NIEHS Meeting:

Women's Reproductive Environmental Health Consortium

January 20, 2012

Directory of Researchers

Women's Reproductive Environmental Health Consortium
NIEHS Meeting: January 20, 2012
Agenda

8:00 a.m.	Arrive NIEHS, Room: Rodbell ABC
8:15-8:30	Welcome and Goals: Gwen Collman, Jerry Heindel, Karin Russ
8:30-9:50	Research Summary Presentations I- Epigenetics
	1. Kevin Osteen- Epigenetic biomarkers
	2. Kaylon Bruner Tran- Placental, ovarian and sperm quality, preterm birth
	3. David Crews- Gene expression, timing of puberty, neurobiological changes
	4. Andrea Gore- Sexually dimorphic effects of EDCs on brain and behavior
	5. Alexander Suvorov, Nicholas Lodato/David Waxman's lab- Genome-wide transcriptional profiling
	6. Nina Holland- Candidate genes and pathways for obesity and pubertal timing
9:50-10:10	*Coffee break*
10:10-11:00	Scientific Session A: Cheryl Walker-New Advances in Epigenetic Methods
11:00-12:10	Research Summary Presentations II
	7. Lou Guillette- Sexually dimorphic epigenetic signatures
	8. Satomi Kohno- Xenoestrogens and sex determination
	9. Ana Soto- Reproductive system, neuroendocrine, and mammary gland
	10. Shuk Mei Ho- Tumorigenesis in the ovary, endometrium and breast
12:10-1:10	*Lunch at NIEHS cafeteria*
1:15- 2:05	Scientific Session B: John McLachlan- Developmental Estrogenization Syndrome
2:05- 3:20	Research Summary Presentations III- Fertility & Fetal outcomes
	11. Shanna Swan- TDS, PCOS, neurodevelopment, growth and obesity
	12. Michael Bloom- Oocyte quality, embryo quality in ART patients
	13. Vasantha Padmanabhan- Neuroendocrine development, birth weight
	14. Hugh Taylor- IVF, DES exposure, PCOS, pregnancy loss
	15. Carmen Williams- NIEHS Reproductive Medicine Group
3:20-3:40	*Break*
3:40-4:30	Developing Collaborations- Research Opportunities:
	Discussion Leaders: Jerry Heindel, Kim Gray, Caroline Dilworth
4:30-5:00	Goals of the Consortium- Getting the Message Out: Karin Russ

Research Summaries of Presenters

Session I – Epigenetics

Speaker 1

Kevin G. Osteen, PhD

Vanderbilt University Medical Center
Women's Reproductive Health Research Center

Overview: Progesterone exposure is a negative risk factor for the development of endometriosis in humans due, in part, to its anti-inflammatory nature; however, women with endometriosis often exhibit reduced endometrial responsiveness to progesterone. TCDD (or dioxin), disrupts the "protective" actions of progesterone. Early life TCDD exposure of mice leads to a uterine phenotype which mimics the progesterone resistant endometrial phenotype observed in women with endometriosis-related infertility. Significantly, our toxicant-induced murine phenotype is also associated with an increased sensitivity to inflammatory signals, which disrupts fertility across multiple generations.

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Current project: Our primary goal is to identify the TCDD-mediated cellular and molecular modifications in somatic and immune cells which negatively impact progesterone action related to reproductive tract function. Using short-term cultures of human endometrial cells, we have identified a loss of stromal cell progesterone receptor-B (PR-B) mRNA and protein expression following treatment with TCDD; a change that increases the negative impact of pro-inflammatory signals on differentiation.

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Models: Primary cultures of human endometrial cells acquired from women with and without endometriosis. Transgenerational model of in utero TCDD exposure in C57bl/6 mice.

Toxicant: 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD or dioxin)

Methods: In vivo and in vitro functional outcomes (fertility, decidualization capacity) following TCDD exposure, including the use of isolated human endometrial cells, chimeric models of experimental endometriosis and transgenerational observations following early life TCDD exposure.

