI), Anne Burke (JH), Anne Steiner (UNC), Maria Rodriguez (UCSF), Bliss Kaneshiro (UH), Michelle Isley (UO), Laura Castleman (Ipsas, UM), Paul Blumenthal (Stanford)

Most recent publications (last 5)

1. Casino C, **Edelman A**, Burke A, Jamshidi R. Paracervical block with combined ketorolac and lidocaine in first trimester abortions. *Obstet Gynecol* 2009; 114:1220-1226.
2. Renner R, Jensen JT, Nichols M, **Edelman A**. Pain control in first trimester abortion: systematic Cochrane review of randomized controlled trials. *Cochrane Library*, issue 4, 2009.
3. Segel S, Hashima J, Gregory T, **Edelman A**, Li H, Guise JM. A new approach to postpartum rounds: patient centered collaborative care improves efficiency. *J Grad Med Ed* 2010;67-72.
4. Isley M, **Edelman A**, Kaneshiro B, Peters D, Nichols M, Jensen JT. Sex education and contraceptive use at coital debut in the United States: Results from cycle 6 of the National Survey of Family Growth. *Accepted to Contraception March 2010*.
5. Kaneshiro B, **Edelman A**, Carlson N, Morgan K, Nichols M, Jensen J. Treatment of unscheduled bleeding in continuous oral contraceptive users with doxycycline. *Accepted to Obstet Gynecol March 2010*

Goetsch, Martha

Area(s) of Research/Scholarly Interest:

Vulvar Vestibulitis and Vulvar Disorders

Family Planning

Paracervical Blocks as part of an interest in effective outpatient anesthesia

Current Grants and Contracts

NVA (National Vulvodynia Association) \$6,000 remaining from a grant obtained by Terry Morgan for histochemical studies of vestibulodynia surgical tissues (2008). With these funds we will analyze the type of lymphocytes found in vestibulodynia. Principal Investigator: Terry Morgan, MD, PhD

Grants planned or in submission 2010

National Vulvodynia Association grant proposal due July 2010 for \$30,000 to study newly menopausal breast cancer patients who develop severe dyspareunia.

Key collaborators

Departmental – Catherine Leclair, MD and Jeffrey Jensen, MD, MPH for projects below.

OHSU –

Lymphocyte Study: Terry Morgan, MD, PhD, Department of Pathology

Breast Cancer Project: Steven Chui, MD, Department of Hematology-Oncology; Arpana Naik, MD, and Rodney Pommier, MD, Department of Surgical Oncology

Extramural –

Breast Cancer Project: Northwest Oncology Associates

Most recent publications (last 5)

Leclair CM, Hart AE, **Goetsch MF**, Carpentier H, Jensen JT. Group B Streptococcus: Prevalence in a Non-obstetric Population. J Low Genit Tract Dis. 2010 Jul;14(3):162-6.

Goetsch MF, Morgan TK, Korcheva, VB, Hong, L, Peters, D, Leclair, CM. Histologic and receptor analysis of primary and secondary vestibulodynia and controls: a prospective study. Am J Obstet Gynecol 2010; 202:614.e1-8.

Goetsch M, Incidence of Bartholin's Duct Occlusion after Superficial Localized Vestibulectomy, American Journal of ObGyn, 2009;200:688.e1-688.e6.

Goetsch M, Morgan T, Korcheva V, Li H, Peters D, Leclair C, Histologic and receptor analysis of primary and secondary vestibulodynia and controls: a prospective study, accepted, AJOG, 2009.

Leclair C, Hart A, **Goetsch M**, Carpentier H, Jensen J, Goup B Streptococcus: prevalence in a non-obstetric population, accepted Journal of Lower Genital Tract Diseases 2009.

Hatfield, Joanna**Area(s) of Research/Scholarly Interest:**

Environment and Health
Robotics outcomes
Perinatal mood disorders

Current Grants and Contracts

none

(On thesis committee for funded MD/MPH student doing robotic outcomes research)

Grants planned or in submission 2010

none

Key collaborators

Departmental none
OHSU (writing case report with path department)
Extramural

Most recent publications (last 5)

Meites et al. A student-initiated interactive course as a model for teaching reproductive health. *Am J Obstet Gynecol*, 187(3 Suppl):S30-3, Sept 2002.

Bret-Harte et al. Plant and soil responses to neighbor removal and fertilization in Alaskan tussock tundra. *Journal of Ecology*, 92(4): 635-647, August 2004.

Winthrop et al. The Clinical Management and outcome of nail salon-acquired *Mycobacterium fortuitum* skin infections. *Clinical Infectious Diseases*, 38(1):38-44, Jan 2004.

Hatfield et al. Conservative treatment of Placenta Accreta. *The Journal of Minimally Invasive Gynecology*, 13(6):510-513, Nov-Dec 2006.

(poster only) Hatfield et al. Gender Disparity and Factors Influencing Level of Interest in a d Career in Obstetrics and Gynecology. Presented at the CREOG and APGO Annual Meeting, March 2007. Salt Lake City, UT

Jensen, Jeffrey

Area(s) of Research/Scholarly Interest

My career has been devoted to the improvement of human health and society through the promotion of safe, effective methods of contraception such that every baby is wanted and planned. As a clinician-scientist with more than 20 years of experience, my efforts encompass clinical care, clinical research, and translational research. Current activities include Principle Investigator at OHSU for the NICHD-funded Contraceptive Clinical trial Network, and co-PI of the Contraceptive Research Development Center at Oregon National Primate Research Center (ONPRC). I also am a member of International Committee for Contraception Research, and collaborate on Population Council-funded clinical trials. I have extensive experience as a research mentor for graduate students in public health, Fellows in Family Planning, and resident physicians. As Director of the Women's Health Research Unit, I provide oversight for the clinical trials program at OHSU that includes cooperative international projects.

Fertility Control:

Basic Science: 1) Selective oocyte-specific contraceptive targets. 2) Non-surgical female sterilization. 3) Nonhuman primate model for translational research (endometriosis, fibroids, contraception)

Clinical: 1) Abortion pain relief. 2) Continuous methods of hormonal contraception. 3) Management of abnormal bleeding associated with hormonal contraception. 4) Intrauterine Contraception

Clinical Epidemiology and Public Health. 1) Adolescent sexuality. 2) Abortion politics. 3) Environmental effects of population growth.

Gynecology:

Vulvar Diseases: 1) Medical management of vulvodynia and vestibulitis. 2) Vulvar Dermatology. 3) Myofascial pain syndromes

Menopause: 1) Hormone replacement therapy. 2) Hormonal alternative therapy

Sexuality: 1) Sexual pain disorders.

Current Grants and Contracts

Federal

| | | | |
|--|-----------|----------------------|--------------|
| HHSN275200403378I | NICHD | \$311,604 | 2/10-7/11 |
| Task Order 5: A multicenter, open-label, randomized, parallel group study to evaluate pharmacokinetic profile effects on the mechanisms of contraceptive efficacy and safety of two progestin-only patches containing different doses of Levonorgestrel (LNG). | | | |
| HHSN275200403378I | NICHD | \$225,857(year 1) | 9/09-9/10 |
| Task Order 4: TORFP-Contraceptive efficacy evaluation of the path female condom. | | | |
| U54 HD029990 | NIH/NICHD | \$ 105,043 | 3/09 - 10/10 |
| Phase 2, randomized study to evaluate safety/efficacy of 2 Contraceptive Vaginal Rings delivering daily dose of 1500/2500 microgram of CDB-2914 on inhibition of ovulation, endometrial changes and bleeding patterns in normal cycling. (Subcontract, P.I. R. Sitruk-Ware Population Council) | | | |
| U54 HD055744 | NIH/NICHD | \$1,200,000 (year 1) | 3/07 - 2/12 |
| Contraceptive Development Center: Contraception by Blockade of Perioovulatory Events in Primates | | | |

U54 Center targeting discovery and development of novel contraceptive agents that prevent one or more periovulatory events in adult, female primates. Project I: “Control of Oocyte Maturation” will address the hypothesis that novel follicle cell- and oocyte-derived proteins control nuclear and cytoplasmic maturation of the oocyte, and can be exploited to prevent timely egg maturation and hence fertility. Project II: “Control of Cumulus-Oocyte Expansion (C-OE)” will identify factors controlling C-OE and whether their antagonists prevent egg release and fertility. Project III: “Control of Follicle Rupture” explores proteases in the ovulatory follicle and whether their inhibition will prevent follicle rupture, egg release and fertility.

Role: Center Co-PI; Project I Co-PI

Other

| | | | |
|-----------|--|-----------|---------------|
| M360-L102 | Medicines360 | \$277,199 | Pending |
| | A Phase 3, randomized, multicenter, open label study of a Levonorgestrel-releasing intrauterine system (20 mcg/day) and Mirena for long term, reversible contraception up to five years. | | |
| SC0901 | Population Council, Inc. | \$105,043 | 03/09-08/10 |
| | Phase 2, randomized study to evaluate safety/efficacy of 2 Contraceptive Vaginal Rings delivering daily doses of 1500/2500 microgram of CDB-2914 on inhibition of ovulation, endometrial changes & bleeding patterns in normal cycling. | | |
| 91555 | Bayer HealthCare Pharmaceuticals, Inc. | \$231,700 | 07/09-07/12 |
| | A Multicenter, Open-Label, Uncontrolled Study to Investigate the Efficacy and Safety of the Transdermal Contraceptive Patch Containing 0.55 mg Ethinyl Estradiol and 2.1 mg Gestodene (Material No. 80876395) in a 21-Day Regimen for 13 cycles in 1650 healthy female subjects. | | |
| SRA-09-43 | Bayer Schering Pharma AG | \$91,569 | 01/09 – 12/10 |
| | Preclinical Studies on Endometrial Xenografts (PI Ov D Slayden) | | |
| 13108 | Bayer HealthCare Pharmaceuticals, Inc. | \$42,000 | 02/09 – 06/12 |
| | A Multicenter, randomized, db, active-controlled, parallel group, 2-arm study to show superiority of oral contraceptive SH T006581D over Ortho Tri-Cyclen Lo on hormone withdrawal-associated symptoms after 6 cycles treatment. | | |
| 310442 | Bayer HealthCare Pharmaceuticals, Inc. | \$249,770 | 02/08 – 02/11 |
| | MC, OL, randomized Study to assess safety & contraceptive efficacy of 2 doses (in vitro 12 ug/24 h & 16ug/24 h) ultra low dose levonorgestrel contraceptive intrauterine systems (LCS) a maximum of 3 yrs in women 18-35 years of age. | | |
| 311642 | Bayer HealthCare Pharmaceuticals, Inc. | \$274,311 | 06/08 – 06/10 |
| | A Multicenter, Open-Label, Three-Arm, Active-Controlled Study to Assess the | | |

Efficacy and Safety of the Oral Contraceptive SH T00186D (0.02 mg ethinyl estradiol as betadex clathrate and 3 mg drospirenone) in Two Flexible extended regimens and a conventional regimen of Yaz in 1756 healthy females for 1 year.

Grants planned or in submission 2010:

- 1) BMGF Grand Challenge “RCT of IRCU IUD and T380A and measured menstrual blood loss (submitted June 10) (\$100,000)
- 2) BMGF Grand Challenge “Polidocanol Foam for nonsurgical sterilization in macaques” (submitted June 10) (\$100,000)
- 3) USAID “Development of the Indomethacin-releasing copper IUD” in collaboration with Women’s Care (submitted June 10) (\$5 million)

Key collaborators

Departmental: Drs. Edelman, Bednarek, Nichols, Renner, Leclair, Goetsch
OHSU: Drs. Stouffer, Hennebold, Zelinski, Wu, Slayden, Hanna (ONPRC)
Extramural: Drs Regine Sitruk-Ware (Population Council), Ian Fraser (Univ of Sydney), Bliss Kaneshiro (Hawaii), Mitch Crenin (Pittsburgh), Michelle Isley (Ohio State), David Archer (EVMS), Matt Reeves (CONRAD)

Most recent publications (last 5)

Edelman AB, Jensen JT, Hennebold JD. A nonhormonal model for emergency contraception: prostaglandin synthesis inhibitor effects on luteal function and lifespan, a pilot study. *Contraception* 2010;81:496-500.

Hanna CB, Yao S, Patta MC, Jensen JT, Wu X. WEE2 is an oocyte-specific meiosis inhibitor in rhesus macaque monkeys. *Biol Reprod* 2010;82:1190-7.

Kaneshiro B, Edelman A, Carlson N, Morgan K, Nichols M, Jensen JT. Treatment of unscheduled bleeding in continuous oral contraceptive users with doxycycline: a randomized controlled trial. *Obstetrics and gynecology* 2010;115:1141-9.

Rodriguez MI, Jensen JT, Darney PD, Little SE, Caughey AB. The financial effects of expanding postpartum contraception for new immigrants. *Obstet Gynecol* 2010;115(3):552-8.

Jensen JT, Stouffer RL, Stanley JE, Zelinski MB. Evaluation of the phosphodiesterase 3 inhibitor ORG 9935 as a contraceptive in female macaques: initial trials. *Contraception* 2010;81:165-71.

Leclair, Catherine

1. **Area(s) of Research/Scholarly Interest:** vulvar health (vulvar skin disorders, vulvodynia, vestibulodynia, recurrent vaginitis), women's sexuality, general gynecology
2. **Current Grants and Contracts:**
 - a. a. NVA Marinoff Career Development Grant (already published study this originally funded, remaining \$2500 set aside for new study already IRB approved to be done with Martha Goetsch, Terry Morgan)
 - b. NVA Vulvodynia Grant: \$25k with co-PI Terry Morgan; study is complete and in process of being written
3. **Grants planned or in submission 2010:**
 - a. Circle of Giving Grant 2010 submitted: declined
 - b. NVA Vulvodynia Grant: \$30k submission planned for July 15, 2010
 - c. NIH RFA Vulvodynia: RO1 submission for Sept 2010 with Jeff Jensen & Maria Rodriguez

Key collaborators

Departmental: Jeff Jensen, Martha Goetsch, Maria Rodriguez, Alison Edelman, Abby Parsons

OHSU: Terry Morgan (Pathology), Dawn Peters (Biostats)

Extramural: none

Most recent publications (last 5)

1. **Leclair CM**, Hart AE, Goetsch MF, Carpentier H, Jensen JT. Group B Streptococcus: Prevalence in a Non-obstetric Population. *J Lower Genital Tract Diseases*, in print 2010
2. Goetsch, MF, Morgan TK, Korcheva VB, Peters D, Li H, **Leclair CM**. Histologic and receptor analysis of primary and secondary vestibulodynia and controls: a prospective study. *Am J Obstet Gynecol*, in print, 2010
3. Lewiss R, Saul, T, Teng J. Gynecological Disorders in Geriatric Emergency Medicine. *Am J Hosp Palliat Care* 2009; 26; 219-227. **Provided vulvar images**. Original published online Feb 26, 2009. <http://ajh.sagepub.com/cgi/content/abstract/26/3/219>
4. Kennedy M, **Leclair C**, Boardman L. Topical and Injectable Therapies for Vulvar Pain, In Goldstein AT, Pukall CF, Goldstein I (Eds.) *Female Sexual Disorders*. UK: Wiley-Blackwell, 2009, pp 156-161.
5. **Leclair CM**, Goetsch MF, Lee KK, Jensen JT. KTP-Nd: YAG Laser Therapy for the Treatment of Vestibulodynia: A Follow-Up Study. *J Reprod Med* 2007; 52:53-58.

Electronic Publications (peer reviewed)

Leclair C. Vulvodynia. <http://pier.acponline.org/physicians/diseases.html> [Date accessed: 2004 Oct 1] In: PIER [online database]. Philadelphia: American College of Physicians, 2004, 2005, 2006, 2007, 2008, 2009, 2010.

"Vulvar Pain: **An Expert Interview with Catherine M. Leclair, MD**", Medscape Ob/Gyn & Women's Health, 9/30/2009. <http://www.medscape.com/viewarticle/709587>

Leslie, Virginia (Jennie)

1. Area(s) of Research/Scholarly Interest

- a. HIV In Pregnancy
- b. Latina Birth Outcomes
- c. Health Disparities - Underserved Women's Reproductive Healthcare and related health policy, nationally and internationally
- d. OBGYN/beginning of life Medical Ethics

2. Current Grants and Contracts: None currently:

- a. Prior: PACTG (Perinatal AIDS Clinical Trial Group) funding
- b. UNC/AHEC Reproductive Health Research Network grant

3. Grants planned or in submission 2010: None currently:

- a. Finish writing most recent paper on HIV in Pregnancy in preparation for publication
- b. Run Latino Generational Birth Outcome Data for Oregon as I have done in North Carolina.

4. Key Collaborators:

- a. Departmental:
 - i. Dr. Michelle Berlin – mentor
 - ii. Dr. Rahel Nardos – international women's health
 - iii. Dr. Suzanne Burlone – health policy, international ObGyn care
- b. OHSU: Maggie Alexander, CNM – International Maternal Mortality
 - i. Dr. Mary O'Hearn and Dr. Judy Guzman – HIV
 - ii. Dr. Susan Tolle – Ethics Dept. Chair
- c. Extramural:
 - i. Stella Dantas, MD; Kaiser OBGYN/ACOG OR Section Legislature Rep.
 - ii. Laura Byerley, MD – Latina healthcare at Virginia Garcia Healthcenter
 - iii. NW AIDS Education and Training Center – HIV providers in area
 - iv. Shelley Galvin, MA – research coordinator UNC-Asheville
 - v. Sina Haeri, MD – MFM fellow at UNC-CH, HIV in pregnancy

5. Most recent publications (last 5)

Guichard I, Leslie J, Shauer M. "Pregnancy & HIV Disclosure: Ethical Considerations for Clinicians When Patients Do Not Disclose." *The Journal of Hospital Ethics*. Winter 2008: Vol. 1, Number 2, p.12-6.

Leslie J, Diehl S, Galvin S. "A Comparison of Birth Outcomes Among US-Born and non-US-Born Hispanic Women in North Carolina." *Maternal*

and Child Health Journal. Jan 2006: Vol. 10, Number 1, p.33-8.

Leslie J, Galvin S, Diehl S. "A Comparison of Birth Outcomes among US-born and non-US-born Hispanic Women in North Carolina." UNC Chapel Hill Women's Health Research Day Presentation, March 2004.

Leslie J, Galvin S, Diehl S, Bennett T, Buescher P. "Infant mortality, low birth weight and prematurity among Latina, Caucasian, and African American women in North Carolina," *American Journal of Obstetrics and Gynecology*. May 2003: Vol. 188, Number 5, p. 1238-40.

Katner HP, Buchanan AD, Boddy MG, James SW, Kumar RA, Fuller RR, Leslie J, Smith MU. Prevention of vertical transmission of HIV-1 with nelfinavir based highly active antiretroviral therapy [poster MoPeD3684]. XIV International AIDS Conference, Barcelona, Spain, July 7-12, 2002.

Leslie J. "Teaching Critical Appraisal of Ob/Gyn Literature to First Year Residents," APGO/CREOG 2002 & 2004, Annual national meeting, oral presentations.

Nichols, Mark

Area(s) of Research/Scholarly Interest

Reducing pain in surgical abortion, teaching abortion technique

Current Grants and Contracts

Only as sub-PI through the WHRU

Grants planned or in submission 2010

Only as a sub-investigator on grants with fellows or faculty colleagues

Key collaborators

Departmental

Jeff Jensen, Alison Edelman, Paula Bednarek

OHSU

Extramural

Mitch Creinin, Paul Blumenthal

Most recent publications (last 5)

1. Singh RH, Ghanem KG, Burke AE, Nichols MD, Rogers K, Blumenthal PD. Predictors and perception of pain in women undergoing first trimester surgical abortion. *Contraception* 78(2):155-161;2008
2. Michelle M. Isley, Alison Edelman, Bliss Kaneshiro, Dawn Peters, Mark D. Nichols, and Jeffrey T. Jensen. Sex education and contraceptive use at coital debut in the U.S.: Results from cycle 6 of the National Survey of Family Growth. Accepted in *JAMA*
3. Stanek AM, Bednarek PH, Nichols MD, Jensen JT, Edelman AB. Barriers associated with the failure to return for intrauterine device insertion following first-trimester abortion. *Contraception*. 79:216-20, 2009
4. Kraemer DF, Yend, P, Nichols, M. An economic comparison of female sterilization of hysteroscopic tubal occlusion with laparoscopic bilateral tubal ligation. *Contraception* 80: 254–260, 2009
5. Kaneshiro B, Jensen JT, Carlson N, Nichols M, Edelman A. Treatment of Unscheduled Bleeding in Continuous Oral Contraceptive Users With Doxycycline: A Randomized Controlled Trial. Accepted by *Obstet Gynecol*

O'Reilly, Meg

Area(s) of Research/Scholarly Interest

Current Grants and Contracts

Grants planned or in submission 2010

Key collaborators

Departmental

OHSU

Extramural

Most recent publications (last 5)

Renner, Maria-Regina

Current research:

Family Planning Research Project: ongoing RCT on **An evaluation of the paracervical block for pain control in first trimester surgical abortion.**

Planned research:

Co-Investigator of a research proposal submitted to the Society of Family Planning: An evaluation of hydrocodone/acetaminophen for pain control in first trimester surgical abortion.

PUBLICATIONS

Renner RM, Edelman AB, Kaunitz AM. Depot medroxyprogesterone acetate contraceptive injections and skeletal health. Editorial to the May issue of Women's Health. *In press.*

Renner RM, Jensen JT. Progestogen-only pills. Book chapter in Gynecology in Practice. *In press.*

Renner RM, Edelman AB. Complications of medical abortion. Clinical Core Content for IPAS. *In press.*

Renner RM, Jensen JT, Nichols MD, Edelman AB. Pain control in first trimester surgical abortion: a systematic review of randomized controlled trials. *Contraception.* 2010; 81:372–388.

Renner RM, Edelman AB, Jensen JT, Nichols MD. Pain control in first trimester surgical abortion. A Cochrane Review. The Cochrane Library 2009, Issue 2.

Gueth U, Renner R, Egelhof T, Singerd G, Holzgreve W, Mayr J. Retroperitoneal displacement of ovary and fallopian tube: a complication of surgical management of incarcerated inguinal hernia in female infants. *J Pediatr Surg.* 2007 May;42(5):E33-5.

Renner R, Eden KB, Osterweil P, Chan BK, Guise JM. Informational factors influencing patient's childbirth preferences after prior cesarean. *AJOG* 2007 May;196(5):e14-6.

[Renner RM, Renner A, Schmid S, Hoesli I, Nars P, Holzgreve W, Surbek DV.](#)

Efficacy of a strategy to prevent neonatal early-onset group B streptococcal (GBS) sepsis. *J Perinat Med.* 2006;34(1):32-8.

Renner R. Doctoral thesis: "Role of tumorbiological, clinical and pathohistological factors concerning the prognosis of carcinomas of the ovaries in FIGO stage Ia to Ic." Department of Gynecology and Obstetrics, University Hospital Hannover, Germany, February 1998 - August 2002. Grade: summa cum laude

ORAL AND POSTER PRESENTATIONS AT SCIENTIFIC MEETINGS (most recent)

Renner RM, Edelman AB, Nichols MD, Jensen JT. Impact of gestational age on pain perception during first trimester surgical abortion. *Accepted for poster presentation at the Association of Reproductive Health Professionals (ARHP) conference 2010.*

Romm, Jillian

Area(s) of Research/Scholarly Interest

Perinatal Loss educational strategies (ongoing research: Medical Student Conference: Bereaved Parents as Educators about Perinatal Loss)

Professionalism/Doctor-Patient communication

Perinatal Mental Health Disorders: curriculum/educational strategies

Current Grants and Contracts

Grants planned or in submission 2010

Key collaborators

Departmental Karen Adams MD

OHSU John Muench MD, MPH

Extramural

Most recent publications (last 5)

Adams KE, Emmons S, Romm J. How resident unprofessional behavior is identified and managed: a program director survey. *American Journal Obstetrics and Gynecology* 2008 Jun; 198(6):692—e1-4; discussion 692.e4-5

Adams KE, O'Reilly M, Romm J, James, K. Effect of Balint training on resident professionalism. *American Journal Obstetrics and Gynecology* 2006 Nov; 195(5):1431-7 Epub 2006 Sept 25.