Endpoints and results: Biomarker analysis of cellular and molecular responses to progesterone in the presence or absence of TCDD exposure (uterine/endometrial expression of relevant genes and proteins, including epigenetic marks and with or without epigenetic modification therapy); Histological and immunohistochemical examination of reproductive and non-reproductive tissues generated from our murine model of early life TCDD exposure.

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Selected publications:

Igarashi TM, Bruner-Tran KL, Yeaman GR, Lessey BA, Edwards DP, Eisenberg E, Osteen KG. Reduced expression of progesterone receptor-B in the endometrium of women with endometriosis and in cocultures of endometrial cells exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Fertil Steril. 2005 Jul;84(1):67-74.

Nayyar T, Bruner-Tran KL, Piestrzeniewicz-Ulanska D, Osteen KG. Developmental exposure of mice to TCDD elicits a similar uterine phenotype in adult animals as observed in women with endometriosis. Reprod Toxicol. 2007 Apr-May;23(3):326-36. Epub 2006 Sep 30.

Bruner-Tran KL, Osteen KG. Developmental exposure to TCDD reduces fertility and negatively affects pregnancy outcomes across multiple generations. Reprod Toxicol. 2011 Apr;31(3):344-50. Epub 2010 Oct 16.

Speaker 2

Kaylon L. Bruner-Tran, PhD

Vanderbilt University Medical Center,
Women's Reproductive Health Research Center

Overview: Our laboratory examines the mechanisms by which early life TCDD exposure leads to the development of reproductive disorders, particularly those which impact pregnancy establishment and maintenance. Concomitant with these studies is the examination of nutritional intervention strategies which may reduce the negative consequences of a previous (or ancestral) TCDD exposure on adult reproductive tract function.

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Current project: A major, current project within the laboratory is to examine the ability of preconception fish oil supplementation of male or female mice to prevent the transgenerational impact of TCDD exposure. Developmental TCDD exposure of either male or female mice leads to an increased risk of infertility or, in the event of pregnancy, an increased risk of preterm birth in the adult (F1) animal. Significantly, a similar increase in infertility and risk of preterm birth was observed in subsequent generations (F2-F4), even in the absence of an additional TCDD exposure. We recently published data demonstrating the ability of preconception fish oil supplementation of toxicant-exposed male mice to prevent preterm birth in his unexposed female partner. We now have similar data demonstrating that preconception treatment of female mice also prevents the developmental TCDD exposure-associated increase in preterm birth. Current studies are examining reproductive outcomes of the F2-F3 generations of mice with ancestral exposure to TCDD in the presence and absence of fish oil supplementation of only the F1 animals. These studies will determine the ability and potential mechanisms by which nutrition influences the transgenerational impact of developmental TCDD exposure on reproductive tract function.

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Model: In utero TCDD exposure of C57bl/6 mice

Toxicant: 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD or dioxin)

Methods: Functional outcomes (observe pregnancy/preterm birth); euthanasia during pregnancy for examination of placental/decidual expression of relevant genes and proteins, histologic examination of tissues/protein expression, sperm morphology/number, ovarian histology.

Endpoints and results: Preterm birth in mice able to become pregnant was associated with premature placental inflammation, reduced progesterone response and an increased sensitivity to inflammation regardless of which parent had been exposed to TCDD. Infertility in F1 males was associated with reduced sperm density and altered sperm morphology while infertility in F1 females appears to be multi-factorial. Fish oil supplementation of F1 males improved sperm number and morphology which was associated with a significant improvement in fertility and full-term pregnancy in an unexposed female. Preconception fish oil supplementation of F1 females led to a non-significant improvement in fertility and was associated with full-term pregnancy in mice becoming pregnant. Studies examining the F2 and F3 offspring of fish oil supplemented F1 mice are underway.

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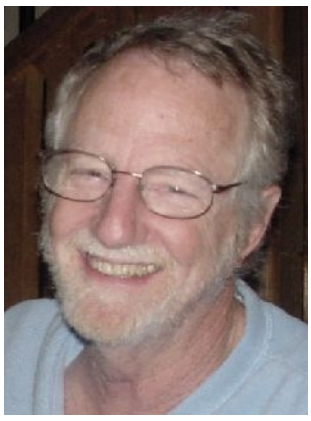
Selected publications:

McConaha ME, Ding T, Lucas JA, Arosh JA, Osteen KG, Bruner-Tran KL. Preconception omega-3 fatty acid supplementation of adult male mice with a history of developmental 2,3,7,8-tetrachlorodibenzo-p-dioxin exposure prevents preterm birth in unexposed female partners. Reproduction. 2011 Aug;142(2):235-41. Epub 2011 Jun 8.

Ding T, McConaha M, Boyd KL, Osteen KG, Bruner-Tran KL. Developmental dioxin exposure of either parent is associated with an increased risk of preterm birth in adult mice. Reprod Toxicol. 2011 Apr;31(3):351-8. Epub 2010 Nov 18.

Bruner-Tran KL, Osteen KG. Developmental exposure to TCDD reduces fertility and negatively affects pregnancy outcomes across multiple generations. Reprod Toxicol. 2011 Apr;31(3):344-50. Epub 2010 Oct 16.

Speaker 3



David Crews, PhD

University of Texas at Austin

Overview: Environmental epigenetics; interaction of transgenerational and stress-induced epigenetic modifications and their effects on neuroendocrine systems controlling physiology, behavior, and neurobiology.

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Current project: Epigenetic Transgenerational Inheritance of Stress Response-Sex Differences

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Model: Rat – Epigenetically modified rats.

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Toxicant: Vinclozolin.

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We study how ancestral exposure to an endocrine disrupting compound causes epigenetic reprogramming that changes how descendant individuals respond to life challenges. A two 'hit' paradigm is used. The first 'hit' consists of embryonic exposure to Vinclozolin. This has been to create a permanent epigenetic imprint that is permanently incorporated into the germline and, hence is manifest each generation in the *absence* of the original causative agent. The second 'hit', 3 generations removed from the first, consists of chronic restraint stress (CRS) during adolescence. Stress in adolescence has powerful and permanent effects on brain and behavior, including epigenetic modifications to the nervous system. The behavioral tasks during adulthood of the F3 descendants were selected because they manifest sexually dimorphic responses. We have demonstrated the feasibility and validity of such studies, revealing substantial interactive effects on brain and behavior. For example, studies indicate the epigenetic modifications induced by ancestral exposure to Vinclozolin alter how descendant males respond to CRS at the level of physiology, behavior, brain metabolic activity, target gene expression, and genome networks, thereby changing the stress response fundamentally. Taken together our data demonstrate that environmentally-induced epigenetic transgenerational inheritance alters brain development and genome activity to modify stress-induced behavioral responses in a sex-specific manner.

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Endpoints and results: Measurements are made at the physiological (i.e. endocrine physiology), behavioral (social behavior, learning and memory, and anxiety), and neurobiological (metabolism and gene regulation in identified brain areas) levels, combined with modern systems biology (brain genomics and gene networks).

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Selected publications:

Crews D, Gore AC. Life imprints: living in a contaminated world. Environ Health Perspect. 2011 Sep;119(9):1208-10. Epub 2011 May 13.

Crews D. Epigenetic modifications of brain and behavior: theory and practice. Horm Behav. 2011 Mar;59(3):393-8. Epub 2010 Jul 12.

Michael K. Skinner, Matthew D. Anway, Marina I. Savenkova, Andrea C. Gore, and David Crews. Transgenerational Epigenetic Programming of the Brain Transcriptome and Anxiety Behavior. PLoS ONE, v.3(11); 2008.

David Crews. Epigenetics and its implications for behavioral neuroendocrinology. Front Neuroendocrinol. 2008 June; 29(3): 344–357.

Speaker 4

Andrea C. Gore, PhD

Gustavus and Louise Pfeiffer Professor
University of Texas at Austin

Overview: Environmental endocrine disruption of brain and behavior – especially neuroendocrine systems controlling reproductive physiology and behavior. We are also completing a transgenerational study looking at effects of prenatal PCB exposures on F1-F3 generations.