Romm J. Teaching empathy, learning about equanimity. *Archives Women's Mental Health* 2007;(3):91-2. Epub 2007 Apr 26. (Invited Editorial)

Burgoine GA, Van Kirk SD, Romm J, Edelman AB, Jacobson SL, Jensen JT. Comparison of perinatal grief after dilation and evacuation or labor induction in second trimester terminations for fetal anomalies. *American Journal of Obstetrics and Gynecology* 2005 Jun;192(6):1928—32.

Romm J. Sexuality during the perimenopause. *Current Women's Health Reports* 2003 Dec;3(6):470-4.

Urogynecology Division

Denman, Mary Anna

Area(s) of Research/Scholarly Interest

Surgical outcomes – two projects currently, one IRB approved, one in submission

Pelvic pain

Connective tissue/extracellular remodeling and pelvic floor dysfunction

Current Grants and Contracts

Right now none

Grants planned or in submission 2010

Considering a robotic grant application, sort of stalled right now

Key collaborators

Departmental

- Currently mostly Tom Gregory

OHSU

Participating in the central sensitivity “group” trying to come up with a meeting time/agenda after a series of collaborative lectures with neuro and anesthesia

Extramural

- One current project is being one center for a study run by Loyolla (Kim Kenton)

Most recent publications (last 5)

Guise J-M, Eden K, Emeis C, Denman M, Marshall N, Fu R, et al. Vaginal Birth After Cesarean: New Insights. Evidence Report/Technology Assessment No. 191. (Prepared by the Oregon Health & Science University Evidence-based Practice Center under Contract No. 290-2007-10057-I.) AHRQ Publication No. 10-E001. Rockville, MD: Agency for Healthcare Research and Quality; March 2010

Vaginal Birth After Cesarean

New Insights on Maternal and Neonatal Outcomes

Jeanne-Marie Guise, MD, MPH, Mary Anna Denman, MD, Cathy Emeis, PhD, CNM,

Nicole Marshall, MD, Miranda Walker, MA, Rongwei Fu, PhD, Rosalind Janik, BA,

Peggy Nygren, MA, Karen B. Eden, PhD, and Marian McDonagh, PharmD OBGYN 115(6);2010.

[Boyles SH](#), [Edwards SR](#), [Gregory WT](#), [Denman MA](#), [Clark AL](#). Validating a clinical measure of levator hiatus size. [Am J Obstet Gynecol](#). 2007 Feb;196(2):174.

[Denman MA](#), [Gregory WT](#), [Boyles SH](#), [Smith V](#), [Edwards SR](#), [Clark AL](#). Reoperation 10 years after surgically managed pelvic organ prolapse and urinary incontinence. [Am J Obstet Gynecol](#). 2008 May;198(5):555.e1-5.

[Saint Clair N](#), [Boyles SH](#), [Clark A](#), [Edwards SR](#), [Denman MA](#), [Gregory WT](#). The presacral space and its impact on sacral neuromodulator implantation. [J Urol](#). 2008 Sep;180(3):988-91.

Edwards, Renee

Area(s) of Research/Scholarly Interest: clinical urogynecology; completion of MBA

Current Grants and Contracts: none

Grants planned or in submission 2010: urogyn division will be submitting grant for NIH Pelvic Floor Network under the leadership of Tom Gregory

Key collaborators

Departmental urogyn division members

OHSU

Extramural

Most recent publications (last 5)

- 1) Rosenblatt P, Pulliam S, Boyles SH, **Edwards, SR**. Suprapubically Assisted Operative Cystoscopy in the Management of Intravesical TVT Synthetic Mesh Segments. *Int Urogynecol J Pelvic Floor Dysfunct.* 2005 Nov-Dec; 16(6):509-11
- 2) Boyles SH, **Edwards SR**, Gregory WT, Clark AL. Complications associated with trans-obturator sling procedures. *Int Urogyn J Pelvic Floor Dysfunct.* 2006 March 28
- 3) Hamilton Boyles S, **Edwards SR**, Gregory WT, Denman MA, Clark AL. Validating a clinical measure of levator hiatus size. *Am J Obstet Gynecol* 2007;196:174.e1-174.e4.
- 4) Saint Clair N, Boyles SH, Clark AL, **Edwards SR**, Denman MA, Gregory WT. The Presacral Space and its Impact on Interstim Implantation, *Journal of Urology*, 2007.
- 5) Denman MA, Gregory WT, Boyles SH, Smith V, **Edwards SR**, Clark AL. Reoperation 10 years after surgically managed pelvic organ prolapsed and urinary incontinence. *Am J Obstet Gynecol* 2008;198:555.e1-555.e5.

Gregory, W. Thomas

Area(s) of Research/Scholarly Interest

Fecal Incontinence
Neurophysiology of Pelvic Floor
Postpartum Pelvic Floor Injuries
Epidemiology of Pelvic Organ Prolapse and Fecal Incontinence
Sacral Neuromodulation
Imaging of Pelvic Floor

Current Grants and Contracts

NIH RO1 HD049541

PI W. Thomas Gregory, MD 40% 06/07-05/12
Total Direct Funding \$1,267,881

Pelvic Floor Nerve Injury at Childbirth Our central hypothesis for this proposal is that measurements of both the bony pelvis and soft tissue pelvic outlet can predict the likelihood of pelvic floor neuromuscular injury and vaginal delivery. We also hypothesize that pelvic floor neuromuscular injury occurs following vaginal delivery, but is less profound after cesarean delivery.

Wessinger Foundation Grant

05/08-05/12

PI W. Thomas Gregory, MD
Total Direct Funding \$30,000

This grant was awarded as an adjunct to **NIH RO1 HD049541** for updating required equipment for that project.

Tartar Trust Foundation

PI Virginia King, MD
Total Direct Funding \$2000
Role: Co-Investigator/Mentor

Lower Urinary Tract Symptoms in Patients with Fibromyalgia. Women with fibromyalgia will use validated questionnaires to characterize pelvic floor symptoms and irritative/painful bladder symptoms. We will correlate Fibromyalgia Impact Questionnaire scores with pelvic floor symptoms. We will also obtain information on urinary frequency in this population through the use of a questionnaire-based voiding diary.

ONE Foundation

PI: Caroline Peterson, PhD
Total Direct Funding \$14,500
Role: CoInvestigator/Mentor

Pilot RCT for CAM Treatment of Pregnancy-Related LBP. This study will see if exercise, spinal manipulation, or neuroemotional technique changes the amount of pain, disability, heart rate variability, bonding with the baby, or complications during birth. The results from this study will be used to design a larger study of pregnant women with low back pain.

Pfizer OAB/LUTS Grant

2/10-6/12

PI Rahel Nardos, MD
Total Direct Funding \$75,000
Role: Co Investigator/Mentor

Examining the Brain's Control Systems in Normal and Overactive Bladder Using DTI and Functional Connectivity MRI

Grants planned or in submission 2010
Pelvic Floor Disorders Network Grant
K24 MidCareer Mentor

Key collaborators

Departmental Urogyn Division Members (including Amanda Clark and Blake Osmundsen)
OHSU Jau-Shin Lou, MD, PhD; Urick Szumowski, PhD; Dawn Peters, PhD
Extramural Simon Podnar, MD (Slovenia); Amy Thurmond, MD (Radiology);

Most recent publications (last 5)

1. Segel S, Guise JM, **Gregory WT**, Edelman A, Hashima J. A New Approach to Postpartum Rounds: Patient Centered Collaborative Care Improves Efficiency. *Journal of Graduate Medical Education*, 2010;2(1);67-72.
2. Podnar S, **Gregory WT**. Can Sphincter Electromyography Reference Values Be Shared Between Laboratories? 2010 *Neurourology and Urodynamics*. In Press
3. **Gregory WT**, Worstell TR, Clark AL, Lou JS. Concentric Needle Quantitative EMG of Pubovisceralis Muscle Group: Normative Data from Asymptomatic Nulliparous Women. *Journal of Pelvic Medicine and Reconstructive Surgery*, 2010; 16(2):91-95.
4. Nardos R, Thurmond A, Worstell T, **Gregory WT**, Comparing Reference Lines in Dynamic Pelvic Floor MRI. *Journal of Pelvic Medicine and Reconstructive Surgery*, 2010. In Press
5. **Gregory WT**, Nardos R, Worstell TR, Thurmond AS, The Impact of Axial Tilt Angle on 2D MRI Assessment of Pelvic Floor Muscles. *Neurourology and Urodynamics*, 2010. In Press

King, Virginia

Area(s) of Research/Scholarly Interest

Current Grants and Contracts

Grants planned or in submission 2010

Key collaborators

Departmental

OHSU

Extramural

Most recent publications (last 5)

Nardos, Rahel

2010: Pfizer OAB-LUTS Competitive Grant Recipient

Project title: Examining the Brain's Control Systems in Normal and Overactive Bladder Using DTI and Functional Connectivity MRI

I also have been doing some research in Tom Gregory's NIPP study particularly looking at Pelvic MRI and characterization of pelvic floor anatomy: Below is the most recent publication.

2009 : American Urogynecologic Society Annual Conference, 2009

1. Bony References for Measuring Pelvic Organ Prolapse by MRI
2. The Impact of Axial Tilt Angle on 2D MRI Assessment of Pelvic Floor Muscles

Both of these abstracts have been written up and accepted for publication

I am also doing a collaborative research with Bahirdar Fistula hospital (Ethiopia)

-Randomized controlled study looking at duration of foley catheterization in post obstetric fistula repair patients.

Gynecologic Oncology Division
Berry, Emily

Area(s) of Research/Scholarly Interest

Current Grants and Contracts

Grants planned or in submission 2010

Key collaborators

Departmental

OHSU

Extramural

Most recent publications (last 5)

Munro, Elizabeth

Area(s) of Research/Scholarly Interest

My current areas of interests are primarily in clinical research, though I am interested in some translational projects as well. Our division currently has a number of clinical trials open which everyone in the division works to enroll patients in. These include the following:

GOG 136—tissue acquisition

GOG 213—ovarian, 1st recurrence, platinum-sensitive

GOG 249—early stage endometrial

Abraxane/Avastin Trial—recurrent ovarian, 3rd line or more

In order to sustain these clinical trials we have been working on increasing our patient population. My goal is to ultimately be able to expand our offerings to include studies for less common conditions such as recurrent, metastatic endometrial cancer and cervical cancer, and offer investigational biologic therapies.

Given the recent introduction of Cervarix and the expanded indications of Gardasil, evolving changes in vaccination practices and HPV strain prevalence are inevitable. I am interested in researching the application of the HPV vaccine, the impact of the vaccine on the prevalence of various viral strains, and cost analysis of vaccination programs.

The impact of the 2009 changes to the FIGO staging system are still not entirely clear, and I have a project initiated with Weiya Zhang R2 to evaluate the impact of restaging patients with the new FIGO staging system for endometrial cancer.

I am planning a coordinated translational study with Dr. MacDonald (Rad Onc in Salem) on fatigue in gyn cancer patients. Preliminary studies in other types of cancer have yielded interesting results with regards to cytokines and impact on fatigue. Ultimately, we hope that we can develop interventions to help patients cope with this widely prevalent side effect.

The role of imaging in diagnosing and following gyn onc patients is also an area where more research is needed, and I am planning a coordinated study of a novel imaging method to detect the degree of hypoxia in tumor cells to predict prognosis in cervical cancer with Dr. Rajendron at UW.

Current Grants and Contracts

None individual – though I participate in GOG & Pharma clinic trials we have as a Division

Grants planned or in submission 2010

none

Key collaborators

Departmental Tanja Pejovic, Emily Berry

OHSU Rad Onc Dept (Sam Wang, Tasha MacDonald)

Extramural MGH Gyn Onc Division, Alex Olawaiye (Pittsburgh), J. Rajendron (UW)

Most recent publications (last 5)

- Friel, A.M., Growdon, W.B., McCann, C.K., Olawaiye, A.B., **Munro, E.G.**, Schorge, J.O., Castrillon, D.H., Broaddus, R.R., and Rueda, B.R. "Mouse models of uterine corpus tumors: clinical significance and utility." (2010) *Front Biosci*; 2: 882-905.
- Rauh-Hain, J.A., Olawaiye, A.B., **Munro, E.G.**, Ko, E., Alarcon, I.A., Del Carmen, M.G., and Duska, L. "Role of computed tomography in the surgical management of patients with bowel obstruction secondary to recurrent ovarian carcinoma." (2010) *Ann Surg Onc*; 17: 853-860.
- Watts, L., Joseph, N., Velazquez, A., Gonzalez, M., **Munro, E.**, Muzikansky, A., Rauh-Hain, J.A., and del Carmen, M.G. "Understanding barriers to cervical cancer screening among Latina women." (2009) *Am J Ob Gyn*. Aug;201(2):199.e1-8.
- Munro, E.G.**, Jain, M., Oliva, E., Kamal, N., Lele, S.M., Lynch, M.P., Guo, L., Fu, K., Sharma, P., Remmenga, S., Growdon, W.B., Davis, J.S., Rueda, B.R., and Batra, S.K. "Upregulation of MUC4 in cervical squamous cell carcinoma: Pathological significance." (2009) *Int J of Gyn Path*, Jan 30.
- Sakamoto, H., Friel, A.M., Wood, A.W., Guo, L., Illic, A., Seiden, M.V., Chung, D.C., Lynch, M.P., Serikawa, T., **Munro, E.**, Oliva, E., Orsulic, S., Kirley, S.D., Foster, R., Zukerberg, L.R., and Rueda, B.R. (2008) "Mechanisms of cables 1 gene inactivation in human ovarian cancer development." *Cancer Biol Ther*. 15; 7(2).

Pande, Nupur

Summary of my research Interests: *There are two fundamental issues that have confounded the ovarian carcinoma community: a) what does the primordial neoplastic lesion consist of; and b) how can the efficacy of current therapies be enhanced towards better outcome for patients? To address these concerns my lab currently focuses on two projects:*

A. Ovarian Tissue stem cells and their micro-environment: Multicellular organisms have evolved a great variety of cell types that perform specialized functions. Stem cell progeny that are destined to differentiate, proliferate transiently, and choose associated tissue cell types. This differentiation process, of great spatial and temporal precision, is at the heart of development and organ homeostasis. The control of this differentiation process is thus a question of tremendous importance from scientific and therapeutic standpoints.

Importantly, the stem cell environment, called the niche, maintains special properties of stem cells and regulates their behavior. To fully utilize the potential of stem cells and their involvement in ovarian cancer development, where drug resistant metastatic recurrence is a major therapeutic barrier, the understanding of mechanisms that control stem cell differentiation and function is essential. I am interested in understanding the features of the molecular nature of ovarian cancer stem cell niche, which will further our understanding of the occurrence of tumors whose characteristics reflect the normal developmental potential of the cognate stem cells.

Our lab would utilize the tissue repository available through the Oregon Ovarian Cancer Registry to: 1) identify the signals that trigger stem cell activation in the context of ovarian tissue; and 2) to define the niche-derived signals required for maintenance of “stemness” versus cell differentiation in the ovary. Employing genetics, molecular biology and microscopy both in vitro and in vivo will allow us to uncover basic principles of how ovarian tissues sustain regeneration.

B. Dietary histone deacetylase inhibitors in ovarian cancer prevention: The epigenetic silencing of tumor suppressor genes mediated by reversible acetylation of histones by histone deacetylases (HDACs) plays an important role in various cancers. Thus, HDAC inhibitors have emerged as accessory therapeutic agents for multiple human neoplasms since they can block the activity of specific HDACs, restore the expression of some tumor suppressor genes and induce cell differentiation, growth arrest or apoptosis. In animal models, sulforaphane (SFN), a naturally occurring compound in cruciferous vegetables, has been an effective chemoprotective and an effective HDAC inhibitor. HDAC inhibitors can induce cell-cycle arrest, promote differentiation, and stimulate tumor cell death. There are two well characterized mammalian pathways that herald programmed cell death (PCD): 1) apoptosis; and 2) autophagy.

My interests lie in the elucidation of autophagic cell death, a highly regulated PCD pathway, regulated by kinase mammalian target of rapamycin (mTOR; also known as FRAP1), mediated by complex intracellular membrane/vesicle reorganization and lysosomal activity. It can either be involved in the turnover of long-lived proteins and whole organelles in a generalized manner or can specifically target distinct organelles (mitochondria, endoplasmic reticulum) imposed by limiting metabolites. Although autophagy mostly allows cells to adapt to stress, massive autophagy can also kill cells. Therefore, it is critically important to carefully evaluate the effect of SFN treatment on autophagy and apoptosis in the ovarian cancer model and to determine the contribution of each of these mechanisms by which cruciferous vegetables might be utilized to decrease ovarian cancer risk as well as used as supplementary ligands that enhance the efficacy of current day therapies.

Pejovic, Tanja

The lethality of gynecological cancer is due in part because we lack effective screening tools and non-invasive methods. The development of such tools and methods will be aided substantially by a better understanding of the molecular processes that account for ovarian cancer risk. In order to address these problems, our laboratory has three primary ongoing projects:

1. Molecular Screening for Ovarian Cancer Risk by understanding the defects in FA/BRCA pathway.

We have sought to identify molecular risk factors for ovarian cancer by studying the Fanconi anemia (FA)/BRCA pathway in primary human ovarian epithelial cells obtained from women at high risk of ovarian cancer (who tested negative for BRCA 1 and 2 mutations). Several lines of evidence support the role of the FA pathway. Our analyses of primary OSE revealed reduced levels of FANCD2 protein in ovarian cancer as well as in ovarian epithelial cells removed from women at risk of ovarian cancer who are BRCA negative but not in normal OSE. These changes are accompanied by reduced levels of mRNA and protein. We have also shown that this change is not present in the corresponding peripheral blood lymphocytes. We have ruled out DNA gene and promoter mutation by complete sequencing of FANCD2 gene. We have ruled out epigenetic CpG hypermethylation of FANCD2 promoter. In ongoing experiments in the lab where we are trying to elucidate the role of acetylation and post transcriptional modulation of DNA repair genes by miRNA in the high risk patient population.

2. The development of a nonhuman primate model of ovarian cancer: the role of ovulation and selective pressure exerted by ovarian hormones.

Limitations in studying the origins and early progression of the disease have hindered the development of strategies for prevention and early detection, and these areas of research may provide the greatest hope of effectively reducing the toll inflicted by EOC. The major difficulties in understanding this disease arise in large part because (1) naturally occurring EOC is not found in most species, aside from primates and hens, and; (2) the major risk factors for EOC (age, menopause, ovarian function and genetics) do not manifest in most species in ways that may be relevant to disease etiology. Thus, studies using conventional animal models may not provide appropriate insight into the human disease; meanwhile, studies in women are ethically and pragmatically prohibitive. Therefore we propose the use of nonhuman primate as a model system to: (1) investigate in vivo changes in gene expression that may be specific for and/or confer a disposition to EOC; (2) evaluate the basis for age and menopause to promote susceptibility to EOC, and; (3) determine whether modulation of a defined DNA-repair pathway in vivo may provide a viable strategy for EOC prevention.

3. Establishment and development of ovarian cancer registry: Oregon Ovarian Cancer Registry and Tissue Repository.

The repository now contains ovarian and blood samples from 224 patients who underwent surgery for benign gynecologic disease, prophylactic surgery to reduce the risk of ovarian cancer or debulking/staging surgery to remove ovarian cancer. The bank has 40 normal ovarian samples, 42 high-risk samples (patients who underwent prophylactic ovarian removal), and 109 ovarian cancer samples (the remaining 33 cases encompass borderline ovarian tumors, 2 teratomas, a stromal, a Sertoli-cell carcinoma, and 2 neuroendocrine tumors of the ovary).

The material obtained /established in each case is represented by

- (i) fresh frozen ovarian tissue from primary tumor and omental and/or metastases
- (ii) ovarian cell culture established and maintained in liquid nitrogen)
- (iii) DNA and RNA extracted from the frozen tissue and/or cell lines

(iv) DNA and RNA obtained from the peripheral blood lymphocytes

The complete clinical and pathologic data is linked to each of 224 cases and the database of clinical and research information is maintained via Progeny software.

Recent papers:

1. Wright J, **Pejovic T**, Fanton J, Stouffer LR (2007) Induction of proliferation in the primate ovarian surface epithelium in vivo. Human Reproduction, Hum Reprod 23(1):129-138.
2. **Pejovic T**, et al (2009) Expression Profiling of the Ovarian Surface Kinome Reveals Candidate Genes for Early Neoplastic Changes. Translational Oncology 2:341-349.
3. Wright J, **Pejovic T**, Lawson M, Jurevic L, Hobbs T, Stouffer RL. 2009 Ovulation in the absence of the ovarian surface epithelium in primates. Biol Reprod 82(3):599-605.
4. Cheng L, Lu W, Kulkarni B, **Pejovic T**, Yan X, Chiang JH, Hood L, Lin B. Analysis of chemotherapy response programs in ovarian cancer by the next-generation sequencing technologies. Gynecologic Oncology, 2010;117(2):159-69.

Maternal-Fetal Medicine Division

Arraut, Amaryllis

Grants planned or in submission 2010 – N/A

Key collaborators

Departmental - Juha Rasanen, Antonio Frias

OHSU

Extramural

Most recent publications (last 5)

Conservative Management of Placenta Accreta 2008

Case report, Obstetrics & Gynecology

An unusual case of endometriosis; presenting as a mons pubis mass 2008

Case report, submitted for review

Bissonnette, John

Area of Research Interest

Our lab is interested in the neural control of respiration. Studies are conducted in transgenic mice. Current work is centered on animals deficient in the transcription factor methyl-CpG-protein 2 (Mecp2). The gene that encodes this DNA binding protein is mutated in the X-linked disorder Rett syndrome, whose phenotype includes disturbances in respiration. Current studies are examining the relationship between GABA inhibition of expiratory neurons and apnea and periodic breathing in Mecp2^{+/-}. Our working hypothesis states that insufficient inhibition causes excess activity in expiratory neurons that in turn shut down inspiration. A portion of these experiments are done in collaboration with Julian Paton (University of Bristol) and Mathias Dutschmann (University of Leeds). We are using double transgenic mice that express green fluorescent protein in GABAergic neurons and their processes to determine if perisomatic innervation of expiratory neurons is defective in mice that lack Mecp2.

In collaboration with Agnieszka Balkowiec (Dental School), a separate project looks at the expression of brain-derived neurotrophic factor (BDNF) transcripts using a respiratory plasticity protocol. It has been suggested that BDNF is a target for Mecp2.

Existing dogma states that Mecp2 is expressed in neurons alone and neuronal depletion accounts for the disease phenotype in Rett syndrome. In collaboration with Gail Mandel (Vollum Institute) we are studying respiratory patterns in mice that have had Mecp2 activated in astrocytes alone after they have become symptomatic. The protocol uses transgenic mice with a stop codon in Mecp2 that can be removed at any postnatal age with tamoxifen treatment. Astrocyte specificity is accomplished by having Cre recombinase under control of glial fibrillary acidic protein promoter.

Current Grants

Insufficient GABA inhibition underlies respiratory disorders in Mecp2 deficient mice. International Rett Syndrome Foundation. 10/01/2008 to 09/30/2010.