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Current project: Sexually Dimorphic Effects of Endocrine Disruptors on Brain and Behavior.

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Model: Rat - prenatal exposure to PCBs.

Toxicant: PCBs (Aroclor 1221), estradiol benzoate.

Methods: Fetal rats are exposed to a low dose of PCBs or estrogen during gestation, days 16 and 18 (during the last trimester). After these exposures, offspring (F1 rats) are left untreated. F1 males and females are allowed to develop, are behaviorally characterized, then euthanized for gene expression and protein immunohistochemistry. In the transgenerational study, exposures limited to the F0 dams, and no further exposures to F1-F3 animals. In these studies we are searching for molecular changes to the nervous system, including gene expression and epigenetic modifications (DNA methylation).

Endpoints and results: We have accumulated evidence for effects of prenatal PCB (and other endocrine disruptor) exposures on the developing hypothalamus. One day after birth, hypothalamic gene expression is already altered. Puberty is accelerated in females, and delayed in males. In young adults, gene and protein expression of key neurotransmitters, receptors, and other neuroendocrine molecules is significantly changed. Concomitant with these neurobiological changes, reproductive physiology (estrous cycles) and behavior (mating) is disrupted. Reproductive aging is also accelerated, together with changes in the molecular biology (DNA methylation and gene expression) of the hypothalamus. Ongoing work is looking at potential transgenerational effects of endocrine disruptors, as well as more detailed behavioral analyses of changes caused by prenatal exposures.

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Selected publications:

Diamanti-Kandarakis E, Bourguignon JP, Giudice L, Hauser R, Prins G, Soto A, Zoeller RT, Gore AC (2009) Endocrine-Disrupting Chemicals: Endocrine Society Scientific Statement. Endocrine Reviews 30: 293-342.

Gore AC, Patisaul HB (2010) Neuroendocrine disruptors: Historical roots, current progress, questions for the future. Frontiers in Neuroendocrinology 31: 395-399.

Walker DM, Gore AC (2011) Transgenerational neuroendocrine disruption of reproduction. Nature Reviews Endocrinology 7: 197-207.

Dickerson SM, Cunningham SL, Patisaul HB, Woller MJ, Gore AC (2011) Endocrine disruption of brain sexual differentiation by developmental PCB exposure. Endocrinology 152: 581-594.

Dickerson SM, Cunningham SL, Gore AC (2011). Prenatal PCBs disrupt early neuroendocrine development of the rat hypothalamus. Toxicology and Applied Pharmacology 252: 36-46.

Crews D, Gore AC (2011) Life imprints: Living in a contaminated world. Environmental Health Perspectives 119: 1208-1210.

Gore AC, Walker DM, Zama AM, Armenti A, Uzumcu M (2011) Early life exposure to endocrine-disrupting chemicals causes lifelong molecular reprogramming of the hypothalamus and premature reproductive aging. Molecular Endocrinology, ePub ahead of print.

Speaker session 5

David J. Waxman

Professor of Cell and Molecular Biology
Professor of Medicine
Boston University
Department of Biology

Alexander Suvorov

Postdoctoral Research Associate in molecular toxicology

Nicholas Lodato

PhD student in cell and molecular biology

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Current project: Gene Expression and Histone Modifications in Mouse Uterus in Response to Prenatal Exposure to BPA.

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Model: CD-1 mouse

Toxicant: Bisphenol A (BPA), Diethylstilbestrol (DES)

Methods: Pregnant CD-1 mice were exposed to 5, 50 or 500 ug/kg/day BPA or 5 µg/kg/day DES by oral administration on days E9 through E18, inclusive. Uterine tissue was harvested from adult mice at estrus or proestrus and used for gene expression analysis (microarrays and qPCR) and histone modification analysis (ChIP-PCR and ChIP-seq).

Endpoint: Genome-wide transcriptional profiling, chromatin marks/histone modifications

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Selected publications:

Zhang K, Waxman DJ. (2010). PC3 prostate tumor-initiating cells with molecular profile FAM65Bhigh/MFI2low/LEF1 low increase tumor angiogenesis. *Mol Cancer.* Dec 29;9:319.