Grants in Submission 2010

Two grants have been submitted to International Rett Syndrome Foundation; one in their Neurobiology of Rett syndrome category and one in their Help Accelerate Rett Therapeutics category. Decisions will be made in August and September for start dates of 10/01/2010. A RO1 application submitted in October 2009 was not awarded.

Collaborators

Departmental: James Maylie

OHSU: Agnieszka Balkowiec (Dental School)

Gail Mandel (Vollum Institute)

Stephanie Kaeck Petrie (Jungers Centre, Core Imaging Centre)

Extramural: Julian FR Paton (University of Bristol)

Mathias Dutschmann (University of Leeds)

Gerd Bartoszyk (Merck Serono, Darmstadt Germany)

Jerod Denton (Vanderbilt)

Selected Publications:

1. Bissonnette JM, SJ Knopp. Separate respiratory phenotypes in methyl-CpG-binding protein 2 (Mecp2) deficient mice. *Pediatric Research* 59: 513-518, 2006
2. Bissonnette JM, SJ Knopp, J Maylie, T Thong. Autonomic cardiovascular control in methyl-CpG-binding protein 2 (Mecp2) deficient mice. *Autonomic Neuroscience: Basic and Clinical*, 136:82-89, 2007
3. Bissonnette JM, SJ Knopp. Effect of inspired oxygen on periodic breathing in methyl-CpG-binding protein 2 (Mecp2) deficient mice. *J Applied Physiol* 104:198-204, 2008
4. Bissonnette JM, AR Hohimer, SJ Knopp: Effect of hypoxia on expiratory activity in fetal sheep. *Respiration Physiology and Neurobiology* 171:110-114, 2010.

Brace, Robert

Overview: Our overall, long-term goal is to understand the physiological mechanisms that regulate amniotic fluid volume under normal conditions and the pathologic aberrations in these mechanisms that result in oligohydramnios and polyhydramnios.

Support: R01HD035890 (PI: RA Brace) 7/1/1999 - 6/30/2010. Continuation and other applications pending.

Studies:

Robertson P *{MFM Fellow}*, Faber JJ, Brace RA, Louey S, Hohimer AR, Davis LE, Anderson DF. Responses of amniotic fluid volume and its four major flows to lung liquid diversion and amniotic infusion in the ovine fetus. *Reprod Sci.* 2009; 16: 88-93. PMID: 19144891

Jellyman JK, Cheung CY, Brace RA. Amniotic fluid volume responses to esophageal ligation in fetal sheep: contribution of lung liquid. *Am J Obstet Gynecol.* 2009; 200:313.e1-6. PMID: 19114273

Faber JJ, Brace RA, Davis LE, Anderson DF. Ovine amniotic fluid volume response to intra-amniotic balloon filling. *Placenta.* 2009; 30: 201-202. PMID: 19095300

Gesteland KM *{MFM Fellow}*, Anderson DF, Davis LE, Robertson P *{MFM Fellow}*, Faber JJ, Brace RA. Intramembranous solute and water fluxes during high intramembranous absorption rates in fetal sheep with and without lung liquid diversion. *Am J Obstet Gynecol.* 2009; 201: 85.e1-6. PMID: 19398093

Cheung CY, Chen DB, Brace RA. Regulation of Caveolin-1 Expression and Phosphorylation by VEGF in Ovine Amnion Cells. *Reproductive Sci*, Accepted.

Anderson DF, Davis LE, Faber JJ, Brace RA. Regulation of intramembranous absorption and amniotic fluid volume by fetal urine. In progress.

Major Findings: The primary finding is that amniotic fluid volume is actively regulated by modulating the rate of intramembranous absorption of amniotic fluid across the amnion and into the underlying fetal blood vessels. Intramembranous transport is primarily an active, unidirectional transfer mechanism that is regulated by biochemicals that are present in fetal urine and the amniotic fluid.

Cheung, Cecilia

Areas of Research Activities

My research program is aimed at investigating the physiological mechanisms that regulate the transport of amniotic fluid across amnion cells. This information is needed in order to generate a comprehensive understanding of the cellular pathways and the role of endogenous factors that regulate amnion fluid volume. The knowledge gained will allow the identification of targets for clinical intervention in resolving conditions of abnormal amniotic fluid volume, and will form the scientific basis for formulating improved strategies for alleviating amniotic fluid volume complications. An understanding of the regulatory mechanisms will enhance the development of better therapeutic treatment for oligohydramnios and polyhydramnios. Such progress will ultimately enhance obstetrical management of high risk pregnancies while improving maternal and perinatal outcome. Specifically, the studies focus on the stimulatory and inhibitory regulators that participate in maintaining amniotic fluid volume within the normal range. Our previous studies have indicated that amniotic fluid volume is regulated by modulating the rate of amniotic fluid transferred across the amnion into fetal blood vessels that vascularize the fetal surface of the placenta, and that the amnion functions as the rate limiting layer for amniotic fluid transport. In addition the transport mechanism appears to involve vesicular transcytosis involving caveolae, and that vascular endothelial growth factor (VEGF) is a potentially important regulator of this transcellular transport. The current and planned studies will further the investigation to elucidate the role of VEGF and its inhibitory isoforms in regulating caveolar transport across amnion cells, and to determine the cell signaling events activated by VEGF and its isoforms to mediate transcellular amniotic fluid transport by vesicular transcytosis. These studies utilize ovine and human amnion cells as experimental models.

Research Support

Funded by the NIH/NICHD for the past 28 years.

Active

1R01HD061541-01A1 (PI: Cheung)

07/01/10 –06/30/15

NIH/NICHD

Project Title: *Cellular Mechanisms of Amniotic Fluid Volume Regulation*

The major goals of the project are to document the transcellular transport mechanisms across amnion cells, to explore the role of VEGF and its isoforms in regulating this transport, to decipher the cell signal transduction pathways mediating this transport, and to correlate the cellular findings with the fetus *in vivo*. These studies utilize ovine amnion cells and the ovine fetus as the experimental model.

Pending

1. 1R03HD065961-01A1 (PI: Cheung)

04/01/11 – 03/30/13

NIH/NICHD

Project Title: *Human Amnion Cell Model for Investigation of Amniotic Fluid Volume Abnormalities*

The major goals of the project are to establish a human cell model for the study of amniotic fluid volume abnormalities, and to utilize this model to investigate the defects in the cellular mechanisms that regulate amniotic fluid volume as the cause of oligohydramnios and polyhydramnios. These studies utilize human amnion cells for all proposed experiments.

2. OHSU Medical Research Foundation (PI: Cheung)

09/01/10 - 08/31/11

Project Title: Cellular Mechanisms of Amniotic Fluid Volume Regulation

The goal of the project is to examine the role of VEGF in regulating fluid transcytosis in amnion cells, and to evaluate the significance of utilizing the ratio of stimulatory to inhibitory VEGF isoforms as determinant of the rate of fluid transport. These studies utilize ovine amnion cells as the experimental model.

3. OHSU Presidential Bridge Funding (PI: Cheung) 07/01/10 – 06/30/11

Project Title: Cellular Mechanisms of Amniotic Fluid Volume Regulation

The goal of the project is to analyze the role of VEGF stimulatory and inhibitory isoforms as well as VEGF receptors in modulating the rate of fluid transport across amnion cells, and to determine the role of splice factors in regulating the expression of VEGF isoforms. The studies utilize ovine amnion cells as the experimental model.

Recently Completed Studies

5R01HD035890-10 (Brace)

06/01/98 - 06/30/10

NIH/NICHD

Role in project: co-investigator

Project Title: *Hypoxia Effects on Amniotic Fluid Volume*

The major goal of this project is to test the hypothesis that fetal hypoxia causes polyhydramnios while fetal hypoxia with placental insufficiency causes oligohydramnios. This project utilizes the chronically catheterized ovine fetus as the experimental model.

Key collaborators

Departmental – Davis, MD; Terry Morgan, MD/PhD; Roger Hohimer, PhD.

OHSU – Debra Anderson, PhD (HRC); Kent Thornburg, PhD; (HRC), Samantha Louie, PhD (HRC).

Extramural – Dongbao Chen, PhD (University of California, Irvine).

5 Most Relevant Publications

1. Brace R.A., and **Cheung C.Y.** Pre-Delivery Changes in Amniotic Fluid Volume and Composition in Sheep. *J Soc Gynecol Investig* 12:396-401, 2005. PMID: 15914042
2. **Cheung, C.Y.**, and R. A. Brace. Hypoxia modulation of caveolin-1 and vascular endothelial growth factor in ovine fetal membranes. *Repro Sci* 2008; 15:469-76. PMID: 18579855
3. **Cheung, C.Y.**, and R.A. Brace. Unidirectional transport across cultured ovine amnion epithelial cell monolayer. *Repro Sci* 2008; 15:1054-8. PMID: 19088374
4. Jellyman J.K., **Cheung C.Y.**, Brace R.A. Amniotic fluid volume responses to esophageal ligation in fetal sheep: contribution of lung liquid. *Am J Obstet Gynecol* 2009; 200:313.e1-6. PMID: 19114273
5. **Cheung, C.Y.**, D.B. Chen, and R.A. Brace. Caveolin-1 expression and regulation by vascular endothelial growth factor in ovine amnion cells. *Repro Sci*, 2010 (In press)

Clock, Charcie

Area(s) of Research/Scholarly Interest

Current Grants and Contracts

Grants planned or in submission 2010

Key collaborators

Departmental

OHSU

Extramural

Most recent publications (last 5)

Davis, Lowell

Area(s) of Research/Scholarly Interest

My interests are in factors that regulate fetal coronary blood vessel growth and cardiac function particularly in states of chronic hypoxemia. I also have a long-time interest in understanding amniotic fluid volume regulation

Current Grants and Contracts

Research Support (Ongoing)

2007-2011 2PO1 HD 34430 Maternofetal Signaling and Lifelong Consequences. K Thornburg PI. Project III Fetal Stressors Alter Long-term Myocyte and Coronary Growth. K Thornburg PI, Role: Coinvestigator. This project will investigate the long-term relationship between cardiac myocyte and coronary vascular development.

Completed Research in the last 3 years

1992-2009 RO1HL45043-05A1 Water compartmentalization in fetal anemia. PI. Co-investigators Roger Hohimer, Mark Morton, George Giraud and Kent Thornburg.

2003-2008 K12 HD43488 Building Interdisciplinary Research Careers in Women's Health at OHSU. Program Director

2006-2007 U10 HD053118 Maternal Fetal Medicine Units Network. PI Lowell Davis Co PI. The goal of this project is to enroll patients in clinical trials within the NICHD network

Grants planned or in submission 2010

R01 Limits of cardiac adaptation in fetal anemia

Key collaborators

Departmental Juha Rasanen, Robert Brace, Cecelia Cheung, Roger Hohimer
OHSU Kent Thornburg
Extramural

Most recent publications (last 5)

P Robertson, J Faber, L Davis, D Anderson. Responses of amniotic fluid volume and its four major flows to lung liquid diversion and amniotic infusion in the ovine fetus. *Reprod Sci.* 2009 Jan;16(1):88-93.

Q Yang, a Hohimer, G Giraud, D Van Winkle, M Underwood, G He and L Davis. Effect of fetal anaemia on myocardial ischemia-reperfusion injury and coronary vasoreactivity in adult sheep. *Acta Physiol (Oxf).* 2008 Dec;194(4):325-34. Epub 2008 Sep 20.

K Gestland, D Anderson; L Davis; P Robertson; J. Faber, R Brace. Intramembranous Solute and Water Fluxes during High Intramembranous Absorption Rates in Fetal Sheep with and without Lung Liquid Diversion. *Am J Obstet Gynecol.* 2009 Apr

S Jonker, M Giraud, G Giraud, N Chattergoon, S Louey, L Davis, J Faber, K Thornburg. Myocyte Proliferation Contributes to Anemia induced Fetal Cardiac Enlargement. *Experimental Physiology Exp Physiol.* 2010 Jan;95(1):131-9.

Frias, Antonio

Area(s) of Research/Scholarly Interest

The overall, long-term goal is to understand the mechanisms that regulate placental growth and perfusion in both normal and pathologic conditions. We use non-human primates to elucidate the impact of maternal diet & obesity and nicotine on placental function. Gene-targeted mice, both null and transgenics are used to investigate the effect of targeting a specific gene on rodent reproduction and placental function. In addition, I am developing with several collaborators, novel imaging methods to quantify placental blood flow. These include dynamic contrast enhanced (DCE) MRI, and ultrasound microbubbles.

Current Grants and Contracts

| | | |
|---|------------|---------------|
| Oregon Medical Research Foundation | Frias (PI) | 8/1/09-8/1/11 |
| Renal histamine synthesis and placental blood flow in mice. | | |

Grants planned or in submission 2010

1. NIH R24 Co-Investigator

The impact of maternal health and diet on development of fetal metabolic systems.

Submitted: 3/24/10. Score 2.2

2. NIH R21 Morgan (PI), Co-Investigator

Reversing fetal programming of hypertension in a mouse model of uteroplacental insufficiency.

Planned submission: October 2010

3. NIH R21 Frias (PI)

Validation of DCE-MRI model to quantify placental perfusion.

Planned submission October 2010. May become part of an R01 instead depending on the data.

4. NIH R01 Frias (PI)

The effect of TLR inhibition on high fat diet induced placental inflammation.

Planned submission June 2011.

Key collaborators

Departmental: Juha Rasanen MD, PhD, Leo Pereira MD

OHSU: Terry Morgan MD, PhD, Kent Thornburg PhD, Jonathan Lindner MD

ONPRC: Kevin Grove PhD, Eliot Spindel MD, PhD, Chris Kroenke PhD,

Extramural: Jacob Friedman, PhD & Carrie McCurdy, PhD at the University of Colorado School of Medicine; Kjersti Aagaard-Tillery MD, PhD at Baylor.

Most recent publications (last 5)

1. **Frias AE**, Morgan TK, Evans AE, Rasanen J, Oh KY, Thornburg K and Grove KL. Maternal high fat diet triggers uteroplacental insufficiency in the nonhuman primate. *JCI (in review)*.
2. Hashima JN, **Frias AE**, Bernard L, Spindel E, Hobbs TR and Rasanen J. Fetal ventricular diastolic filling characteristics: role of fetal heart rate and pulmonary vascular impedance. *Reproductive Sciences (in press)*.
3. Oh KY, **Frias AE Jr**, Byrne LB, Kennedy AM. Isolated short femur – What could this mean? *Ultrasound Q* 2008; 24(2):89-92. PMID: 18528244

4. Jones CA, London NR, Chen H, Park KW, Sauvaget D, Stockton RA, Wythe JD, Suh W, Larrieu-Lahargue F, Mukouyama Y, Lindblom P, Seth P, **Frias A**, Nishiya N, Ginsberg MH, Gerhardt H, Zhang K and Li DY. Robo4 stabilizes the vascular network by inhibiting pathologic angiogenesis and endothelial hyperpermeability. *NATURE MEDICINE* 2008; 14(4):448-453 (*Cover Article*). PMID: 18345009
5. Oh KY, Rassner U, **Frias AE Jr**, Kennedy AM. The fetal posterior fossa: Clinical correlation of findings on prenatal ultrasound and fetal magnetic resonance imaging. *Ultrasound Q* 2007; 23(3):203-210. PMID: 17805191

Guise, Jeanne-Marie

Area(s) of Research/Scholarly Interest

Current Grants and Contracts

Grants planned or in submission 2010

Key collaborators

Departmental

OHSU

Extramural

Most recent publications (last 5)

Hohimer, Roger

Areas of Research/Scholarly Interest

Fetal cerebral blood flow
Fetal Breathing movements
Perinatal brain damage
Fetal cardiac function and coronary growth

Current Grants and Contracts

2/03-6/14 R01 5R01NS045737- “Cellular Mechanisms of Fetal White Matter Injury” A.R Hohimer (Co-Invest), S.A.Back (PI). The long-term objectives are to define the pathophysiologic relationships of blood flow, acute white matter damage and mechanisms of oligodendroglial vulnerability in periventricular white matter.

1/06-12/10 5R01NS054044-045 “Role of extracellular matrix in hypoxic-ischemic perinatal white matter injury”, S.A.Back (PI). In a perinatal rat model relevant to human PWMI, we will define mechanisms by which acute degeneration of late OL progenitors (preOLs) after H-I triggers a chronic disruption of normal myelination. We will test the overall hypothesis that the predilection of the preterm white matter to chronic myelination disturbances after H-I is related to the acute degeneration of preOLs that triggers chronic reactive astrocytosis.

Grants planned or in submission 2010

Tissue Doppler Detection of Regional Function in the Fetal Sheep Heart
(R01 planned for fall probably with Rasanen as PI)

Key collaborators

Departmental

Davis
Rasanen
Brace
Cheung

OHSU

Stephen Back , MD/PHD Peds

Most recent publications (last 5)

(1-5)

1. **Bissonnette JM, Hohimer AR, and Knopp SJ.** Effect of hypoxia on expiratory muscle activity in fetal sheep. *Respir Physiol Neurobiol* 171: 110-114, 2010.
2. **Buser JR, Segovia KN, Dean JM, Nelson K, Beardsley D, Gong X, Luo NL, Ren J, Wan Y, Riddle A, McClure MM, Ji X, Derrick M, Hohimer AR, Back SA, and Tan S.** Timing of appearance of late oligodendrocyte progenitors coincides with enhanced susceptibility of preterm rabbit cerebral white matter to hypoxia-ischemia. *J Cereb Blood Flow Metab*, 2010.
3. **McClure MM, Riddle A, Manese M, Luo NL, Rorvik DA, Kelly KA, Barlow CH, Kelly JJ, Vinecore K, Roberts CT, Hohimer AR, and Back SA.** Cerebral blood flow heterogeneity in preterm sheep: lack of physiologic support for vascular boundary zones in fetal cerebral white matter. *J Cereb Blood Flow Metab* 28: 995-1008, 2008.

4. **Robertson P, Faber JJ, Brace RA, Louey S, Hohimer AR, Davis LE, and Anderson DF.** Responses of amniotic fluid volume and its four major flows to lung liquid diversion and amniotic infusion in the ovine fetus. *Reprod Sci* 16: 88-93, 2009.
5. **Yang Q, Hohimer AR, Giraud GD, Van Winkle DM, Underwood MJ, He GW, and Davis LE.** Effect of fetal anaemia on myocardial ischaemia-reperfusion injury and coronary vasoreactivity in adult sheep. *Acta Physiol (Oxf)* 194: 325-334, 2008.

Marshall, Nicole

My research focus is on optimizing maternal health status before, during, and beyond pregnancy to improve maternal and neonatal outcomes. I am specifically interested in preventing excessive weight gain during pregnancy, which is linked to chronic obesity in both mothers and their offspring. Obesity is a critical public health epidemic that urgently needs to be addressed, both locally and on the national level.

C. Selected peer-reviewed publications (in chronological order).

Journal

1. **Marshall NE**, Bowman KV, Michalak JC, Schomberg PJ, Burton GV, Sandler HM, Cascino TL, Jaeckle KA, Buckner JC. Ototoxicity of cisplatin plus standard radiation therapy vs. accelerated radiation therapy in glioblastoma patients. *J Neurooncol* 2006 May; 77(3):315-20.
2. Turok DK, Simonsen SE, **Marshall NE**. Trends in Levonorgestrel Emergency Contraception Use, Births, and Abortions: The Utah Experience. *Medscape J Med* 2009; 11(1):30-8.
3. Guise J-M, Denman MA, Emeis C, **Marshall N**, Walker M, Fu R, Janik R, Nygren P, Eden KB, McDonagh M. Vaginal Birth After Cesarean: New Insights on Maternal and Fetal Outcomes. *Obstet Gynecol* 2010 June; 115(6):1267-78.

Evidence Reports

Guise J-M, Eden K, Emeis C, Denman MA, **Marshall N**, Fu R, Janik R, Nygren P, Walker M, McDonagh M. Vaginal Birth After Cesarean: New Insights. Evidence Report/Technology Assessment No. 191. (Prepared by the Oregon Health & Science University Evidence-based Practice Center under Contract No. 290-2007-10057-I). AHRQ Publication No. 10-E001. Rockville, MD: Agency for Healthcare Research and Quality. March 2010.

Abstracts

1. Jeroen Vanderhoeven, **Nicole Marshall**, Sally Segel, Hong Li, Patricia Osterweil, Jeanne-Marie Guise. "Evaluating in-situ simulation and team training on response to shoulder dystocia." Society for Maternal-Fetal Medicine, San Diego, California, January 2009
2. **Nicole Marshall**, Jeroen Vanderhoeven, Sally Segel, Hong Li, Karen Eden, Jeanne-Marie Guise. "Impact of simulation and team training on the recognition and management of post-partum hemorrhage." American College of Obstetricians and Gynecologists Annual Clinical Meeting, Chicago, Illinois, May 2009
3. **Nicole Marshall**, Perrie O'Tierney, Samantha Louey, Kent Thornburg. "Placental antioxidant expression in sheep following placental insufficiency." International Federation of Placenta Associations Meeting, Adelaide, Australia, October 2009
4. Michael Varner, **Nicole Marshall** for the Eunice Kennedy Shriver NICHD Maternal-Fetal Medicine Units Network "The Association of Cord Serum Cytokines with Neurodevelopmental Outcomes." Society for Maternal-Fetal Medicine, Chicago, IL, February 2010
5. **Nicole Marshall**, Gwen Fraley, Cori Feist, Saraga Reddy, Michael Burns, Leonardo Pereira. "Chorionic Villus Sampling for Abnormal Screening Compared To Historical Indications: Prevalence of Abnormal Karyotypes." Society for Gynecologic Investigation, Orlando, FL, March 2010

D. Research Support

National Medical Fellowships, Mayo Clinic
2004

Buckner (mentor)

Bristol-Meyers Squibb Academic Medicine Fellow

The goal of this project was to determine the ototoxicity of cisplatin in patients undergoing chemotherapy for glioblastoma. This work was presented at the Society for Neuro-Oncology meeting and published in the Journal of Neurooncology.

HHSA 290 2007-10057-1 (Guise)

09/02/2008-03/31/2010

AHRQ

NIH Consensus Development Conference: Vaginal Birth after Cesarean

The goal of this project was to conduct an evidence report comparing vaginal birth after cesarean verses repeat cesarean to inform the NIH Consensus Development Conference. Role: Investigator

N.L. Tartar Research Fellow Award, OHSU

Thornburg (mentor)

07/01/2009-06/30/2010

The goal of this project is to determine how antioxidant expression changes in normal and compromised sheep placental tissues following uteroplacental embolization. The initial work was presented at the International Federation of Placental Associations meeting and the manuscript is in progress.

Maylie, James

Area(s) of Research/Scholarly Interest

For the past 15 years, the collaboration of my laboratory with Dr. Adelman's laboratory in the Vollum Institute at OHSU, has been dedicated to understanding the structure, function, and physiological roles of several different K⁺ channels. During this time, we cloned the SK channel family and discovered that they are heteromeric assemblies with calmodulin that mediates their Ca²⁺ gating. We first examined their functional importance in skeletal muscle suggesting that their aberrant T-tubular expression in denervated and perhaps myotonic dystrophic skeletal muscle provides the basis for the apparent paradox that a hyperpolarizing K⁺ channel may underlie the hyperexcitability in these conditions. We then described the first role for SK channels in synaptic transmission and in their modulation of induction threshold of synaptic plasticity at Schaffer collateral to CA1 synapses that correlates with its affect on learning and memory paradigms. Subsequently, we showed that SK2 channels in CA1 are themselves plastic, via activity-dependent SK2 trafficking, that contributes to the activity-dependent LTP at Schaffer collateral to CA1 synapses. The main goal of my current research is to show that synaptic SK2 channels and NMDARs are physically coupled by the binding of 14-3-3 dimers that requires LTP-dependent PKA phosphorylation of SK2 and NR2A.

Ongoing research projects: in addition to those listed under NIH funding in CV the following projects are under development:

- 1) Role of cellular potassium channels in the fertilization calcium signal and formation of the fertilization membrane – in progress.
- 2) Estrogen modification of NMDA-dependent synaptic plasticity in the hippocampus – taken over by Dr. Wendy Wu, BIRCWH fellow.
- 3) Role of SK and Kv1 channels in seizure susceptibility – in progress.

Current Grants and Contracts

R01 MH081860-03 Maylie (PI)

07/01/08-01/31/13

SK channels: Roles and mechanisms for dendritic excitability and plasticity

The major goal of this study is to test the hypothesis that SK channels in hippocampal CA1 dendrites limit electrotonic propagation of dendritic EPSPs, reducing the fidelity of EPSP-spike (E-S) coupling, and limit retrograde back-propagating action potentials (b-APs), thereby affecting the induction of synaptic plasticity due to theta-burst pairing (TBP) of Schaffer collateral inputs with postsynaptic b-APs.

R01 MH076752-04 Adelman (PI)

08/01/06-07/31/11

SK2-associated protein kinase CK2: molecular basis

The driving hypothesis for this application is that the N- and C-terminal domains of the SK2 channel regulate associated CK2 activity in response to dynamic metabolic signals and that SK2-associated CK2 activity influences neuronal excitability and the induction of synaptic plasticity.

R01 NS38880-10 Adelman (PI)

07/01/00-11/30/13

Molecular Physiology of SK2 Channels in CA1 Neurons

The SK2 gene encodes two isoforms, SK2-L and SK2-S. The major goal of this study is to test the hypothesis that the SK2-L N-terminal domain confers dendritic and spine localization and function to SK2 channels that is accomplished by selective association with targeting proteins.

1R01NS065855-01 (Adelman and Herson)

06/01/09-05/31/14

SK2 channels as novel neuroprotective targets against cerebral ischemia

This grant proposes to study the cellular mechanisms by which increased SK channel activity protects hippocampal neurons from ischemia-induced cell death, investigate whether the increased neuronal survival is accompanied by cognitive improvement, and test a treatment regimen for mice administered SK channel agonists after in vivo ischemia.

1R21NS071314-01 Adelman (PI)

05/01/2010-04/30/2012

MOLECULAR DEFINITION OF THE SLOW AHP CHANNELS IN CA1 NEURONS

The slow afterhyperpolarization (AHP) channels regulate intrinsic excitability in many central neurons, and their activity is important for normal sleep-wake cycle, arousal, attention, and in modulating sensory processing, behaviors, emotions and memory consolidation. We will clone the slow AHP channels and define their requisite components. Determining the identities of the slow AHP channels will provide a powerful target for therapeutic approaches to multiple central pathologies such as Alzheimer's disease, schizophrenia, epilepsy, attention deficit syndrome, and sleep disorders, as well as for cognitive impairment during normal aging.

Grants planned or in submission 2010

None

Key collaborators:

Departmental: John Bissonnette

OHSU: John Adelman (Vollum Institute), Paco Herson (Anesthesiology)

Extramural:

Most recent publications (last 5)

Allen D, Fakler B, Maylie J, Adelman JP (2007) Organization and regulation of small conductance Ca²⁺-activated K⁺ channel multiprotein complexes. *J Neurosci* 27:2369-2376.

Bissonnette JM, Knopp SJ, Maylie J, Thong T (2007) Autonomic cardiovascular control in methyl-CpG-binding protein 2 (Mecp2) deficient mice. *Auton Neurosci* 136:82-89.

Bruening-Wright A, Lee WS, Adelman JP, Maylie J (2007) Evidence for a deep pore activation gate in small conductance Ca²⁺-activated K⁺ channels. *The Journal of general physiology* 130:601-610.

Lin MT, Lujan R, Watanabe M, Adelman JP, Maylie J (2008) SK2 channel plasticity contributes to LTP at Schaffer collateral-CA1 synapses. *Nature neuroscience* 11:170-177.

Lujan R, Maylie J, Adelman JP (2009) New sites of action for GIRK and SK channels. *Nat Rev Neurosci* 10:475-480.

Pereira, Leonardo

Area(s) of Research/Scholarly Interest:

1. Preterm labor/preterm birth: accurate prediction of delivery, elucidation of mechanisms, identification of novel therapeutic targets, development of effective therapies
2. Multifetal pregnancies: elucidation of mechanism of preterm labor, prediction of delivery timing
3. Intra-amniotic infection: diagnosis, consequences, and development of new treatment strategies

Current Grants and Contracts:

1. March of Dimes. Pereira (PI) 3/1/2008-2/28/2011
Prematurity Research Initiative
Identification of Cervical-Vaginal Biomarkers of Recurrent Preterm Birth by Proteomic Analysis: Serial sampling of women with prior preterm birth and comparison of first, second, and third trimester CVF protein profiles.
Role: PI
2. Industry Grant Pereira (PI) 10/31/2007-9/30/2010
Proteogenix, Inc.
Development of a non-invasive multi-analyte test to detect intra-amniotic infection and predict preterm birth in women presenting with preterm labor and intact amniotic membranes.
Role: Site PI
3. Medical Research Foundation of Oregon Pereira (PI) 01/01/2010-12/31/2010
Proteomic Analysis of Maternal Serum to Improve Our Prediction of Preterm Delivery.
Role: PI

Grants planned or in submission 2010

1. March of Dimes Prematurity Research Initiative
Identification of the mechanism responsible for preterm labor in twin gestations and prediction of preterm birth in twins using proteomic analysis
LOI submitted: full grant submission if invited: July 2010
2. March of Dimes Prematurity Research Initiative
Identification of Cervical-Vaginal Biomarkers of Recurrent Preterm Birth by Proteomic Analysis: Serial sampling of women with prior preterm birth and comparison of first, second, and third trimester CVF protein profiles.
LOI submitted: 1 year extension if invited: July 2010
3. NIH R21
Proteomic identification of serum biomarkers of recurrent preterm birth
Planned submission October 2010
4. NIH RO1

Maternal antibiotic therapy for intra-amniotic infection delays preterm birth and prevents fetal lung injury and neurologic impairment
Planned submission November 2010

Key collaborators

Departmental: Jorge Tolosa MD, MSCE, Antonio Frias MD, Juha Rasanen MD, PhD

OHSU: Peta Grigsby PhD: ONPRC, Bob Schelonka MD: Neonatology, Terry Morgan MD: Pathology, Larry David PhD: Proteomics

Extramural: MFMU-Network

Most recent publications (last 5):

1. **Pereira L**, Reddy A, Alexander A, Lapidus JA, Lu X, Gravett MG, Nagalla SR. Insights into the multifactorial nature of preterm birth: Proteomic profiling of the maternal serum glycoproteome and maternal serum peptidome among women in preterm labor. *Am J Obstet Gynecol* 2010; in press.
2. Airolidi J, **Pereira L**, Cotter A, Gomez R, Berghella V, Prasertcharoensuk W, Rasanen J, Chaithongwongwatthana S, Mittal S, Kearney E, Tolosa JE. Amniocentesis prior to physical exam indicated cerclage in women with midtrimester cervical dilation: results from the Expectant Management compared to Physical Exam-indicated Cerclage (EM-PEC) international cohort study. *Am J Perin* 2009; 26(1):63-8.
3. Berghella V, Prasertcharoensuk W, Cotter A, Rasanen J, Mittal S, Chaithongwongwatthana S, Gomez R, Kearney E, Tolosa JE, **Pereira L**. Does indomethacin prevent preterm birth in women with cervical dilatation in the second trimester? *Am J Perin* 2009; 26(1):13-9.
4. **Pereira L**, Cotter A, Gómez R, Berghella V, Prasertcharoensuk W, Chaithongwongwatthana S, Rasanen J, Mittal S, Daly S, Airolidi J, Tolosa JE. Expectant management compared to physical exam-indicated cerclage in selected women with a dilated cervix between 14^{0/7}-25^{6/7} weeks: Results from the EM-PEC international cohort study. *Am J Obstet Gynecol* 2007;197(5):483-5.
5. **Pereira L**, Reddy AP, Jacob T, Thomas A, Schneider KA, Dasari S, Lapidus JA, Lu X, Rodland M, Roberts CT Jr., Gravett MG, Nagalla SR. Identification of novel protein biomarkers of preterm birth in human cervical-vaginal fluid. *J Proteome Res* 2007;6(4):1269-76.

Rasanen, Juha

Area(s) of Research/Scholarly Interest

Fetal cardiovascular physiology

Current Grants and Contracts

None

Grants planned or in submission 2010

RO1 application for experimental fetal sheep research on cardiovascular physiology

Key collaborators

Departmental

Lowell Davis, Roger Hohimer, Antonio Frias, Leah Bernard, Jason Hashima

OHSU

David Sahn, Srinivasa Nagalla, Primate Center: Peta Grigsby, Eliot Spindel

Extramural

James C. Huhta, Tampa, Florida, Acharya Ganesh, Tromso, Norway, Olli Vuolteenaho, Oulu, Finland

Most recent publications (last 5)

Haapsamo M, Martikainen H and Rasanen J. Low-dose aspirin and uterine haemodynamics on the day of embryo transfer in women undergoing IVF/ICSI: a randomized, placebo-controlled double-blind study. Hum Reprod 24:861-866, 2009.

[Erkinaro T](#), [Kavasmaa T](#), [Ylikauma L](#), [Makikallio K](#), [Haapsamo M](#), [Acharya G](#), [Ohtonen P](#), [Alahuhta S](#) and [Rasanen J](#). Placental and Fetal Hemodynamics After Labetalol or Pindolol in a Sheep Model of Increased Placental Vascular Resistance and Maternal Hypertension. Reprod Sci 16:749-757, 2009.

Nagy II, Railo A, Rapila R, Hast T, Sormunen R, Tavi P, Räsänen J and Vainio S. Wnt-11 signaling controls ventricular myocardium development by patterning N-cadherin and β -catenin expression. Cardiovasc Res 85:100-109, 2010.

Makikallio K, Acharya G, Erkinaro T, Kavasmaa T, Haapsamo M, Huhta JC and Rasanen J. Ductus venosus velocimetry during acute fetal acidemia in a sheep model of increased placental vascular resistance. Am J Physiol Heart Circ Physiol 298:H1229-1234, 2010.

Hashima JN, Frias AE, Bernard L, Spindel ER, Hobbs TR and Rasanen J. Fetal ventricular diastolic filling characteristics in a primate model: The role of fetal heart rate and pulmonary vascular impedance. Reprod Sci (in press).

Tolosa, Jorge

Area(s) of Research/Scholarly Interest: They include Clinical Epidemiology, Evidence based best health practices, clinical trials, preterm labor/birth, ultrasound in pregnancy, maternal disease in pregnancy, and prevention of morbidity and mortality of mothers and babies. I apply epidemiological tools for the investigation of the effects of exposures such as tobacco or pesticides on the outcome of pregnancy. I have a special interest in global health, capacity building and transference of skills to reduce fetal, neonatal and maternal morbidity and mortality. As PI for the Maternal Fetal Medicine Units Network of NICHD, I contribute with my interest and training in Clinical Epidemiology, design and development of RCT's and with my expertise in administration and management of complex collaborative multisite studies.

Tobacco in Pregnancy International Research Group: In 2008 I led the creation of an international working group on Tobacco in Pregnancy, with > 60 investigators and policy makers from all regions of the world. I secured funding from the National Cancer Institute and the Centers for Disease Control and Prevention in the U.S. Systematic reviews of the literature focused on middle and low income countries were completed. After a meeting of investigators in the U.S., a global research agenda was developed, the results were disseminated and research proposals are in development. In addition to the publications in which I am a co-author- listed below- a special issue of the Journal *Acta Obstetricia Gynecologica Scandinavica* was issued in April 2010, after a call for submissions was made with > 20 additional manuscripts published. I was the guest editor for this issue.

Although this research did not involve enrolment of patients, it demonstrates my ability to conceptualize, organize, secure funding, and complete research projects that are novel and have significance in the area of scope of Maternal Fetal Medicine and International Health, such as preterm birth and low birthweight. An R-21 application is in development to study determinants of smoking cessation in pregnancy and postpartum, in the U.S. and internationally, with me as PI, in collaboration with CDC and NCI.. We are developing a pilot study in the city of Medellin in Colombia to determine the knowledge and attitudes of providers with respect to exposure to and use of Tobacco in Pregnancy. This collaborative study include Britt Severon 3rd year medical student at OHSU, Dr. Kate Goldade PhD from the University of Minnesota, Dr Bernardo Agudelo from Universidad de Antioquia and Dr Luis Guillermo Echavarria from Universidad Pontificia Bolivariana, both in Medellin, Antioquia, Colombia. I have written to Dr Thomas Becker in the Department of Preventive and Public Health at OHSU to invite them to participate. I am the senior investigator in this project. If successful, it will be developed as a national strategy in Colombia and tested in other countries..

Longitudinal Study of Fetal Growth Restriction (FGR): A multicenter international, longitudinal study to evaluate pathophysiological changes in fetuses diagnosed with FGR led by investigators at OHSU (J. Hashima, J. Rasanen, and J.E. Tolosa) is on-going at 2 centers in the US, 2 in Scandinavia and three in South America. Using state-of-the art echocardiographic parameters and Doppler ultrasound, a detailed description of the changes that occur centrally and peripherally in the fetus are made. A novel secure web based data entry system has been created. 6 cases have been enrolled. The study is expected to end in 03-2012 and will be followed by a RCT of intervention, once we determine the best parameters to predict best timing for delivery of the compromised fetus.

Assessment of Exposure to acetaminophen and possible effects on fetal cardiovascular physiology in pregnancy: This is a collaborative descriptive study developed by me at OHSU with Drs J. Hashima, J. Rasanen and L. Bernard all from the Division of MFM. The protocol has been IRB approved at OHSU, at

Fundación Santa Fe, Universidad de los Andes in Bogotá, Colombia, Universidad Javeriana in Bogotá, Colombia and Pontificia Universidad Bolivariana in Medellín, Colombia. Drs Rasanen and Hashima will travel with me to Colombia in November 2010 to complete training and certification of the centers. I will travel to Colombia in August and September 2010 to lead meetings of investigators related to this project and the one described in the previous paragraph.

Prevalence of Genital Tract Infections In Symptomatic Women and Use of rapid diagnostic tests; in Bogotá, Colombia, 2008. Pilot Study. Collaborative International Project Departamento de Obstetricia y Ginecología, Universidad Nacional de Colombia, Secretaría Distrital de Salud de Bogotá, LigaSida, Department of Obstetrics & Gynecology, Division of Maternal Fetal Medicine, Oregon Health & Science University, Portland, Oregon, EEUU, Global Network for Perinatal & Reproductive Health, Portland, Oregon, EEUU

Objective: Describe the prevalence and etiology of infections of the genital tract, using the syndromic approach as recommended by WHO and to perform an initial assessment of the use and diagnostic characteristics of rapid diagnostic tests at the point of care.

Methodology: Cross sectional study. Included were women with symptoms of vaginal discharge or itching who consulted during 2007-2008 at three sites in Bogotá, Colombia. Their age was 14 to 49 years old. Exclusion criteria: women with severe medical conditions, history of hysterectomy, pregnant, presenting menstrual discharge, no history of sexual activity or those who reported receiving antibiotic therapy in the previous 14 days. Consecutive sampling. Syndromic diagnosis according to the World Health Organization for *N. gonorrhoeae*, *C. trachomatis*, syphilis, *Trichomonas vaginalis*, *Candida*, bacterial vaginosis and HIV. Sensitivity and specificity of the rapid diagnostic tests used were determined against the “gold standard” diagnostic test for each infection. Planned follow-up two weeks after initial visit. **Results:** One hundred and thirty one women were included. Bacterial Vaginosis was present in 46%, followed by candidiasis in 16%. Syphilis was the sexually transmitted infection most frequently diagnosed in 7 % of cases and *C. trachomatis* in 6%. No cases of *N. gonorrhoeae* were identified. The most frequent syndromic diagnosis was vaginitis. The rapid diagnostic tests had a specificity close to 100%; sensitivity varied with a 90% for syphilis, 81% for bacterial vaginosis and lower precision, of 60%, for candida. The frequency of positive cases for chlamydia and gonorrhoeae was too low to assess the diagnostic precision of the rapid tests. **Conclusions:** Infections of the genital tract in symptomatic women are mainly endogenous in nature. The prevalence of sexually transmitted infections was 16%. The use of rapid diagnostic tests at the point of care is possible. Currently (06-2010) a large cohort of 1,400 women is being enrolled to test the use of syndromic management compared to “gold standard” diagnostic tests and when possible rapid tests. Funded by Colciencias in Colombia and the Office of the Secretary of Health in Bogotá. I am the senior investigator for the project which is expected, will change the national guidelines on diagnosis of RTI's. in Colombia.

Evaluation of exposure to pesticides in workers in the flower industry in Colombia. In 2006 I developed a working group for the study of pesticide exposure in humans, using a model in the flower industry in Colombia, as the majority > 70%, of the workers are women, with 12% of the exposed population being pregnant at a given point in time. This collaborative study is developed with Instituto Nacional de Salud in Colombia and Universidad El Bosque, both in Bogotá, Colombia and the Centers for Disease Control and Prevention in the US. We have completed a survey of pesticides and herbicides used and practices of management of flowers. We published in the leading Colombian journal. (Varona et al, see publications). A second study was just completed with collection of > 1000 urine samples from flower workers with different levels of exposure to pesticides and herbicides, to measure residues or metabolites at the environmental health laboratory of CDC in Atlanta.. This information in addition to providing us with novel science related to exposures, will help us determine if there is ground for

development of an R0-1 application for a 5-10 year cohort study to study associations between levels of pesticides and herbicides in humans and in pregnancy and overall reproductive health outcomes.

Collaboration with University of Hawaii:

Angiotensinogen A(-6)G promoter genotype and idiopathic preterm labor in Japanese Hawaiian Women. Idiopathic PTL is a disease of relative uteroplacental insufficiency similar to preeclampsia and IUGR; and may therefore be associated with A(-6). In turn, the frequency of A(-6) should be significantly increased in idiopathic PTL compared to normal term pregnancy controls.

Placental Biometry and outcome of pregnancy: measurements x-y-z on placentas from cases defined as 1. Fetal growth restriction; 2. Preterm birth; 3. Pre-eclampsia; 4. Diabetes; Controlling for fetal gender.

Adnexal Masses in Pregnancy: On-going project led by Dr William Go, MD fellow in MFM and Dr. Ivica Zalud from the University of Hawaii with Drs Roya Sohaey, MD, Leslie Harpin, MD from the Dept of Radiology, Monica Rincon, MD, Rene Riano, MD and myself from Ob/Gyn. To complete an abstract for the 2011 SMFM meeting.

Participation in the Maternal Fetal Medicine Units Network (MFMUN of NIH-NICHD): Summary of activities since the start of the project in 04-06 to 05-10. I have been PI for this project since 01-08

The Center at OHSU has gained substantial experience in all activities of the MFMUN in the current funding cycle (2006-2011), the first time it joined the MFMUN. It has shown progressive improvement in all areas of performance in the MFMUN. OHSU initiated work on the MFMUN in collaboration with Kaiser Permanente (K-P) in Oregon. Although OHSU had been successful at establishing a reliable and efficient system for recruitment of participants at K-P, recruitment was stopped for one month in 2008. Due to financial difficulties in 2009 K-P reduced and then terminated participation in all MFMUN activities on November 2009. OHSU suffered a period of transition in leadership in the Division of MFM, with two directors being the PI's for the MFMUN from 04-06 to 12-07. A site visit, requested by the current PI, Dr Tolosa, to NICHD and BCC was completed in December 2007. In January 2008 Dr. Tolosa assumed the role of PI and all responsibilities for the MFMUN at OHSU. A new site for recruitment of participants was identified and successfully established by July 08, Providence-Sacred Heart Medical Center (P-SHMC) in Spokane, Washington. A site visit to the OHSU center was organized by Dr. Tolosa in September 2008 and Ms Michelle M. DiVito, MSN, who has extensive experience in all activities of the MFMUN visited the sites part of the center, including P-SHMC. She produced a substantial report with specific recommendations for improvement in activities of the MFMUN, where needed. Those recommendations were implemented. There are weekly conference calls held between OHSU and P-SHMC. Dr. Tolosa is a practicing MFM at OHSU and spends time every month at P-SHMC, engaged in development of the MFMUN. At P-SHMC there are 5 hospitalists Sandra Fornwalt, MD, Jack Childress, MD, Amy Occhino, MD, Evan Forsnes, MD, Kenneth Jacobs, MD who are all board certified Ob/Gyn's who report to the perinatologist. They provide prenatal care for all the high risk patients and do all the deliveries for the high risk pregnancies. One of the hospitalists, Dr. Sandra Fornwalt, MD who has been at P-SHMC for the last 2 years is currently the PI for the MFMUN. Dr Paul Speer, MD, an academic MFM, very knowledgeable on the MFMUN, provides part time coverage once a week every month (see biosketch and letter of support). One full time MFM's is completing recruitment to start June 2011 and a second full time MFM is being actively recruited. The combination of the time at P-SHMC from Drs. Tolosa and Speer, and their experience with the MFMUN; the additional FTE's in MFM available from June 2011, the continued availability of the 5 hospitalists and the full support of the administration at P-SHMC, (see letter Dr Katherine Tuttle), assure P-SHMC will continue to be a successful site for the MFMUN. At OHSU there is now stability in leadership with Dr. Leonardo Pereira as Director of the Division of MFM beginning 01-09 and Dr. Aaron Caughey, MD, PhD beginning as Chair of the

Department effective 07-10. See his letter of support and biosketch. They are both academically oriented, active researchers. Dr. Pereira will be the alternate PI for the MFMUN and has been successful at having his first proposal for a secondary analysis to the MFMUN approved. It is in process to study proteomic markers of PTB in samples of serum obtained in the STTARS MFMUN protocol. This work will be done in Dr. Pereira's lab at OHSU and is funded by OHSU. Dr. Tolosa and Pereira have worked successfully together for the last 8 years and have been very productive academically.

Below is an overview of our center's performance in the network during the current grant cycle. During this initial period of participation within the MFMU Network we have proven the ability to carry out study work over the long term and execute protocols appropriately. As of the April 2010 MFMU Network Center Performance report, we have had no protocol violations. In addition, we are tied for first place in the retention/completion section having lost no patients to follow-up. Over the last two years, while much of our current team has been in-place, we have seen improvements in our Data Quality and have increased our ranking for timeliness of data entry and transmission from 14th to 5th place in the network. Our team is working diligently to build upon these successes and move the MFMU research forward as evidenced by our contributions outlined below.

A Randomized Clinical trial of Treatment for Gestational Diabetes: Began in 11-02, 4 years before OHSU joined the MFMUN, and ended 11-07. Knowing that recruitment into the RCT was going to be limited, OHSU established all the procedures required for successful enrollment and randomization of participants, data collection and collection of biological samples at birth, including creation of a 24/7 system of coverage for research assistants to secure and label all required samples. OHSU enrolled 3 participants.

A Randomized Clinical Trial of Antioxidants to Prevent Preeclampsia (CAPPS): This study started in 07-03, three years before OHSU joined the MFMUN, and ended in 02-08. A total of 69 women were recruited for CAPPS RCT and 17 for the CAPPS Prediction Arm. As indicated in a progress report after a site visit by NICHD and BCC on 12-07, "Once going, OHSU was able to keep CAPPS recruitment at a similar curve as some of the smaller network centers."

Randomized Clinical Trial of Thyroxine Therapy for Subclinical Hypothyroidism of Hypothyroxinemia Diagnosed during pregnancy (TSH): The TSH trial was initiated by the MFMUN in 10-06 and ended in 11-09. OHSU received IRB approval to begin recruiting patients 02/12/2007. OHSU screened 1307 patients and of these patients 11 were randomized. All 11 patients were randomized between 04-08 and 04-10. The ratio of randomized patients/total number of patients screened equals the one for the MFMUN as a whole.

A Randomized Trial of 17 Alpha-Hydroxyprogesterone Caproate for Prevention of Preterm Birth in Nulliparous Women with a short Cervix: (SCAN): The SCAN trial was initiated by the MFMUN in 03-07. OHSU received IRB approval for patient recruitment in 07-07. In 04-08, our center had not randomized any patients. Our center sought out new methods for improving recruitment and as a result, by 07-09 we had randomized 8 patients. As of 04-10 OHSU has screened 664 patients and of these patients 10 have been randomized. This ratio of screened to randomized patients is consistent with that of the MFMU Network as a whole. The most recent MFMUN report ranked OHSU 7th in total number of patients screened per month for the past 3 months among the 14 other centers in the network.

A Registry Study of Novel Swine-Origin H1N1 Influenza A Virus Among Hospitalized Pregnant and Immediately Postpartum Women (H1N1): Study timeline October 1, 2009 - May 31, 2010. OHSU recruited 17 eligible patients ranking 9th place in overall recruitment.

An Observational Cohort Study to Evaluate Measures of Quality of Obstetric Care Assessment of Perinatal Excellence (APEX): Started in 04-08 with a projected end date of 02-11. Processes implemented to improve data quality have decreased the average number of queries per 1000 fields

from 4.9 in 07-08 to 2.82 in 04-10. In addition, data timelines has improved dramatically with a decrease in average percent of overdue forms from 14.3% to 0.10% in less than 2 years time.

A Randomized Trial of Fetal ECG ST Segment and T Wave Analysis as an Adjunct to Electronic Fetal Heart Rate Monitoring (STAN): In 01-10, Grand Rounds at OHSU were organized by the PI Dr. Tolosa. Dr. Michael Varner MD from the University of Utah presented the STAN study to the faculty, residents, fellows and nurses at OHSU. His presentation was taped and distributed to BCC for use at other MFMUN sites. IRB approval at OHSU has been obtained; two devices were assembled with supervision by Neoventa in 05-10. .

Committee Participation: Publications Committee: Dr Tolosa joined this committee in 01-08 when he assumed the role of PI at OHSU. He has contributed by participating in the prioritization process of secondary analysis submitted to the MFMUN. He has reviewed all the proposals submitted to the committee for the last two years; he has attended the conference calls where proposals were selected for completion by BCC. He has reviewed the abstracts resulting from the selected proposals before being submitted to the SMFM and SGI. He has provided editorial comment to manuscripts assigned to him by the MFMUN. He has attended conference calls that are routinely scheduled and has attended all the meetings of the subcommittee scheduled during the Steering Committee meetings in Bethesda.

H1N1: Dr. Tolosa serves in the subcommittee and has contributed to protocol development. He will be reviewing with other members of the network medical records for cases of maternal mortality. He has attended all subcommittee meetings held at the time of the Steering Committee meetings in Bethesda.

ALPS: Dr. Tolosa serves in the subcommittee and contributed to development of the original application to the National Heart, Lung & Blood Institute, which co-funded the project. He has participated in conference calls and all subcommittee meetings held at the time of the Steering Committee meetings in Bethesda.

Concept protocol development: “Randomized Clinical Trial of Delayed Umbilical Cord Clamping (DCC) in Preterm Infants” Jorge E. Tolosa, MD, MSCE, Kimberly Boggess, MD, (UNC) Judith Mercer, PhD, CNM(Brown). Dr Tolosa led development of a novel proposal to determine if delayed cord clamping (DCC) in the preterm neonate (24 to < 32 weeks) reduces the risk of IVH (all grades), late onset sepsis, death and neurodevelopmental impairment (NDI), when compared with neonates with immediate cord clamping (ICC). It was not selected to move forward after a second presentation.

“Randomized Clinical Trial of Labor Induction vs. Expectant Management for PPROM between 34-36 6/7 Weeks Gestation” Sally Segel, MD, (OHSU), Cynthia Gyamfi, MD (Columbia), Sean Blackwell, MD, (UTH) & Jorge E. Tolosa, MD, presented a concept in 04-10 To determine if expectant management including antibiotics in patients with PPROM from 34 0/7- 36 5/7 weeks gestation decreases a composite of neonatal morbidity and mortality.

Proposals for secondary analysis, publications and presentations at National meetings:

Soon after Dr. Tolosa assumed as PI of the MFMUN at OHSU, **in 2008, one** proposal for a secondary analysis to the MFMUN was developed. This first proposal was selected by the MFMUN. It was accepted by the SMFM and presented as a poster to the 2009 SMFM meeting. The manuscript was completed in record time and has been published. **“The Effect of Maternal Weight on Neonatal Outcome in Women Receiving a Single Course of Antenatal Corticosteroids”** Jason N Hashima, M.D., M.P.H., (OHSU) Yinglei Lai, PhD, Ronald J. Wapner, M.D, Jay D. Iams, M.D., Yoram Sorokin, M.D., Donald J. Dudley, M.D. et al. Am J Obstet Gynecol; 202(3) March 2010. 263.e1-263.e5 **In 2009:** We submitted **eight** proposals for secondary analysis of which **3** were selected by the MFMUN. All 3 were accepted for presentation at national meetings, 1 at the 2010 SMFM, in collaboration with another center in the MFMUN, the University of Utah: **“The Association of Cord Serum Cytokines with Neurodevelopmental Outcomes (NDD)”** **Objective:** Test whether inflammatory cytokine levels in umbilical cord blood are associated with Cerebral Palsy or NDD. No association was found. Varner, M (Utah), Marshall, N (OHSU); and 2 at

the SGI in 2010 **Placental Villous Hypermaturation (PVH) is Associated with Idiopathic Preterm Birth(PTB)**. We hypothesized that relative placental insufficiency may be associated with idiopathic PTB. PTB was found to be associated with PVH, suggesting that relative placental insufficiency may be a common cause of PTB. Morgan (OHSU) and Tolosa,(OHSU). **Relationship between fetal station and successful vaginal delivery in nulliparous women:** To study the relationship between fetal station on admission to labor and delivery and successful vaginal delivery (VD) in nulliparous women. Results: In nulliparous women admitted to labor and delivery in spontaneous labor or for labor induction, unengaged fetal station is a risk factor for cesarean delivery. Segel (OHSU),Carreno, MD (UT-H). (See Appendix for the abstracts. All 3 manuscripts are in preparation). **In 2010:** We submitted **six** proposals for secondary analysis of which **2** were selected by the MFMUN and combined into 1. PI: Dr Pereira, alternate PI in this application. **Prediction of preterm birth in twin gestations through analysis of maternal serum Annexin A2, Profilin 1, and L-Plastin levels at 24-27 weeks gestation.**

Current Grants and Contracts:

MFMUN for NICHD.

Grants planned or in submission 2010:
MFMUN submitted to NICHD on 06 01 10.

Planning an R-21 to NCI on Tobacco in Pregnancy

Planning an application to CDC through the Primary Prevention Center at OHSU's Dept of Preventive and Public Health, which is funded by CDC. Possible application for a descriptive study in 20101 a in Medellin, Colombia

Key collaborators

Departmental: Leonardo Pereira for the MFMUN. WHRU for administrative support. Juha Rasanen for ultrasound projects in Colombia part of the GNPRH.

OHSU: Terry Morgan.

Extramural: Multiple investigators at CDC, NCI, mentors and co-investigators in the US and aboard who are involved with the work of the GNPRH.

Most recent publications (last 5)

Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, Wapner RJ, Varner MW, Rouse DJ, Thorp, JM Jr., Sciscione A, Catalano P, Harper M, M.D. M.Sc., Saade G., Lain KY, Sorokin Y, Peaceman AM, **Tolosa, JE**, Anderson GB. for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network, Bethesda, MD. Multicenter Randomized Treatment Trial of Mild Gestational Diabetes. *N Engl J Med* 2009;361:1339-48.

Geirsson RT, **Tolosa JE**. Smoking, tobacco exposure and pregnancy. Editors Message. *Acta Obstetrica et Gynecologica*. 2010;89:414-415.

Bloch M, Tong VT, Novotny TE, England LJ, Dietz PM, Kim SY, Samet JM, **Tolosa JE**. Tobacco Use and Secondhand Smoke Exposure Among Pregnant Women in low- and middle-Income Countries: A Call to Action. *Acta Obstetrica et Gynecologica*. 2010;89: 418-422.

Oncken CH A, Dietz PM, Tong VT, Belizán JM, **Tolosa JE**, Berghella V, Goldenberg RL,

Lando HA, Samet JM, Bloch MH. Prenatal Tobacco Prevention and Cessation Interventions for Women in Low- and Middle-Income Countries. *Acta Obstetricia et Gynecologica*. 2010;89:442-453.

England LJ, Shin Y. K, Tomar S, Ray C, Gupta PC, Eissenberg T, Cnattingius S, Tita A Th N, Winn D, Djordjevic M, Lambe M, Stamilio D, Chipato T, **Tolosa JE** Non-Cigarette Tobacco Use Among Women and Adverse Pregnancy Outcomes. *Acta Obstetricia et Gynecologica*. 2010;89:454-464.

Tobacco Use and Secondhand Smoke Exposure during Pregnancy in low- and middle-income countries: the need for social and cultural research. Nichter M, Greaves L, Bloch M, Paglia M, Scarcini I, **Tolosa JE**, Novotny T. *Acta Obstetricia et Gynecologica*. 2010; 89:454-464.

Wu, Wendy

Area(s) of Research/Scholarly Interest

1. Regulation of intrinsic and synaptic plasticity by ion channels
2. Physiology of synaptic transmission
3. Cellular substrates of associative learning and aging-related learning deficits
4. Aging- and gender-specific differences in neural plasticity

Current Grants and Contracts

Currently supported by Drs. Maylie and Adelman's R01s.

Grants planned or in submission 2010

Resubmission of R01 in October 2010.

Key collaborators

Departmental

Dr. James Maylie

OHSU

Dr. John Adelman (Vollum Institute)

Extramural

NA

Most recent publications (last 5)

1. Wehr M, Hostick U, Kyweriga M, Tan A, Weible AP, Wu H, **Wu WW**, Callaway EM, Kentros C (2009) Transgenic silencing of neurons in the mammalian brain by expression of the allostatin receptor (AlstR). *Journal of Neurophysiology*. 102(4):2554-62
2. **Wu WW**, Chan CS, Surmeier DJ, Disterhoft JF (2008) Coupling of L-type Ca^{2+} channels to $K_v7/KCNQ$ Channels Creates a Novel, Activity-Dependent Homeostatic Intrinsic Plasticity. *Journal of Neurophysiology*. 100(4):1897-908.
3. Oh MM, **Wu WW**, Power JM, Disterhoft JF (2006) Galantamine increases excitability of CA1 pyramidal neurons. *Neuroscience*. 137:113-23.
4. Disterhoft JF, **Wu WW**, Ohno M (2004) Biophysical alterations of hippocampal pyramidal neurons in learning, ageing and Alzheimer's disease. *Ageing Res Review*. 3(4):383-406.
5. **Wu WW**, Chan CS, Disterhoft JF (2004) The Slow Afterhyperpolarization Governs the Development of NMDA Receptor-Dependent Afterdepolarization in CA1 Pyramidal Neurons During Synaptic Stimulation. *J Neurophysiol*. 92:2346-56.

Wyatt, Solange
Area(s) of Research/Scholarly Interest

Current Grants and Contracts

Grants planned or in submission 2010

Key collaborators
 Departmental
 OHSU
 Extramural

Most recent publications (last 5)

Integrative Medicine Division

Luo, Yunpeng

Area(s) of Research/Scholarly Interest

Current Grants and Contracts

Grants planned or in submission 2010

Key collaborators

Departmental

OHSU

Extramural

Most recent publications (last 5)

Shinto, Lynn

Area(s) of Research/Scholarly Interest:

Research on complementary, alternative, and integrative medicine therapies. Interested in safety, efficacy, and mechanism of action of nutritional supplements such as omega-3 fatty acids, antioxidants, diet, and mind-body therapies. Interested in evaluating safety, effectiveness, and cost-effectiveness of integrative medicine.

Current Grants and Contracts

Lipoic acid & omega-3 fatty acids in Alzheimer's disease 04/01/2010-03/31/2013

NIA/NIH R01AG033613-01A1

PI: Shinto 50% effort

A double-blind, placebo-controlled study that will evaluate lipoic acid plus omega-3 fatty acids in patients with probable Alzheimer's disease. We hypothesize that an 18 month supplementation of LA plus omega-3 and LA alone will delay cognitive and functional decline compared to those receiving placebo in people with AD. One hundred participants will be randomized to placebo or lipoic acid plus omega-3s.

The primary outcome measures are activities of daily living (ADL) and the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-cog). Secondary measures include: brain atrophy (measured by MRI); Mini-mental state exam (MMSE); Quality of Life-AD; Inflammatory markers (tumor-necrosis factor alpha, interleukin-6, osteoprotegerin); lipid levels (cholesterol, LDL, HDL, triglycerides). Fatty acid levels and lipoic acid levels will also be measured.

Consortium PROCAIM Practice Network Pilot Study 07/01/10-10/31/10

PI: Deborah Ackerman, PhD

Col: Shinto, 13 % effort

Oppenheimer CAIM Seed Grant

The overarching goal is to establish a practice network of academically-based integrative medicine clinics that will facilitate high quality research on the utilization and effectiveness of treatments the member clinics provide. A number of integrative medicine clinics, who are members of a national Consortium, will utilize the UCLA PROCAIM web-based survey system to collect and pool patient data from all sites and study the effectiveness of the treatments they provide.

Fish oil for depression in multiple sclerosis 07/01/04-06/30/09 (no cost extension)

Funded by NCCAM/NIH 1K23 AT002155-01

PI: Shinto, 15 % effort

Primary mentor: Dennis Bourdette, MD

This is a Mentored Patient-Oriented Research Career Development Award. The primary aim of this pilot study is to determine if fish oil supplementation is an effective and safe adjunctive treatment for mild to moderate depression in people with MS. The study will also assess the effect of fish oil on levels of inflammatory cytokines that are associated with both depression and MS. This will be a 3-month randomized, double-blind, placebo controlled pilot trial of fish oil supplementation for the treatment of mild-moderately depressed people with MS. Fatty acid levels will be measured by red blood cell membrane fatty acid analysis. Safety will be assessed by subject adverse events report and laboratory measures.

Subjects that respond to treatment, after 3-months, will have the option to continue in the study for another 3-months.

Grants planned or in submission 2010

Pending

CAM Utilization Patterns, Outcomes, and Commitment: A Holistic Approach

Submitted to NCCAM/NIH R01AT005063-01A1

PI: Ackerman (UCLA/OCOM)

To answer several important questions about real-world treatment effectiveness of CAM interventions and the impact on motivations for future use of CAM, we will conduct a prospective open cohort study of CAM patients with chronic conditions. We will recruit two cohorts: clinic-based patients and CAM users recruited through Internet ads. The study will utilize a web-based data collection system to collect longitudinal information. Patients will complete a series of standardized, validated instruments at intervals over one year and answer additional questions about treatment utilization, CAM related attitudes and behaviour, satisfaction with care, and global ratings of symptom change.

If funded OHSU's Integrative Medicine clinics (CWH, Neurology Wellness) will be one of 5 sites that will recruit subjects.

Co-I: Shinto

Key collaborators

Departmental:

OHSU: Neurology: Dennis Bourdette, MD, Vijayshree Yadav, MD, MCR, Joseph Quinn, MD

Ob-Gyn (CWH Integrative Medicine): Anne Nedrow, MD, MBA

Extramural: UCLA/OCOM: Deborah Ackerman, PhD

Most recent publications (last 5)

1. Yadav V, **Shinto L**, Bourdette D. Complementary and Alternative Medicine (CAM) for the Treatment of Multiple Sclerosis: A perspective. Expert Opinion in Clinical Immunol, 2010 (in press).
2. Yadav V, Marracci GH, Munar My, Cherala G, Stuber L, Alvarez L, **Shinto L**, Koop D, Bourdette D. Pharmacokinetic Study of Lipoic Acid in Multiple Sclerosis: Comparing Mice and Human Pharmacokinetic Parameters. Multiple Sclerosis 2010 (in press).
3. **Shinto L**, Marracci G, Baldauf-Wagner S, Strehlow A, Yadav V, Stuber L, Bourdette D. Omega-3 Fatty Acid Supplementation Decreases Matrix Metalloproteinase-9 Production in Relapsing-Remitting Multiple Sclerosis. Prostaglandins, Leukotrienes & Essential Fatty Acids 2009; 80 (2-3): 131-136. Shinto and Marracci co-first authors.
4. **Shinto L**, Calabrese C, Morris C, Yadav V, Griffith D, Frank R, Oken B, Baldauf-Wagner S, Sinsheimer S, Bourdette D. A randomized pilot study of naturopathic medicine in multiple sclerosis. Journal of Alternative and Complementary Medicine 2008; 14(5): 489-96.
5. Wang W, **Shinto L**, Connor WE, Quinn JF. Nutrition Biomarkers in Alzheimer's Disease: The Association between Carotenoids, n-3 Fatty Acids, and Dementia Severity. J of Alzheimer's Disease 2008; 13(1): 31-8.

Internal Medicine Division

Baskin, Heather

Area(s) of Research/Scholarly Interest

Current Grants and Contracts

Grants planned or in submission 2010

Key collaborators

Departmental

OHSU

Extramural

Most recent publications (last 5)

Miller, Jill

Area(s) of Research/Scholarly Interest

Current Grants and Contracts

Grants planned or in submission 2010

Key collaborators

Departmental

OHSU

Extramural

Most recent publications (last 5)

REI Division

Amato, Paula

Area(s) of Research/Scholarly Interest

- Prevention of mitochondrial disease using a novel spindle transfer technique.
- Environmental impact on reproductive health.
- Metabolic endocrine interactions.

Current Grants and Contracts

Source of Support: Oregon Health & Science University, Center for Women's Health Circle of Giving

Program Title: Obstetrics and Gynecology, Oregon Health & Science University

Project Title: Prevention of mitochondrial disease transmission using a novel nuclear transfer technique

Principal-Investigator: Shoukhrat Mitalipov, Ph.D.

Co-Investigator: P Amato, M.D.

% Effort: 10%

Amount: \$125,000

Years of Award: 2010-11

Goal: Find a way to genetically fix inherited diseases passed from a mother to child through DNA

Grants planned or in submission 2010: March of Dimes

Key collaborators

Departmental: Drs. David Lee & Phillip Patton

OHSU: Dr. Mitalipov (ONPRC)

Extramural

Most recent publications (last 5)

- Maskarinec G, Verheus M, Steinberg FM, **Amato P**, Cramer MK, Lewis RD, Murray MJ, Young RL, Wong WW. Various doses of soy isoflavones do not modify mammographic density in postmenopausal women. J Nutr. 2009 May;139(5):981-6. Epub 2009 Mar 25.
- Rausch ME, Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, Steinkampf MP, McGovern FG, Cataldo NA, Gosman GG, Nestler JE, Giudice LC, Leppert FC, Myers ER, Coutifaris C; **Reproductive Medicine Network**. Predictors of pregnancy in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2009;94:3458-66.
- **Ethics Committee of the American Society for Reproductive Medicine**. Donating spare embryos for stem cell research. Fertil Steril 2009; 91:667-70.
- **Ethics Committee of the American Society for Reproductive Medicine**. Interests, obligations, and rights of the donor in gamete donation. Fertil Steril 2009;91:22-7.
- Wong WW, Lewis RD, Steinberg FM, Murray MJ, Cramer MA, **Amato P**, et al. Soy isoflavones supplementation and bone mineral density in menopausal women: a 2-y multicenter clinical trial. Am J Clin Nutr 2009 Nov;90(5):1433-9. Epub 2009 Sep 16.

Battaglia, David

Area(s) of Research/Scholarly Interest

Current Grants and Contracts

Grants planned or in submission 2010

Key collaborators

Departmental

OHSU

Extramural

Most recent publications (last 5)

Lee, David

Area(s) of Research/Scholarly Interest

The preservation of reproductive potential in young cancer survivors.

Current Grants and Contracts

R01B-Bioengineering primate follicles: from immature eggs to live births.

NIH/NICHD RL1-HD058294

The Oncofertility Consortium: Fertility Preservation for Women.

Interdisciplinary Research Consortia: RM-06-008

Richard Stouffer, Principal Investigator

David Lee, M.D. and Mary Zelinski, Ph.D., Co-investigators

Funding: \$3,369,420

Study period: 9/30/2007-6/30/2012

Bidwell Foundation gift - Ovarian Tissue Preservation Research Fund. This program has three arms:

- 1) Research**, to make the potential ovarian and egg preservation strategies more consistently successful, **2) Education**, to make future and present health professionals aware of the options for fertility preservation for children and young women facing fertility damaging therapy, and **3) Clinical**, to provide care for these children and young women.

Grants planned or in submission 2010

Key collaborators

Departmental

OHSU

Extramural

Most recent publications (last 5)

1. Molskness TA, Stouffer RL, Burry KA, Gorrill MJ, **Lee DM**, Patton PE: Circulating levels of free and total vascular endothelial growth factor (VEGF-A), sVEGF receptor-1 and -2, and angiogenin during ovarian stimulation in nonhuman primates and women. *Hum Reprod* 2004;19:822-30.
2. Patton PE, Novy MJ, **Lee DM**, Hickok LR: The diagnosis and reproductive outcome following surgical treatment of the complete septate uterus, duplicated cervix and vaginal septum. *Am J Obstet Gynecol* 2004;190:1669-78.
3. Yeoman RR, Wolf DP, **Lee DM**. Coculture of monkey ovarian tissue increases survival after vitrification and slow-rate freezing. *Fertil Steril* 2005;83(Suppl. 1):1248-54.
4. Goff B, Mandel L, Lentz G, VanBlaricom A, Oelschlager A-M, **Lee D**, Galakatos A, Davies M, Nielsen P. Assessment of resident surgical skills: is testing feasible? *Am J Obstet Gynecol* 2005;192:1331-40.
5. Molskness TA, Stouffer RL, Burry KA, Gorrill MJ, **Lee DM**, Patton P. Circulating levels of total angiopoietin-2 and the soluble Tie-2 receptor in women during ovarian stimulation and early gestation. *Fertil Steril* 2006;86:1531-3.

Patton, Phillip

Area(s) of Research/Scholarly Interest

Angiogenic factors during controlled ovarian hyperstimulation

Vitamin D levels in women with chronic fatigue

Current Grants and Contracts

U54 HD18185-22 (Stouffer PI)

NIH/NICHD - \$299,927

Cooperative Research on Infertility in Primates

Project III - "Angiogenic and Angiolytic Factors in Natural and Controlled Ovarian Stimulation (COS) Cycles"

Richard Stouffer, Ph.D., Principal Investigator

Phillip Patton, M.D., Co-investigator % Effort: 5

Study period: April 2004-March 2011

Grants planned or in submission 2010

U54 resubmission (Stouffer PI)

Key collaborators

Departmental Amato, Lee, Battaglia

OHSU Stouffer

Extramural Enochian

Most recent publications (last 5)

1. Sampson JE, Ouhibi N, Lawce H, **Patton PE**, Battaglia DE, Burry KA, Olson SB: The role for preimplantation genetic diagnosis in balanced translocation carriers. *Am J Obstet Gynecol* 2004;190:1707-13.
2. Molskness TA, Stouffer RL, Burry KA, Gorrill MJ, Lee DM, **Patton P**. Circulating levels of total angiopoietin-2 and the soluble Tie-2 receptor in women during ovarian stimulation and early gestation. *Fertil Steril*. 2006;86:1531-3.
3. Munks EB, Edelman AB, Jensen JT, Nichols MD, Burry K, **Patton P**. IVF patients' attitudes toward multifetal pregnancy reduction. *J Reprod Med* 2007;52:635-8.
4. Stanek M, Borman S, Molskness T, Larson J, Stouffer RL, **Patton PE**. Insulin and IGF stimulation of VEGF production in luteinized granulosa cells: comparison between PCOS and non-PCOS women. *J Clin Endocrinol Metab*. 2007;92:2726-33. Epub 2007 May 8.
5. Hurliman AK, Speroff L, Stouffer RL, **Patton PE**, Lee A, Molskness TA. Changes in circulating levels and ratios of angiopoietins during pregnancy but not during the menstrual cycle and controlled ovarian stimulation. *Fertil Steril*. 2010;93:1493-9. Epub 2009 May 23.

Joint Appointment Faculty – Division of Reproductive Sciences at ONPRC
Bethea, Cynthia

Area(s) of Research/Scholarly Interest

Cynthia Bethea and her staff are working with primate, rodent and cell culture models to understand the mechanisms by which estrogen and progesterone act in serotonin neurons. Serotonin deficits occur in patients who are clinically depressed. Twice as many women as men suffer from depression, and many depressive episodes are associated with the withdrawal of estrogen and progesterone at the end of each menstrual cycle, following parturition and after menopause. Researchers in this laboratory are using laser capture of serotonin neurons, microarray analysis, quantitative PCR, in situ hybridization, immunocytochemistry, ligand binding and western blotting to characterize the estrogen and progesterone regulation of gene and protein expression in serotonin neurons. They have found that serotonin neurons use a recently discovered form of the estrogen receptor called ER β . Estrogen acts through ER β on tryptophan hydroxylase, the enzyme that governs serotonin synthesis. The expression of this enzyme is increased at the mRNA and protein levels by ovarian hormones. In addition, they have found that the 5HT $1A$ auto receptor, which acts like a brake on serotonin neurons, is decreased at the mRNA and protein levels by ovarian hormones. Thus, ovarian hormones both increase serotonin production and increase the rate at which the neurons release serotonin. Recent studies have shown that estrogen and progesterone inhibit the expression of genes that lead to premature cell death in laser captured serotonin neurons. Protein analysis has indicated that estrogen and progesterone prevent cell death by a caspase-independent mechanism. Studies are underway to characterize DNA fragmentation by TUNEL assay in serotonin neurons. Additional studies have shown that estrogen and progesterone promote neuroplasticity by increasing the expression of genes that promote dendritic spine proliferation in laser captured serotonin neurons. Dendritic spines provide the majority of excitatory synapses in the CNS. Studies are underway to characterize the proteins involved. Together the data indicate that estrogen and progesterone increase serotonin production, increase excitatory synapses on serotonin neurons and prevent serotonin cell death. Understanding the mechanisms by which ovarian hormones act in serotonin neurons has opened new avenues for the development of selective estrogen receptor modulators that activate ER β . Like estrogen, these drugs will act beneficially in the brain, heart and bones, but they will not have estrogen's negative peripheral effects in the breast and uterus.

BIOGRAPHY

Cynthia Bethea is a scientist in the Division of Reproductive Sciences and an adjunct professor in the Departments of Physiology and Pharmacology, Behavioral Neuroscience and OB/GYN in the OHSU School of Medicine. After being awarded a B.S. from Winthrop University in 1972 and an M.S. in zoology at Clemson University in 1974, she earned her Ph.D. in physiology from Emory University in 1978. She conducted postdoctoral research in neuroendocrinology at the Reproductive Endocrinology Center of the University of California at San Francisco until she came to the center in 1981.

KEY PUBLICATIONS

Bethea CL, Reddy AP, Tokuyama Y, Henderson JA, Lima FB. 2009. Protective actions of ovarian steroids in the serotonin system of macaques. *Frontiers in neuroendocrinology* 30:212-238. PMID 19394356

Bethea CL, Reddy AP, Pedersen D, Tokuyama. 2009 Expression profile of differentiating serotonin neurons derived from rhesus embryonic stem cells and comparison to adult serotonin neurons. *Gene Expression Patterns* 9:94-108. PMID: 18996226

Bethea CL, Centeno ML, Cameron JL. 2008. Neurobiology of stress-induced reproductive dysfunction in macaques. *Mol Neurobiol* 38: 199-230. PMID: 18931961

Bethea CL, Lu NZ, Gundlah C, Striecher JM. 2002. Diverse actions of ovarian steroids in the serotonin neural system. *Frontiers in Neuroendocrinology* 23:41-100. PMID: 11906203

Current Grants and Contracts

R01 MH62677 Bethea (PI) 06/01/06-05/31/11

NIH/NIMH

Ovarian Steroid Regulation of Serotonin in Primates

Major goal: Determine the cellular and molecular actions of estrogen and progesterone in serotonin neurons of nonhuman primates.

Role: PI

R01 MH86542 Bethea (PI) 05/01/2010-04-30/2015

NIH/NIMH

Steroid Regulation of Serotonin in Males

Major goal: Determine the steroid receptor compliment of serotonin neurons in male monkeys. Manipulate activation of ER and AR and determine behavioral, cellular and molecular effects related to serotonin neural function.

Role: PI

R01 HD62618 Cameron (PI) 03/01/10-02/28/15

NIH/NICHD

Role of serotonin in mediating stress-induced infertility

Major goal: Continue studies to determine the mechanisms by which common life stresses impair activity of the reproductive axis and to perform a small pilot clinical study to determine if administration of a selective serotonin uptake inhibitor in women with Functional Hypothalamic Amenorrhea is able to restore menstrual cycles.

Role: Co-PI

Conn, Michael

Area(s) of Research/Scholarly Interest

Mechanism of hormone action; mechanism of rescue of mutant proteins by pharmacoperone drugs

Current Grants and Contracts

National Institutes of Health, NIDDK/NIGMS, "HTS for Pharmacoperones,"
R01 DK085040 04/01/10-03/31/13

National Institutes of Health, NCRR, "Mouse Models for Human Diseases of Protein Folding, June 4, 7-9th % (estimated by program officer, expected to be paid. Awaiting council review Oct 2010.

OTRADI Innovation and Commercialization Fund, State of Oregon "High-throughput screening for pharmacoperones: a new class of therapeutics". Advised of intent to fund.

Grants planned or in submission 2010

National Institutes of Health, NIGMS, "Structure and Trafficking of the GnRHR: Protein Processing in Health and Disease," submitted July, 2010

Key collaborators

Departmental

OHSU Dr. Anda Cornea, Dr. Sergio Ojeda

Extramural Dr. Alfredo Ulloa-Aguirre, Dr. Alfredo Leanos-Miranda, Dr. William Crowley, Dr.

Douglas Cyr, Dr. Raj Kumar

Most recent publications (last 5)

1. Janovick JA and Conn PM. (2010) Salt bridge integrates GPCR activation with protein trafficking. *Proc Nat Acad Sci.* 107(9):4454-8, 2010. (E⁹⁰K does not show constitutive activity in mouse GnRHR). PMID: 20160100
2. Zariñán T, Perez-Solís MA, Maya-Núñez G, Casas-Gonzales P, Conn PM, Dias, JA, Ulloa-Aguirre A. (2010) Dominant negative effects of human follicle-stimulating hormone receptor expression-deficient mutants on wild-type receptor cell surface expression. Rescue of oligomerization-dependent defective receptor expression by using cognate decoys. *Mol Cell Endocrinol.* 321: 112-122. PMID: 20206665
3. Ayala Yáñez, R and Conn PM. (2010) Protein disulfide isomerase chaperone ERP57 decreases plasma membrane expression of the human GnRH receptor. *Cell Biochem Funct.* 28(1):66-73. PMID: 20029959.
4. Conn PM and Ulloa-Aguirre A. (2010) Trafficking of G-protein-coupled receptors to the plasma membrane: insights for pharmacoperone drugs. *Trends Endocrinol Metab.* 21(3):190-197. PMID: 20005736
5. Re M, Pampillo M, Savard M, Dubue C, McArdle CA, Millar RP, Conn PM, Gobeil F Jr, Bhattacharya M, Babway AV. The human gonadotropin releasing hormone type I receptor is a functional intracellular GPCR expressed on the nuclear membrane. *PLOS1.* 2010. (in press)

AREA OF RESEARCH / SCHOLARLY INTEREST:

Peta L. Grigsby, PhD, heads the *Pregnancy and Perinatal Research Group* in the Division of Reproductive Sciences at the Oregon National Primate Research Center. Her current research focuses on the elucidation of the inflammatory pathways (endocrine-immune interactions) that cause preterm labor and associated fetal and neonatal injury (i.e., cerebral white matter damage and lung injury), and the development of new approaches to prevent prematurity and its consequences including, early diagnostic and targeted therapeutic strategies which would have a positive impact on fetal and neonatal health. Her independent research program has evolved through expanded interdisciplinary collaboration among clinician scientists with neonatal and pediatric specialties and basic scientists with expertise in microbiology, reproductive immunology, pathology and cardiovascular physiology. In this regard, Peta's field of research has been expanded from preterm labor studies to include studies of placental development and fetal growth.

This new research initiative, lead by Dr. Victoria Roberts (Staff Scientist, ONPRC) and in collaboration with Dr. Kent Thornburg (Director, Heart Research Center OHSU) seeks to understand the ability of the developing placenta to respond to an adverse *in utero* environment and to determine the mechanisms underlying placental plasticity which are at the root of the developmental origins phenomenon. This work is providing the essential groundwork for our future understanding of the mechanisms of programmed disease. A better understanding of placental plasticity will provide a basis for developing interventional strategies to improve vascular supply (i.e., increase umbilical flow) and/or placental function (i.e., nutrient transport) when placental insufficiency is clinically evident.

CURRENT GRANT SUPPORT:

ACTIVE

4 R00 HD055053-02
NIH/NICHD

Grigsby (PI)

06/01/2009 – 05/31/2012

Compartmental analysis of proteomic biomarkers during intra-uterine infections

The objectives of this research proposal are to characterize the mechanistic and temporal relationships among biomarker expression profiles (e.g., IGFBP-1 proteolytic fragments, calgranulin B and annexin II) in maternal and fetal compartments during defined stages of ascending infection with genital mycoplasmas (from choriodecidual to intra-amniotic models). It is our hypothesis that spatial and temporal characteristics of specific proteomic biomarkers in cervical vaginal fluid (CVF), amniotic fluid, maternal and fetal blood, will act as surrogates for the stage of progression of intra-uterine infection; similarly, changes in biomarker expression profiles during maternal therapeutic interventions (antibiotic and anti-inflammatory agents), will serve as prognostic indicators.

Role: Principal Investigator

P51RR00163-50 **Robertson (PI)** 05/01/2009 - 04/30/2014

NIH/NCRR

Support for National Primate Research Center

Role: Assistant Scientist (partial salary support)

Collins Medical Trust **Grigsby (PI)** 01/01/2010 – 12/31/2010

OHSU Foundation

Primate Model of Ureaplasma in utero Infection: Prevention of Neurologic Sequelae

The objectives of this research proposal are to delineate the extent of cerebral white matter inflammation and neuronal injury caused by genital mycoplasmas (*U. parvum*) and to assess the efficacy of maternal antibiotic *plus* anti-inflammatory therapy in ameliorating fetal brain inflammation. It is our hypothesis that prenatal treatment of *U. parvum* intra-amniotic infection (IAI) with specific antibiotics combined with appropriate anti-inflammatory agents will delay preterm delivery and mitigate fetal origins of neonatal cerebral white matter injury.

Role: Principal Investigator

Murdock Charitable Trust **Grigsby (PI)** 04/01/2010–03/31/2012

Non-Federal Foundation Grant

Characterization of Ureaplasma invasion of chorion and amnion epithelial cell layers in vitro

High School Teacher Mentorship

Role: Mentor

GRANTS PLANNED FOR SUBMISSION 2010:

Grigsby (PI)

R01

NIH/NICHD

06/01/2011 – 05/31/2016

Fetal Inflammatory Response Syndrome: Role of Ureaplasmas

The objectives of this proposal are to elucidate the pathophysiologic mechanisms of intra-amniotic infection and the fetal inflammatory response syndrome, and to characterize fetal hemodynamic adaptations which portend cerebral white matter damage, pulmonary injury and histologic chorioamnionitis and which may be ameliorated by novel interventional strategies.

Role: Principal Investigator

Grigsby (PI)

R21

NCRR/NIH/NICHD

06/01/2011 – 05/31/2013

Primate Model of Ureaplasma Intra-amniotic Infection: Prevention of Neurologic Sequelae

The objectives of this research proposal are to define the cellular consequences and extent of cerebral white matter inflammation and neuronal injury caused by *U. parvum* intra-amniotic

infection and to assess the efficacy and safety of maternal azithromycin therapy to prevent neurologic damage in the fetus and adverse neurobehavioral consequences in the infant.

Role: Principal Investigator

KEY SCIENTIFIC COLLABORATORS:

ACTIVE

(2009-present) **Robert L. Schelonka, M.D.**

Associate Professor of Pediatrics, Division Head Neonatology

Oregon Health & Science University, Portland OR, USA

(2009-present) **Cindy McEvoy, M.D.**

Associate Professor of Pediatrics (Neonatology), Oregon Health & Science University, Portland OR, USA

(2009-present) **Terry K. Morgan, M.D., Ph.D.**

Assistant Professor of Pathology, Director of Cytopathology and Placental Pathology Heart Research Ctr Scientist, Oregon Health & Science University, Portland OR, USA

(2009-present) **Leonardo Pereira, M.D.**

Assistant Professor of Obstetrics and Gynecology, Division Head Maternal Fetal Medicine, Oregon Health & Science University, Portland, OR, USA

(2008-present) **Juha Räsänen M.D., Ph.D.**

Associate Professor of Obstetrics and Gynecology, Maternal Fetal Medicine, Oregon Health & Science University, Portland, OR, USA

(2009-present) **Antonio Frias, M.D.**

Assistant Professor of Obstetrics and Gynecology, Maternal Fetal Medicine, Oregon Health & Science University, Portland, OR, USA

(2008-present) **Ken B. Waites, M.D., F.A.A.M.**

Professor of Pathology, Director of Clinical Microbiology, Department of Pathology, University of Alabama at Birmingham, AL, USA

(2008-present) **Rose M. Viscardi, M.D.**

Associate Professor of Pediatrics, Division of Neonatal-Perinatal Medicine, University of Maryland School of Medicine, Baltimore, MD, USA

(2009-present) **Turhan Coksaygan, DVM., Ph.D.**

Assistant Professor of Pathology, University of Maryland School of Medicine, Baltimore, MD, USA

(2007-present) **Kent Thornburg, Ph.D.**

Director, Heart Research Center (OHSU)

Professor of Cardiology, M. Lowell Edwards Chair of Research in Clinical Cardiology, Oregon Health & Sciences University, Portland OR, USA

PEER-REVIEWED PUBLICATIONS: (MOST RECENT 6)

1. **Grigsby PL**, Sooranna SR, Adu-Amankwa B, Pitzer B, Brockman DE, Johnson MR and Myatt L (2006). Regional expression of prostaglandin E₂ and F_{2α} receptors in human myometrium, amnion and choriondecidua with advancing gestation and labor. *Biology of Reproduction*; **75**(2): 297-305. (Article Citations, 12)
 2. Sooranna SR, **Grigsby PL**, Engineer N, Liang Z, K Sun, Myatt L, and Johnson MR (2006). Myometrial prostaglandin E₂ synthetic enzyme mRNA expression: spatial and temporal variations with pregnancy and labour. *Mol Hum Reproduction*; **12**(10): 625-31. (Article Cit, 7)
 3. Tattersall M, Engineer N, Khanbani S, Sooranna SR, Roberts V, **Grigsby P**, Liang Z, Myatt L and Johnson M (2008). Prolabour myometrial gene expression: are preterm labour and term labour the same? *Reproduction* **135**(4):569-79. (Article Citations, 2)
 4. Waites KB, Schelonka RL, Xiao L, **Grigsby P** and Novy MJ (2009). Congenital and opportunistic Infections: Ureaplasma species and Mycoplasma hominis *Seminars in Fetal and Neonatal Medicine*; 14:190-199
 5. **Grigsby PL**, Novy MJ, Adams K, Sadowsky DW and Gravett MG (2010). Choriondecidual inflammation: A Harbinger of the Preterm Labor Syndrome. *Reproductive Sciences* 17(1): 85-94. PMID: 19843879.
 6. Hinton AC, **Grigsby PL**, Pitzer BA, Brockman DE, Ittenbach RF, Hinton RB and Myatt L (2010). Hormonal Regulation of Prostaglandin E₂ Receptors: Localization and Expression in Rat Cervical Tissue. *Reproductive Sciences* 17(2): 136-146. PMID: 19801535
- Grigsby PL**, Novy MJ, Sadowsky DW, Long M, Morgan T, Acosta E and Waites KB (2010). Azithromycin and anti-inflammatory therapy for intra-amniotic infection with *Ureaplasma parvum* in a non-human primate model. *American Journal of Obstetrics and Gynecology* – Editor's Choice **(In Final Preparation)**

Hennebold, Jon

Area(s) of Research/Scholarly Interest

My laboratory has been systematically characterizing the entire rhesus macaque transcriptome in the ovulatory follicle, through the initiation of events necessary for ovulation up to the time of follicle rupture, as well as in the corpus luteum during its development, peak function (i.e., period of maximal progesterone synthesis), and regression in nonfertile cycles. Moreover, using a gonadotropin/steroid ablation and replacement approach, my collaborators and I have been able to define which genes are directly regulated by luteotropic gonadotropins and/or steroid hormones. Through such an approach, several novel or previously underappreciated pathways/processes have been discovered, many of which presently serve as the basis for our ongoing research projects.

Contraceptive Research and Development

Proteases as Targets for the Development of Novel Contraceptives: As part of a Contraceptive Development and Research Center (CDRC) grant, one project aims to determine the contraceptive potential of manipulating the individual molecular components that allow for ovulation and cumulus-oocyte expansion. One particular focus includes the systematic identification of protease-encoding genes that are upregulated following the ovulatory gonadotropin surge. It is well known that protease activity increases in the preovulatory follicle following the midcycle surge of luteinizing hormone, which in turn allows for the breakdown of adjacent extracellular matrix components, release of the oocyte, and fertilization. The exact number of protease encoding genes that are upregulated and the extent of their induction in the primate preovulatory follicle were poorly defined prior to the initiation of this study. Therefore, the identification of those proteases genes that increase in expression at different times after the administration of an ovulatory stimulus was accomplished by DNA microarray analysis of individual follicles obtained from rhesus macaques undergoing a controlled ovulation protocol. The resultant data revealed that the majority of the upregulated protease genes belong to the metalloproteinase superfamily and, specifically, matrix metalloproteinase (i.e., MMP1, 9, 10, and 19) and a disintegrin and metalloproteinase with thrombospondin-like repeats (i.e., ADAMTS1, 5, and 15) subfamilies. To define the functional significance of the ovarian MMP and ADAMTS family members in primate ovulation, a broad-spectrum metalloproteinase inhibitor (GM6001/Ilomastat) was injected into the follicle of rhesus macaques at the time that they received an ovulatory stimulus. The results of these studies demonstrated that intrafollicular injection of GM6001 blocks follicle rupture. Despite preventing oocyte release, metalloproteinase inhibition had no effect on subsequent luteal function and lifespan. These studies support the hypothesis that agents capable of blocking follicle rupture will serve as effective non-hormonal targets for contraception without altering other aspects of female reproduction, including ovarian/menstrual cyclicity.

Inhibiting Fertilization by Blocking Cumulus-Oocyte Expansion: Another objective of the aforementioned CDRC grant also includes determining if blocking the synthesis or action of oocyte- and granulosa/cumulus-derived proteins that control the expansion of the cumulus-oocyte complex (C-OE) will prevent timely oocyte release and fertilization. As determined by DNA microarray and subsequently validated by quantitative real-time PCR, mRNA levels for several genes encoding proteins involved in C-OE in nonprimate species also changed in accordance with the observed time of C-OE in the macaque follicle in vivo (which occurs between 12 and 24 hrs after an ovulatory stimulus), including those involved in prostaglandin (PG) E₂ synthesis (e.g., PG-endoperoxide synthase-2, PTGS2; PGE synthase, PTGES) and signaling (e.g., PGE₂ receptor subtypes 1-4, PTGER1-4). These findings are consistent with data obtained from rodent models, wherein inhibition of PG synthesis or PGE₂ receptor signaling blocks C-OE and consequently the ability of sperm to fertilize the oocyte. Collectively,

our results support further studies to examine the effectiveness and reversibility of inhibitors of the PG synthesis and signaling system as nonhormonal contraceptives.

Infertility and Ovarian Pathology:

Determining the Role of Prostaglandins as Critical Mediators of Luteal Formation and Regression: Our recently completed genomic studies were conducted with the goal of providing an in depth characterization of those genes that change in expression within the corpus luteum throughout the luteal phase, which includes the period of luteal formation, function, and luteolysis. From such studies, it was discovered that genes involved in the synthesis, metabolism, and response to PGs are dynamically regulated in the primate corpus luteum through the luteal phase. Since PGs are potent bioactive lipids capable of regulating numerous cellular activities, these results suggest that they may also be critical for different aspects of luteal physiology. Our recent studies revealed a limited capacity for rhesus macaques to form a functional corpus luteum following the direct intraluteal delivery of a selective inhibitor of PTGS2, the enzyme that catalyzes the rate-limiting step of PG synthesis. These results demonstrate for the first time that PG synthesis is necessary for the development and function of the primate corpus luteum, which is critical for implantation and the maintenance of pregnancy if fertilization occurs.

Liver X Receptor Regulation of Luteal Regression: Further evaluation of the rhesus macaque transcriptome through the luteal phase revealed that those genes encoding proteins involved in maintaining an adequate supply of cholesterol, the substrate for progesterone (as well as other steroids), are dynamically regulated through the period of luteal regression. Specifically, increased levels of mRNAs encoding proteins that actively transport intracellular stores of cholesterol to extracellular acceptor proteins (e.g., ATP binding cassette transporters A1 and G1; or ABCA1 and ABCG1, respectively) were observed in the steroidogenic cells of the macaque corpus luteum during the period of functional regression. The removal of cellular cholesterol is a process termed reverse cholesterol transport, which is regulated through the action of the nuclear receptor superfamily members liver X receptors (LXR) α and β . Subsequent studies conducted in the laboratory have demonstrated that there is an upregulation of LXR α expression that parallels the induction of reverse cholesterol transport genes in the macaque corpus luteum. Moreover, direct exposure of rhesus monkey luteal cells to LXR agonists in vitro resulted in diminished cholesterol uptake, increased cholesterol efflux, and reduced steroidogenic potential. Published studies to date regarding the action of LXR in the induction of the reverse cholesterol transport system have focused solely on the role of this process in limiting the toxic effects of cholesterol on cells. Our findings, however, suggest a novel role for LXR and the reverse cholesterol transport system in the primate corpus luteum, whereby cholesterol is rapidly depleted from the steroidogenic cells to facilitate luteal regression.

Proteomic Assessment of Normal and Abnormal Follicle Development: Through a pilot project included in an NICHD Specialized Cooperative Center in Reproduction and Infertility Research (SCCPIR) grant (P.I., R.L. Stouffer), my laboratory used a proteomics approach to systematically characterize the ovulatory follicle proteome and to identify proteins whose levels change through the periovulatory interval in rhesus monkeys and in abnormal preovulatory follicle development in women. To accomplish the goals of the former, follicular fluid was collected from the single, naturally-selected rhesus monkey follicle prior to (0h) and at specific times after (12 and 36h) the administration of an ovulatory stimulus (e.g., hCG). Individual proteins were identified through the use of an electron spray ionization-mass spectrometer (ESI-MS/MS). The resultant proteins identified were found to be very similar to those listed within the human plasma proteome database. To accomplish the goal of the latter aim, follicular fluid was collected from women seeking infertility treatment for a male factor or those donating oocytes

(controls), as well as from women undergoing infertility treatments due to polycystic ovary syndrome (PCOS). While the endocrine abnormalities that often occur in PCOS patients have received considerable attention, (i.e., hyperandrogenism, excessive luteinizing hormone production by the pituitary), the effects of this syndrome on developing ovulatory follicles is not clear. Thus, differences in the abundance of individual proteins between in the control and PCOS follicular fluid proteome were identified by two different methodologies. One approach included the use of 2-dimensional electrophoresis to identify proteins with varying levels in control and PCOS follicular fluid, with their identity subsequently being determined by ESI-MS/MS. These studies were performed in collaboration with the SCCPIR proteomics core facility located at the University of North Carolina at Chapel Hill. The second approach involved the expertise and resources of Proteogenix, a biotechnology company that uses proteomic approaches to identify novel diagnostic markers of disease, including intra-amniotic infection and preterm labor (Co-founded by Dr. Charles Roberts, Associate Director, ONPRC). Through these complementary approaches, a number of unique proteins involved in immune function were identified that are either over- or under-expressed in the follicular fluid from PCOS follicles versus control follicles. Collectively, these studies may prove valuable in understanding the etiology of PCOS and/or yielding new diagnostic markers of abnormal follicle development.

Current Grants and Contracts

- 2007-2012 NICHD U54 HD055744, Contraception by Blockade of Periovulatory Events. Project II: Control of Follicular Maturation and Rupture. Co-Investigator.
2009-2011 NICHD R01 HD42000-6. Prostaglandin Synthesis and Action in the Primate Corpus Luteum. Principal Investigator.

Grants planned or in submission 2010

- Pending NICHD U54 HD018185, Cooperative Research on Infertility in Primates. Project I: Epidermal Growth Factor Family Members as Critical Mediators of Primate Oocyte Maturation. Co-Principal Investigator with Dr. Marco Conti, UCSF.

Key collaborators

OHSU: OB/GYN & ONPRC:

Dr. Richard Stouffer, Dr. Mary Zelinski, Dr. Shoukhrat Mitalipov, Dr. Alison Edelman, Dr. Jeffrey Jensen, Dr. Paula Amato

External: Dr. Marco Conti, UCSF; Dr. Musa Zamah, UCSF

Most recent publications (last 5)

H. Sritanaudomchai, M. Sparman, M. Tachibana, L. Clepper, J. Woodward, S. Gokhale, D. Wolf, **J.D. Hennebold**, W.B. Hurlbut, M. Grompe, S. Mitalipov. CDX2 in the formation of the trophectoderm lineage in primate embryos. *Developmental Biology* 335:179-187, 2009.

R.L. Bogan, **J.D. Hennebold**. The reverse cholesterol transport system as a potential mediator of luteolysis in the primate corpus luteum. *Reproduction* 139:163-176, 2010.

A.B. Edelman, J.T. Jensen, **J.D. Hennebold**. A non-hormonal model for emergency contraception: Prostaglandin synthesis inhibitor effects on luteal function and lifespan, a pilot study. *Contraception* 81:496-500 2010.

H. Sritanaudomchai, H. Ma, L. Clepper, S. Gokhale, R.L. Bogan, **J.D. Hennebold**, D. Wolf, S. Mitalipov. Discovery of novel imprinted genes by transcriptional analysis of primate parthenogenetic embryonic stem cells. *Human Reproduction* Accepted, 5/2010.

M.C. Peluffo, S.L. Barrett, R.L. Stouffer, **J.D. Hennebold**, M.B. Zelinski. Cumulus-oocyte complexes from small antral follicles during the early follicular phase of menstrual cycles in rhesus monkeys yield oocytes that reinitiate meiosis and fertilize in vitro. *Biology of Reproduction* Accepted, 5/2010.

Mitalipov, Shoukhrat**Area(s) of Research/Scholarly Interest:**

Early embryonic development, Pluripotent stem cells, Reprogramming, Gene therapy, Assisted Reproductive Technologies

Current Grants and Contracts:

1 R01 3057604 Mitalipov (PI) 4/1/10-3/31/15
NIH/NICHD
Mitochondrial Gene Therapy

1 R01 3057604 Mitalipov (PI) 2/1/10 – 1/31/15
NIH/NICHD
Altered Nuclear Transfer

1R01HD057121-01A2 Mitalipov (PI) 8/15/09 – 6/30/14
NIH/NICHD
Histocompatible Primate Embryonic Stem Cells

Deriving oocytes from ES cells Mitalipov (PI) 5/1/09- 4/30/11
NIH/NCRR (Pilot Project)

Correcting mitochondrial gene mutations in human oocytes Mitalipov (PI) 7/1/10 - 6/30/11
The Center for Women's Health Circle of Giving

Grants planned or in submission 2010:

P01 HD047675 Schatten (PI) 2/1/10 – 11/30/15
NIH/NICHD
Pluripotent Stem Cells in Development and Disease
Role: PI for Project I

Key collaborators

Departmental: Richard Stouffer, Jon Hennebold, Betsy Ferguson
OHSU: Paula Amato, David Battaglia, David Koeler, Markus Grompe
Extramural: too many to list.

Most recent publications (last 5)

1. Hathaitip Sritanaudomchai, Hong Ma, Vikas Dighe, Lisa Clepper, Sumita Gokhale, Randy Bogan, Jon Hennebold, Don Wolf & Shoukhrat Mitalipov. Discovery of a novel imprinted gene by transcriptional analysis of primate parthenogenetic embryonic stem. Hum Reprod. 2010 Jun 3. [Epub ahead of print]
2. Masahito Tachibana, Michelle Sparman & Shoukhrat Mitalipov. Chromosome transfer in mature oocytes. Nature Protocols. 2010;5(6):1138-47.

3. Blin G, Nury D, Stefanovic S, Neri T, Guillevic O, Brinon B, Bellamy V, Rücker-Martin C, Barbry P, Bel A, Bruneval P, Cowan C, Pouly J, Mitalipov S, Gouadon E, Binder P, Hagège A, Desnos M, Renaud JF, Menasché P, Pucéat M. A purified population of multipotent cardiovascular progenitors derived from primate pluripotent stem cells engrafts in postmyocardial infarcted nonhuman primates. *J Clin Invest*. 2010 Apr;120(4):1125-39 PMID: 20335662
4. Sritanaudomchai H, Sparman M, Tachibana M, Clepper L, Woodward J, Gokhale S, Wolf D, Hennebold J, Hurlbut W, Grompe M, Mitalipov S. CDX2 in the Formation of the Trophectoderm Lineage in Primate Embryos. *Dev Biol*. 2009. 335. 179–187. PMID: 19733166
5. Masahito Tachibana, Michelle Sparman, Hathaitip Sritanaudomchai, Hong Ma, Lisa Clepper, Joy Woodward, Ying Li, Cathy Ramsey, Olena Kolotushkina & Shoukhrat Mitalipov. Mitochondrial gene replacement in primate offspring and embryonic stem cells. *Nature*. 2009 Sep 17;461(7262):367-72. Epub 2009 Aug 26. PMID: 19710649

Slayden, Ov

Area(s) of Research/Scholarly Interest

Female reproductive tract physiology; Steroid hormone action in the female reproductive tract; Reproductive tract disorders including endometriosis, breakthrough uterine bleeding, and uterine fibroids.

Current Grants and Contracts

R01 U54 HD 055744-01 NIH

03/31/07-02/29/12

Contraception by Blockade Periovalutary: Project 3—Control of Gamete Transport and Fertilization

The goal of this project is to investigate a novel strategy for female contraception that utilizes a new class of drugs, the Selective Estrogen Receptor Modulators (SERMs).

Role: Co-PI

Bayer Schering Pharma AG, Germany

08/31/06-12/31/11

Preclinical Studies on NHP Endometrial Xenografts

The goal of this study is to assess the action of estrogen receptor beta agonists in ectopic rhesus macaque and human endometrium in immunodeficient mice.

Role: PI

Bayer Schering Pharma AG, Germany

06/01/07-5/01/11

Preclinical Studies on Human Leiomyoma in Immunodeficient Mice

The goal of this study was to develop a new model for studies of uterine fibroids where human fibroid explants are engrafted into immunodeficient.

Role: PI

Astra Zeneca

07/01/09-7/31/11

Suppression of menstrual bleeding in rhesus macaques with chemokine inhibitors.

We are testing two proprietary compounds that specifically block the receptors for IL8 and MCP-1 and that could provide a therapy for excessive menstrual bleeding.

Role: PI

Bayer Schering Pharma AG, Germany

07/01/09-7/31/11

Effect of novel androgens on ectopic endometrium in rhesus macaques.

Our goal is to investigate new androgen-based therapies for endometriosis.

Role: PI

Grants planned or in submission 2010

New R01 (October 5 2010)

Blockade of growth and progression of endometriosis in rhesus macaques.

Our goal is to assess the effect of selective PGE2 receptor inhibitors on growth, progression and associated pain of endometriosis in rhesus macaques.

Key collaborators

Departmental Richard Stouffer; Mary Zelenski,

OHSU: Jeffrey Jensen, Philip Patton, Alison Edelman

Extramural

Joe Arosh Assistant Professor of Veterinary Integrative Biosciences and Veterinary Medicine Texas A&M University

Hilary Critchley Professor of Reproductive Medicine, Centre for Reproductive Biology University of Edinburgh Scotland)

Karl Heiner Fritzmeier ; Bayer Schering Pharma Berlin

Regine Sitruk-Ware MD Distinguished Scientist Population Council, Rockefeller University

Most recent publications (last 5)

Brenner RM, Slayden OD, Nath A, Tsong YY, Sitruk-Ware R. Intrauterine administration of CDB-2914 (Ulipristal) suppresses the endometrium of rhesus macaques. *Contraception*. 2010 Apr;81(4):336-42. PubMed PMID:20227552

Keator CS, Custer EE, Hoagland TA, Schreiber DT, Mah K, Lawson AM, Slayden OD, McCracken JA. Evidence for a potential role of neuropeptide Y in ovine corpus luteum function. *Domest Anim Endocrinol*. 2010 Feb;38(2):103-14. PubMed PMID: 19782503.

Bazer FW, Slayden OD. Progesterone-induced gene expression in uterine epithelia: a myth perpetuated by conventional wisdom. *Biol Reprod*. 2008 Nov;79(5):1008-9. PubMed PMID: 18953018.

Fensome A, Adams WR, Adams AL, Berrodin TJ, Cohen J, Huselton C, Illenberger A, Kern JC, Hudak VA, Marella MA, Melenski EG, McComas CC, Mugford CA, Slayden OD, Yudit M, Zhang Z, Zhang P, Zhu Y, Winneker RC, Wrobel JE. Design, synthesis, and SAR of new pyrrole-oxindole progesterone receptor modulators leading to 5-(7-fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrrole-2-carbonitrile (WAY-255348). *J Med Chem*. 2008 Mar 27;51(6):1861-73. PubMed PMID: 18318463.

Maginnis G, Wilk J, Carroll R, Slayden OD. Assessment of progestin-only therapy for endometriosis in macaque. *J Med Primatol*. 2008 Feb;37 Suppl 1:52-5. PubMed PMID: 18269529.

Stouffer, Richard

Areas of Interest

Area(s) of Research/Scholarly Interest

Female Reproductive Endocrinology, with emphasis on the regulation and function of the ovulatory follicle and corpus luteum in primates. Nonhuman primate model for in vitro fertilization and embryo transfer. Novel approaches to treating infertility and providing contraception

Current Grants and Contracts

R01 HD20869 Stouffer (PI)

3/1/06 - 2/28/11

NIH/NICHD

Progesterone Receptors and Action in the Primate Ovary

The goals of this project are to investigate the regulation of progesterone receptor mRNAs and proteins in the macaque corpus luteum and to examine the local role(s) of progesterone in luteal development in the periovulatory interval, in maintenance of luteal structure-function during the menstrual cycle, and in rescue of the corpus luteum during early pregnancy.

Role: PI

U54 HD18185 Stouffer (PI)

4/1/04 -3/31/11 (Bridge Funding 4/09-3/11)

NIH/NICHD

Center in Reproduction Research. Cooperative Research on Infertility in Primates

The goal of this Specialized Cooperative Center is to address the causes and cures of human infertility disorders as they relate to neural, gonadal and gamete deficits. Project III, entitled “Angiogenic and Angiolytic Factors in Natural and Controlled Ovarian Stimulation (COS) Cycles”, will test the hypothesis that methods used to generate multiple follicles/corpora lutea during ART cycles in rhesus monkeys and women lead to an exaggeration or aberration in ovarian production of vascular endothelial-specific substances that could cause ovarian hyperstimulation syndrome (OHSS). Project IV, entitled “Androgen Exposure in Female Prepubertal Monkeys: Relevance to PCOS?” tests the hypothesis that exposure of normal prepubertal female macaques to elevated levels of testosterone, observed in polycystic ovarian syndrome, will cause changes in the neuroendocrine-ovarian axis associated with this disease (PCOS). Subcontracts: University of CA-San Diego SCCPIR (**HD 012303**) entitled “Prepubertal exposure to testosterone in prepubertal monkeys”, and Univ of VA SCCPIR (**HD028934**), same title, for collaboration on Project IV.

Role: Center, PI; Project III, PI; Project IV, Co-PI; Admin Core, PI; Subcontracts PI

U54 HD055744 Stouffer/Jensen (Center Co-PIs)

3/1/07 - 2/28/12

NIH/NICHD

Contraceptive Development & Research Center: Contraception by Blockade of Periovulatory Events in Primates

The goal of this U54 Center is to target the discovery and development of novel contraceptive agents that prevent one or more periovulatory events in adult, female primates during the menstrual cycle. Project II: “Control of Ovulation” will identify factors controlling cumulus-oocyte expansion and follicle rupture and whether their antagonists prevent egg release and fertility.

Includes ARRA Supplement (9/1/09-8/31/11) to accelerate research in the CDRC.

Role: Center Co-PI; Project II Co-PI

U54 Roadmap RR024347 Woodruff (PI)

9/1/07 - 8/31/12

The Oncofertility Consortium: Fertility Preservation in Women

NIH/NCRR/NICHD

RO1 HD058294 Stouffer (PI)

Bioengineering Primate Follicles: From Immature Eggs to Live Births

As part of the Oncofertility Consortium: Fertility Preservation in Women, translational studies will be performed in nonhuman primates to develop methods for (a) in vitro growth and maturation of primate antral follicles in a 3-D architecture that allows coordinated follicle cell-oocyte development, (b) in vivo follicle growth and oocyte maturation following ovarian autotransplantation, and (c) assessment of the fertilization and embryonic potential of oocytes derived as described above.

Role: PI of RO1

R01 HD050356 Wright (PI)

11/1/09 – 11/30/11

NIH/NICHD

Biology of the Primate Ovarian Surface Epithelium

The major goal of this project is to determine structural and dynamic characteristics of this cellular monolayer, which surrounds the ovary, during the normal reproductive cycle. Experiments are designed to examine the response of the OSE to changes in ovarian physiology and the effects of steroid products generated by dominant ovarian structures. Specific goals will determine the role of progesterone and estrogen on OSE cell cycle progression, arrest, and apoptotic potential.

Role: Co-Investigator

R01 HD42000 Hennebold (PI)

7/27/09 - 6/30/11

NIH/NICHD

Prostaglandin Synthesis and Action in the Primate Corpus Luteum

The major goal of this project will be to understand the role of prostaglandin-E₂ in macaque luteal development and function, as well as the role of prostaglandin-F_{2α} in its regression during non-fertile cycles.

Role: Co-Investigator

P51 RR00163 Robertson (PI)

5/1/09 - 4/30/14

NIH/NCRR

Support for Oregon Regional Primate Research Center

Role: Senior Scientist and Head, Division of Reproductive Sciences

Grants planned or in submission 2010

SCCPIR (HD18185) Center – competitive renewal, in review, 2011 – 2016

R01 HD20869 – competitive renewal, 2011- 2016

Key collaborators

Departmental - Drs. Jeffrey Jensen, Phillip Patton, David Lee, David Battaglia, Alison Edelman, Tanja Pejovic.

OHSU – ONPRC: Drs. Jon Hennebold, Mary Zelinski, Jay Wright

Extramural – Dr. T. Woodruff, Northwestern; Dr. J. Chang, UCSD

Most recent publications (last 5)

Xu M, West-Farrell ER, Stouffer RL, Shea LD, Woodruff TK, Zelinski MB. Encapsulated three-dimensional culture supports development of nonhuman primate secondary follicles. *Biol Reprod*, 81:587-94. Epub 2009. PMID: 19474063

Edelman AB, Carlson NE, Cherala G, Munar MY, Stouffer RL, Cameron JL, Stanczyk FZ, Jensen JT. Impact of obesity on oral contraceptive pharmacokinetics and hypothalamic-pituitary-ovarian activity. *Contraception*, 80:119-27. Epub 2009. PMID: 19631786, PMCID: PMC2736633.

Xu F, Stouffer RL. Existence of the lymphatic system in the primate corpus luteum. *Lymph Res Biol*, 7:159-168, 2009. PMID: 19778204

Wright JW, Pejovic T, Lawson M, Jurevic L, Hobbs T, Stouffer, RL. Ovulation in the Absence of the Ovarian Surface Epithelium in the Primate. *Biol Reprod*, 82:599-605, 2010. PMID: 19923253

Jensen JT, Stouffer RL, Stanley JE, Zelinski MB. Evaluation of the phosphodiesterase 3 inhibitor ORG 9935 as a contraceptive in female macaques: initial trials. *Contraception*. 81:165-71, 2010. PMID: 20103457; PMCID: PMC2813210.

Selected Peer-reviewed Publications (2005-present)

Xu J, **Stouffer RL**, Searles RP, Hennebold JD. Discovery of LH-regulated genes in the primate corpus luteum. *Mol Hum Reprod* 11(3):151-9. Epub 2005. PMID: 15723857

Xu J, Xu F, Hennebold JD, Molskness TA, **Stouffer RL**. Expression and role of the CRH/urocortin-receptor-binding protein (CRH/UCN-R-BP) system in the primate corpus luteum during the menstrual cycle. *Endocrinology* 148:5385-5395, 2007. PMID: 17690

Bogan RL, Murphy MJ, **Stouffer RL**, Hennebold JD. Systematic determination of differential gene expression in the primate corpus luteum during the luteal phase of the menstrual cycle. *Mol Endocrinol* 22:1260-1273, 2008. PMID: 18258683

Peluffo MC, Young KA, Hennebold JD, **Stouffer RL**. Expression and regulation of tumor necrosis factor (TNF) and TNF-receptor family members in the macaque corpus luteum during the menstrual cycle. *Mol Reprod Dev*, 76:367-378, 2008. PMID: 18932199

Bishop CV, Hennebold JD, **Stouffer RL**. The effects of luteinizing hormone ablation/ replacement versus steroid ablation/ replacement on gene expression in the primate corpus luteum. *Molec Hum Reprod*, 15:181-193, 2009. PMID: 19168862

Additional recent publications of importance to the field (in chronological order)

Xu F, **Stouffer RL**. Local delivery of angiopoietin-2 into the preovulatory follicle terminates the menstrual cycle in rhesus monkeys. *Biol Reprod* 72:1352-1358, 2005. PMID: 15703373

Wright JW, **Stouffer RL**, Rodland KD. High dose estrogen and clinical SERMs induce growth arrest, p21 and p53 in primate ovarian surface epithelial cells. *J Clin Endocrinol Metab* 90:3688-3695, 2005. PMID: 15755852

Tesone M, **Stouffer RL**, Borman SM, Hennebold JD, Molskness TA. Vascular endothelial growth factor (VEGF) production by the monkey corpus luteum during the menstrual cycle: Isoform-selective messenger RNA expression in vivo and hypoxia-regulated protein secretion in vitro. *Biol Reprod* 73:927-934, 2005. PMID: 15987827

Stanek MB, Borman SM, Molskness TA, Larson JM, **Stouffer RL**, Patton PE. Insulin and IGF stimulation of VEGF production in luteinized granulosa cells: comparison between PCOS and non-PCOS women. *J Clin Endocrinol Metab* 92:2726-2733, 2007. PMID: 17488794

Wright JW, Pejovic T, Fanton J, **Stouffer RL**. Induction of proliferation in the primate ovarian surface epithelium in vivo. *Hum Reprod* 23:129-138, 2008. PMID: 18000169

Bogan RL, Murphy MJ, **Stouffer RL**, Hennebold JD. Prostaglandin synthesis, metabolism, and signaling potential in the rhesus macaque corpus luteum throughout the luteal phase of the menstrual cycle. *Endocrinology*, 149:5861-5871, 2008. PMID: 18635657

Bishop CV, Sparman ML, Stanley JE, Bahar A, Zelinski MB, **Stouffer RL**. Evaluation of antral follicle growth in the macaque ovary during the menstrual cycle and controlled ovarian stimulation by high-resolution ultrasonography. *Am J Primatol*, 71:1-11, 2009. PMID: 19189308

Xu M, West-Farrell ER, **Stouffer RL**, Shea LD, Woodruff TK, Zelinski MB. Encapsulated three-dimensional culture supports development of nonhuman primate secondary follicles. *Biol Reprod*, Sep;81(3):587-94. Epub 2009. PMID: 19474063

Xu F, **Stouffer RL**. Existence of the lymphatic system in the primate corpus luteum. *Lymph Res Biol*, 7:159-168, 2009. PMID: 19778204

Wright JW, Pejovic T, Lawson M, Jurevic L, Hobbs T, **Stouffer, RL**. Ovulation in the Absence of the Ovarian Surface Epithelium in the Primate. *Biol Reprod*, Epub 2009. PMID: 19923253

Personal Statement

My career has been devoted to understanding the structure, function and regulation of the ovary, with emphasis on studies using the nonhuman primate as a “translational model” for applications to normal ovarian function and ovarian disorders in women. Since my graduate training, I have combined whole animal and cellular studies to unravel the mechanisms controlling follicle maturation and ovulation, and the development, function and regression of the corpus luteum, during the ovarian cycle. My current R01 grant has been active since 1980, first at the University of Arizona and then at the Oregon National Primate Research Center (under the current HD 20869), and provided valuable knowledge on the mechanisms and actions of gonadotropins (LH/CG) and local factors (notably the steroid progesterone) in controlling key events for normal ovarian cyclicity (i.e., ovulation, luteal development and luteolysis). Since joining the ONPRC scientific staff, I’ve included molecular approaches in these studies, particularly in collaboration with Drs. R. Brenner and O. Slayden to analyze progesterone receptors, and Dr. J. Hennebold to perform genome-wide analyses of changes in gene activity in the primate follicle and corpus luteum, and their regulation by gonadotropins and steroids. Dr. Hennebold also has training in immunology and, as Co-I on this grant; he will provide valuable expertise in completion of the new proposed aims. In my capacities as Head, Division of Reproductive Sciences, ONPRC, and current Director (or Co-Director) of NICHD-funded cooperative research centers in infertility (U54 SCCPIRR HD18185) and contraception (U54 CDRC HD55744), I have a broad perspective of the ongoing national and international efforts to promote women’s reproductive health, and the value of combined systems, cellular and molecular studies in nonhuman primates to address critical issues related to overcoming infertility, as well as control of fertility. The ONPRC considers use of nonhuman primates for studies of reproductive health as one of its key missions; hence I am in a unique site with resources to perform such projects.

Wright, Jay

Areas of research interest:

Our research focus is on the normal biology of the ovarian surface epithelium, in the context of ovarian cancer etiology and the development of novel methods of early detection and prevention of epithelial ovarian cancer.

Epithelial ovarian cancer (EOC) originates primarily in the ovarian surface epithelium, is difficult to detect prior to Stage III, and is currently preventable only through surgical elimination of the ovary and neighboring fallopian tube (a site of origin of some tumors diagnosed as EOC). No animal model is available for naturally occurring EOC, and this disease has only been reported in women, nonhuman primates and hens. We have selected the rhesus monkey as a model system to investigate the normal biology of the ovarian surface epithelium and the fimbrial epithelium, due to similarities to women in regards to ovarian and reproductive physiology. We are investigating the effects of the natural menstrual cycle, age and sex steroids on these cells *in vivo*.

Collaborative efforts are expanding studies to include women and the effects of age, menopause, ovarian function and genetics on EOC etiology and risk.

Current grants:

R01 HD050356-01 Wright (PI)
NIH/NICHD

11/01/06-10/30/11

Biology of the Primate Ovarian Surface Epithelium

The goals of this project are to characterize protein expression in the normal primate ovarian surface epithelium during the natural menstrual cycle, to determine whether ovarian products (estrogen and progesterone) regulate the epithelium, and to determine whether the epithelium is necessary for ovarian function. The significance of the ovarian surface epithelium is poorly understood, although it gives rise to the vast majority of ovarian cancers in women. Developing our understanding of normal ovarian surface epithelial biology may be critical in formulating strategies for prevention, detection, and treatment of ovarian cancer.

OHSU Foundation Wright (Co-PI)
3/31/11

4/1/09-

Novel Strategies for Ovarian Cancer Prevention

The nonhuman primate is an ideal model to study ovarian cancer etiology, due to the absence in most laboratory or domestic animals of the most common ovarian cancer that occurs in women (epithelial). The rhesus monkey is a model system we are utilizing for pre-clinical studies into ovarian cancer prevention and early detection. This award supports ongoing studies to understand the normal primate ovarian surface epithelium *in vivo*, including gene expression in the OSE during the natural menstrual cycle, the long term effects of OSE ablation on ovarian function, and comparison of protein expression between the rhesus monkey OSE versus the OSE from normal and genetically at risk women.

Oregon Clinical & Translational Research Institute/Oregon National Primate Research Center Pilot Grant
(Co-PI) Dates TBD

The primary risk factors for ovarian cancer are age, menopause, ovulation and family history of breast or ovarian cancer. These processes are not effectively modeled in nonprimate species and therefore have not been adequately studied to unravel their basis for mediating ovarian cancer risk. We will develop transcriptional profiles of *in vivo* gene expression by the cells of origin for most ovarian cancers—the

ovarian surface epithelium—in women and the nonhuman primate, rhesus macaque. Samples will be obtained from young and aged (post menopause) donors with defined reproductive and family histories. Data may establish whether there are gene expression changes, including epigenetic alterations, that occur with age, increased ovulation number, menopause and/or a family history of ovarian cancer. Findings from this study could identify novel screening methods to effectively evaluate risk.

Grants planned or in submission:

R01 application investigating (1) gene expression in the OSE and fimbrial epithelium (FE) *in vivo* in the context of age, menopause and reproductive and family history; (2) the effects of hormone replacement therapy on the normal OSE and FE in the nonhuman primate, and; (3) the role and regulation of a DNA repair protein, FANCD2, in human and nonhuman primate OSE *in vitro* and *in vivo*, which exhibits epigenetic downregulation in women with a family history of ovarian cancer.

R01 renewal of HD050356 to (1) investigate the effects of normal reproductive processes (development, the menstrual cycle and menopause) on OSE and FE morphology, gene and protein expression and malignant potential; (2) determine the long term consequences of ovarian epitheliectomy on the ovary and fertility, and (3) establish whether the normal OSE may be replaced by non-OSE or modified OSE cells with decreased malignant potential.

Key collaborators

Division: Dr Richard Stouffer, Division Head

OHSU: Dr Tanja Pejovic, OB&GYN and Division Director, Gynecologic Oncology

Extramural: Dr Melinda Yates, Postdoctoral Fellow University of Texas M.D. Anderson Cancer Center, Department of Gynecologic Oncology

Publications:

Wright JW, Stouffer RL, Rodland KD 2003 Estrogen inhibits cell cycle progression and retinoblastoma phosphorylation in rhesus ovarian surface epithelial cell culture. *Mol Cell Endocrinol* 208:1-10.

Wright JW, Stouffer RL, Rodland KD 2005 High dose estrogen and clinical SERMs induce growth arrest, p21, and p53 in primate ovarian surface epithelial cells. *J Clin Endocrinol Metabolism* 90(6):3688-95.

Molskness TA, Hess DL, Maginnis GM, **Wright JW**, Fanton JW, Stouffer RL 2007. Characteristics and regulation of the ovarian cycle in Vervet monkeys (*Cercopithecus aethiops*). *Am J Primat* 69(8):890-900.

Wright J, Pejovic T, Fanton J, Stouffer RL. 2008 Induction of proliferation in the primate ovarian surface epithelium *in vivo*. *Hum Reprod* 23(1):129-138.

Wright J, Pejovic T, Lawson M, Jurevic L, Hobbs T, Stouffer RL. 2010 Ovulation in the absence of the ovarian surface epithelium in primates. *Biol Reprod* 82(3):599-605.

Zelinski, Mary

Area(s) of Research/Scholarly Interest

My research is centered on understanding the basic mechanisms underlying the function of the ovary during the menstrual cycle in the female rhesus monkey with the goal of applying this knowledge through conducting translational research pertinent to important areas of reproductive health in women such as oncofertility, infertility and contraception.

A primary goal of the oncofertility research is to merge the principles of tissue engineering and biomaterial science with ovarian biology to develop novel fertility preservation options for girls and young women who must undergo treatments that threaten their fertility. One strategy to prevent oocyte exposure to the toxic effects of therapy is to remove eggs or ovarian tissue for cryopreservation prior to therapy. Once treatment is complete, the goal is to either transplant thawed ovarian tissue, or isolate the follicles from the tissue, mature them *in vitro*, and use them for *in vitro* fertilization. Our laboratory is currently validating a matrix scaffold that supports the 3-D architecture of the primate follicle and permits the coordinated development of the follicle wall and oocyte *in vitro*; evaluating the role of gonadotropic hormones and growth factors in promoting the growth and maturation of primate follicles and their enclosed oocytes *in vitro*; and assessing the fertilization and embryonic potential of primate oocytes derived from *in vitro* matured follicles. In addition, we are using novel, state-of-the-art cryopreservation techniques to improve the post-thaw viability of follicles and their enclosed oocytes to optimize transplantation protocols as well as to perform 3D culture of preantral follicles post-thaw for patients where ovarian transplantation is contraindicated due to the potential for transmission of malignant cells. Data from these experiments will be rapidly translated to the human clinic to offer ovarian follicle maturation as a fertility preservation option. A second strategy for fertility preservation is to protect the gametes/ovary prior to the patient receiving radio- or chemotherapy. Recent studies in macaques assessed sphingosine-1-phosphate (S1P) as an ovarian-protective agent in X-irradiated ovaries. A long-acting S1P analog administered prior to ovarian X-irradiation protected a cohort of preantral follicles and allowed production of live offspring devoid of DNA damage, providing proof-of-concept that inhibition of apoptosis locally within the ovary has potential for preserving fertility in cancer survivors.

Studies in macaques are also ongoing to develop novel selective estrogen receptor modulators to block gamete transport for contraception in females. Development of a male contraceptive is also underway targeting reversible inhibition of spermatogenesis using a novel, non-hormonal oral contraceptive agent.

Current Grants and Contracts

U54- HD 055744-01 Stouffer (PI)3/1/07 - 2/28/12

NIH/NICHD

Contraception by Blockade of Perioovulatory Events in Primates

The goal of this U54 Center is to target the discovery and development of novel contraceptive agents that prevent one or more perioovulatory events in adult, female primates during the menstrual cycle.

Project III: Control of Gamete Transport and Fertilization

The goal of the project is to investigate a novel strategy for female contraception that utilizes a Selective Estrogen Receptor Modulators (SERM). Our hypothesis is that anti-estrogenic SERM therapy,

targeting the reproductive tract, will result in a selective blockade of spermatozoa/oocyte transport and thereby provide contraception. There is no overlap.

Role: Co-Principal Investigator

Nonhuman Primate Contraceptive Core (NPCC):

The objective of the NPCC is to maintain a breeding colony of cynomolgus macaques to provide cost-effective contraceptive trials of ovary/reproductive tract-specific agents as reversible contraceptive agents in a nonhuman primate model. The NPCC provides services and coordination of animal protocols during evaluation of contraceptive efficacy. There is no overlap.

Role: Co-Principal Investigator

U54 Roadmap RR024347 Woodruff (PI)

NIH/NCRR/NICHD

5RL1-HD058293

7/1/09 – 6/30/12

R01A: Assessment of Ovarian Tissue Cryopreservation Methods in Nonhuman Primates (Zelinski PI)

As part of the Oncofertility Consortium: Fertility Preservation in Women, translational studies will be performed in nonhuman primates to a) compare two methods of ovarian tissue cryopreservation (slow freeze vs. vitrification) and assess follicle and oocyte viability in all stages of follicle maturity; b) assess the fertilization and embryonic potential of primate oocytes derived from cryopreserved ovarian tissue and cumulus-oocyte complexes; and c) adapt new cryo-technology under development around the globe to the nonhuman primate model. The techniques for follicle culture and assessment of fertilization and embryonic potential of oocytes will be the same as those described for (see below) R01B. However, the specific aims of R01A are focused on cryopreservation/vitrification of ovarian cortex to yield healthy follicles and oocytes, thus the aims are distinct between R01A and R01B.

Role: Principal Investigator

U54 Roadmap RR024347 Woodruff (PI)

9/1/07 – 8/31/12

NIH/NCRR/NICHD

5RL1-HD058294

R01B: Bioengineering Primate Follicles: From Immature Eggs to Live Births Stouffer (PI)

As part of the Oncofertility Consortium: Fertility Preservation in Women, translational studies will be performed in nonhuman primates to develop methods for (a) in vitro growth and maturation of primate antral follicles in a 3-D architecture that allows coordinated follicle cell-oocyte development, (b) in vivo follicle growth and oocyte maturation following ovarian autotransplantation, and (c) assessment of the fertilization and embryonic potential of oocytes. The specific aims of R01B are distinct from R01A. However, the specific aims of R01B are focused on developing the encapsulated 3D culture of follicles as well as autotransplantation of ovarian cortex, and do not focus on cryopreservation.

Role: Co-Principal Investigator

GPRC49165 Tash (PI)

12/1/08-6/30/11

NIH/NCRR ONPRC Pilot Project

Reversible Inhibition of Spermatogenesis in Non-Human Primates by Novel Non-hormonal Oral Contraceptive Agent, H2-Gamendazole

A novel agent for male contraception will be tested for efficacy and reversibility in male rhesus monkeys in collaboration with scientists at the Interdisciplinary Center for Male Contraceptive Research and Drug Development, University of Kansas Medical Center. There is no overlap.

Role: Co-Investigator

Grants planned or in submission 2010

NIH/NICHD

U54 HD18185 Center in Reproduction Research Cooperative Research on Infertility in Primates

Richard L. Stouffer, P.I.

Mary Zelinski Co-I (with Shoukhrat Mitalipov)

Pilot Project: Deriving Oocytes from Rhesus Monkey ES Cells

Mary Zelinski Co-I (with Diana Gordon)

Education Outreach Core

Gates Foundation, Grand Challenges in Global Health

Mary Zelinski, Co-I

Joseph Tash, Kansas University Medical Center, Co-I.

Gunda Georg, University of Minnesota, Co-I.

H2-Gamendazole as a Novel Oral Non-Hormonal Male Contraceptive

Key collaborators

Departmental - Drs. Jeffrey Jensen, Richard Stouffer, David Lee.

OHSU – ONPRC: Drs. Jon Hennebold, Ov Slayden, Richard Stouffer, Kevin Grove, Martha Neuringer, Steve Kohama, Francis Pau. Dept. of Hematology and Oncology: Dr. Rebecca Block.

Extramural – Drs. T. Woodruff and L. Shea, Northwestern; Dr. J. Chang, UCSD; Dr. M. Ottinger, U-Maryland, College Park; Dr. C. VandeVoort, CNPRC; Drs. G. Fahy and S. Mullen, 21st Century Medicine; Dr. J. Tash, KUMC; Dr. Gunda Georg, U of Minnesota; Dr. J. Tilly, Massachusetts General; Dr. P. Verboost, Merck (formerly NV Organon, Netherlands); M. Murphy, Pacific Northwest National Laboratories; Dr. A. Mayerhofer, U of Munich.

Most recent publications (last 5)

Xu M, West-Farrell ER, Stouffer RL, Shea LD, Woodruff TK, Zelinski MB. Encapsulated three-dimensional culture supports development of nonhuman primate secondary follicles. *Biol Reprod* 81:587-594, 2009. PMID 19474063

Smits J, Dolmans MM, Donnez J, Fortune JE, Hovatta O, Jewgenow K, Picton HM, Plancha C, Shea LD, Stouffer RL, Telfer EE, Woodruff TK, Zelinski MB. [Current achievements and future research directions in ovarian tissue culture, in vitro follicle development and transplantation: implications for fertility preservation.](#) *Hum Reprod Update*. 2010 Feb 1. [Epub ahead of print] PMID: 20124287

Shiying Jin S, Lei L, Shea LD, Zelinski MB, Stouffer RL, Woodruff TK. Markers of growth and development in primate primordial follicles are preserved after slow cryopreservation. *Fertil Steril* 93:2627-32, 2010. PMID: 20074723

Peluffo M, Stouffer RL, Hennebold JD, Zelinski MB. Cumulus oocyte complexes from small antral follicles during the early follicular phase of spontaneous cycles in rhesus monkeys can expand and yield oocytes capable of maturation in vitro. *Biol Reprod*. 2010 Jun 2. [Epub ahead of print] PMID: 20519694

Jensen JT, Stouffer RL, Stanley JE, Zelinski MB. Evaluation of the Phosphodiesterase 3 inhibitor ORG9935 as a contraceptive in female macaques: initial trials. *Contraception* 81:165-171, 2010. PMID: PMC2813210. PMID: 20103457

Joint Appointment Faculty – Other

Thornburg, Kent

Area(s) of Research/Scholarly Interest

Women's Health/Physiology of Pregnancy

Prenatal origins of adult disease

Maternal Body Composition in Pregnancy including obesity

Placental Physiology

Current Grants and Contracts

2PO1 HD 34430 Thornburg (PI) 06/01/07-05/31/12 \$800k/YR

Program Project Grant: Maternofetal Signaling and Lifelong Consequences

The major goals of this project are to study the role of maternal-fetal stressors and lifelong consequences.

5R21 HL093617 Thornburg (PI) 07/01/08 – 06/30/10 \$275K

Thyroid hormone inhibits cardiomyocyte replication in the fetus.

The major goal of this project is to determine whether the thyroid hormone, T3, is a suppressant of cardiomyocyte proliferative growth in vivo during fetal life and to determine the degree to which the non classical receptors act through the PI3K pathway to suppress the cell cycle. T3 is a candidate growth suppressant that could lead to low cardiomyocyte numbers for a lifetime in human babies born to hyperthyroid mothers.

T32HL094294 Thornburg (PI) 09/01/09 - 08/31/14 \$300K/YR

Training in Translational Science and Cardiovascular Research

This is a training grant designed to train MD and PhD postdoctoral fellows in translational science and cardiovascular research.

1 R01 HL102763-01 Thornburg (PI) 04/01/10 – 03/31/15 \$250K/YR

Thyroid regulation of cardiomyocyte maturation (Pending Council approval)

The goal of this application is to determine the role of T3 in regulating maturation of the myocardium in near term sheep.

1 R01 HL094570-01A1 Rugonyi (PI) 04/01/2009 – 03/31/2013

\$250K/yr

Dynamic changes in the chick developing heart in response to altered hemodynamics

The major goal of this project is to quantify hemodynamic forces during cardiac development, using subject-specific computational models of the heart outflow tract of chicken embryos under normal and altered hemodynamic conditions.

1 R01 AG032339-01A2 Barker (PI) 07/01/2010-06/30/2013 \$150K/yr

The developmental origins of disease and deterioration in old age

The goal of the project is to determine the associations between early life growth patterns and aging.

NIH (Turker, PI) KT Role: consultant Just funded, don't have all the info

Social and Ethical Aspects of Epigenetics

Pending:

1 R24
\$1M/YR.

Grove, Friedman, Thornburg (Co-PIs)

The impact of maternal health and diet on development of fetal metabolic systems

This grant examines the impact of maternal obesity and high fat diet (HFD) during pregnancy on placental function and the development of metabolic systems (pancreas, liver and muscle) in fetal and juvenile offspring. These studies also investigate dietary interventions and supplements that may reduce or prevent the fetal complications caused by chronic consumption of a HFD during pregnancy. This includes studies of by A. Frias on regulation of placental blood flow in HFD monkeys.

Completed Research Support

5R21 HD 49906
06/30/09

Thornburg (PI)

07/01/05 –

High Resolution Mapping of Placental Gene Expression

The major goal of this project was to develop research tools to improve our understanding of gene expression patterns in the human placenta.

Grants planned or in submission 2010

Key collaborators

Departmental

I have minor collaborations with Drs. Frias, Davis, Cheung and Brace.

OHSU

I collaborate with people in many depts. including engineering, cardiology etc.

Extramural

I have collaborators in UK, Finland, Australia, New Zealand, India, Saudi Arabia

2010 publications

1. Hunt JS and Thornburg KL. Placenta. *Int J Dev Biol.* 2010, 54:227-229.
2. Thornburg KL, Hunt JS. Contemporary comparative placenta research - an interview with Allen Enders. *Int J Dev Biol.* 2010 54: [Epub ahead of print] PMID: 19876818
3. Kajantie E, Thornburg KL, Barker DJP, Osmond C, Eriksson J. In preeclampsia, the placenta grows slowly along its minor axis. *Int J Dev Biol.* 2010 54:469-473.
4. Barker DJ, Thornburg KL, Osmond C, Kajantie E, Eriksson JG. The surface area of the placenta and hypertension in the offspring in later life. *Int J Dev Biol.* 2010 54:525-530. PMID: 19876839.
5. Liu A, Wang R, Thornburg KL, Rugonyi S. Dynamic variation of hemodynamic shear stress on the walls of developing chick heart. *Engineering with Computers.* Special Issue. (In Press)
6. Eriksson JG, Thornburg KL, Osmond C, Kajantie E, Barker DJ. The prenatal origins of lung cancer. I. The fetus. *Am J Hum Biol.* 2010. [Epub ahead of print]

7. Barker DJ, Thornburg KL, Osmond C, Kajantie E, Eriksson JG. The prenatal origins of lung cancer. II. The placenta. *Am J Hum Biol.* 2010. [Epub ahead of print]
8. Thornburg KL, O'Tierney PF, Louey S. The placenta is a programming agent for cardiovascular disease. *Placenta.* 2010 Suppl:S54-9. Epub 2010.
9. Eriksson JG, Kajantie E, Osmond C, Thornburg K, Barker DJ. Boys live dangerously in the womb. *Am J Hum Biol.* 2010 [Epub ahead of print]
10. Crossley II DA, Jonker S, Hicks JW, Thornburg KL. · Maturation of the Angiotensin II Cardiovascular Response in the Embryonic White Leghorn Chicken (*Gallus gallus*). *J Comp Physiol* 2010 (in press).

O'Tierney PF, Chattergoon NN, Louey S, Giraud GD, Thornburg KL. Atrial Natriuretic Peptide Inhibits Angiotensin II-Stimulated Proliferation in Fetal Cardiomyocytes. *J Physiol.* 2010 [Epub ahead of print]

Barker DJ, Gelow J, Thornburg K, Osmond C, Kajantie E, Eriksson JG. The early origins of chronic heart failure: impaired placental growth and initiation of insulin resistance in childhood. *Eur J Heart Fail.* 2010 [Epub ahead of print]

Affiliate Faculty

Eisner, Alvin

Area(s) of Research/Scholarly Interest

Effects of hormonal change on vision and the eye:

Major emphasis concerns effects of aromatase inhibition as adjuvant endocrine therapy for breast cancer

Secondary emphasis has concerned effects of phytoestrogen consumption on vision

Have also published on related menstrual-cycle vision effects; interested in hormone therapy

Current Grants and Contracts

None

Grants planned or in submission 2010

Submitted in June for Sept. study section review: R21 entitled "Visual and Ocular Effects of Aromatase Inhibition for Breast Cancer"

Advancing Novel Science in Women's Health Research (ANSWHR) (R21) (PAS-10-226), to be submitted in Oct

Key collaborators

Departmental

OHSU Shih-Wen Luoh, M.D., Ph.D., Knight Cancer Institute (co-investigator on submitted R21)

Steven Bailey, M.D., Casey Eye Institute (co-investigator on submitted R21)

John Vetto, M.D., Knight Cancer Institute (co-author on several recent papers)

Extramural Shaban Demirel, O.D., Ph.D. Discoveries in Sight, Devers Eye Institute, Legacy Health System

Most recent publications (last 5)

- A. Eisner** and S. Demirel. Variability in short wavelength automated perimetry: a dependence on phytoestrogen consumption? Acta Ophthalmologica Epub before print: Nov 24 2009. DOI: [10.1111/j.1755-3768.2009.01799.x](https://doi.org/10.1111/j.1755-3768.2009.01799.x) PMC journal in process, NIH ms submission ref. # 156784
- A. Eisner**, E.J. Thielman, J. Falardeau, and J.T. Vetto. Vitreo-retinal traction and anastrozole use. Breast Cancer Research and Treatment 117: 9-16 (2009). DOI: [10.1007/s10549-008-0156-5](https://doi.org/10.1007/s10549-008-0156-5) PMC2728165 [Available on 2010/9/1]
- A. Eisner** and M.D. Toomey. The color appearance of stimuli detected via short-wavelength-sensitive cones: comparisons with visual adaptation and visual field data for peri- or post-menopausal women under 70 years of age. Vision Research 48:2363-2372 (2008). DOI: [10.1016/j.visres.2008.01.029](https://doi.org/10.1016/j.visres.2008.01.029) PMID: PMC2653205
- A. Eisner**, J. Falardeau, M.D. Toomey, and J.T. Vetto. Retinal hemorrhages in anastrozole users. Optometry and Vision Science 85:301-308 (2008). DOI: [10.1097/OPX.0b013e31816bea3b](https://doi.org/10.1097/OPX.0b013e31816bea3b)
- A. Eisner**, M.D. Toomey, J. Falardeau, J.R. Samples, and J.T. Vetto. Differential effects of tamoxifen and anastrozole on optic cup size in breast cancer survivors. Breast Cancer Research and Treatment 106:161-170 (2007). DOI: [10.1007/s10549-006-9486-3](https://doi.org/10.1007/s10549-006-9486-3) PMC2045691