Ling G, Sugathan A, Mazor T, Fraenkel E, Waxman DJ. (2010). Unbiased, genome-wide in vivo mapping of transcriptional regulatory elements reveals sex differences in chromatin structure associated with sex-specific liver gene expression. *Mol Cell Biol.* Dec;30(23):5531-44.

Wauthier V, Sugathan A, Meyer RD, Dombkowski AA, Waxman DJ. (2010). Intrinsic sex differences in the early growth hormone responsiveness of sex-specific genes in mouse liver. *Mol Endocrinol.* Mar;24(3):667-78.

Speaker 6

Nina T. Holland, PhD

Director of Children's Environmental Health Laboratory and SPH Biorepository
CERCH, School of Public Health
University of California, Berkeley

Overview: Molecular Epidemiology of Children's Environmental Health, Reproductive Toxicology, Functional Genomics (PON) and Epigenetics

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Current project: Epigenetic Effects of Prenatal Exposures to Pesticides and Other Pollutants on Puberty.

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Model: Agricultural cohort Mexican-American mothers and children from CA (CHAMACOS)

Toxicant: Organichlorines, OPs, PBDEs and other pollutants, assessed during pregnancy and childhood development

Methods: Pyrosequencing (Alu and LINE-1) and Illumina Infinium 450K methylation BeadChip

Endpoints and results: Global and site-specific DNA methylation was assessed in 254 newborn- and 9-year-old CHAMACOS children. We found that global DNA methylation increased with age and differ by sex but the measures were not correlated across the three assays. 15.5% of all investigated CpG sites, representing >15,000 genes, were differentially methylated between children at birth and 9 years of age. More than 2% of CpG sites investigated in >1,900 genes showed significant differences in methylation by sex. Candidate genes and pathways involved in age and sex differentiation, and in response to early life exposures, have been identified for future analyses of their effects on obesity and puberty.

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Selected publications:

Nina T. Holland, Alexandra Fucic, Micheline Kirsch-Volders et al. "Micronuclei in neonates and children: effects of environmental, genetic, demographic and disease variables." *Mutagenesis* 26 (1): 51–56. 2011.

Karen Huen, Kim Harley, Asa Bradman, Brenda Eskenazi, Nina Holland. "Longitudinal changes in PON1 enzymatic activities in Mexican–American mothers and children with different genotypes and haplotypes". *Toxicology and Applied Pharmacology 244,* 181–189, 2010.

Jonathan Chevrier, Nina T. Holland, Brenda Eskenazi et al. "Maternal Thyroid Function during the Second Half of Pregnancy and Child Neurodevelopment at 6, 12, 24, and 60 Months of Age." *Journal of Thyroid Research.* 2011.

Kim G. Harley, Karen Huen, Nina T. Holland, Brenda Eskenazi et al. "Association of Organophosphate Pesticide Exposure and Paraoxonase with Birth Outcome in Mexican-American Women." *PLoS ONE.* August 31, 2011.

Paurene Duramad and Nina T. Holland. "Biomarkers of Immunotoxicity for Environmental and Public Health Research." *International Journal of Environmental Research and Public Health* 8: 1388-1401. 2011.

Nina T. Holland, Karen Huen, Brenda Eskenazi et al. "Paraoxonase Polymorphisms, Haplotypes and Enzyme Activity in Latino mothers and Newborns." *Environmental Health Perspectives* 114: 985–991. 2006.

Scientific Session A: New Advances in Epigenetic Methods

Cheryl Lyn Walker

Director, Texas A&M
Institute of Biosciences and Technology

Overview: We are studying the mechanisms by which EDCs engage the cell's epigenetic machinery to induce developmental reprogramming of the epigenome to increase cancer risk. Our focus is on non-genomic signaling of nuclear hormone receptors (i.e. ER), signaling pathways that regulate epigenetic programming (i.e. PI3K and MAPK) and the "readers, writers and erasers" of the epigenetic code that are the target of these pathways (i.e. histone methyltransferases).

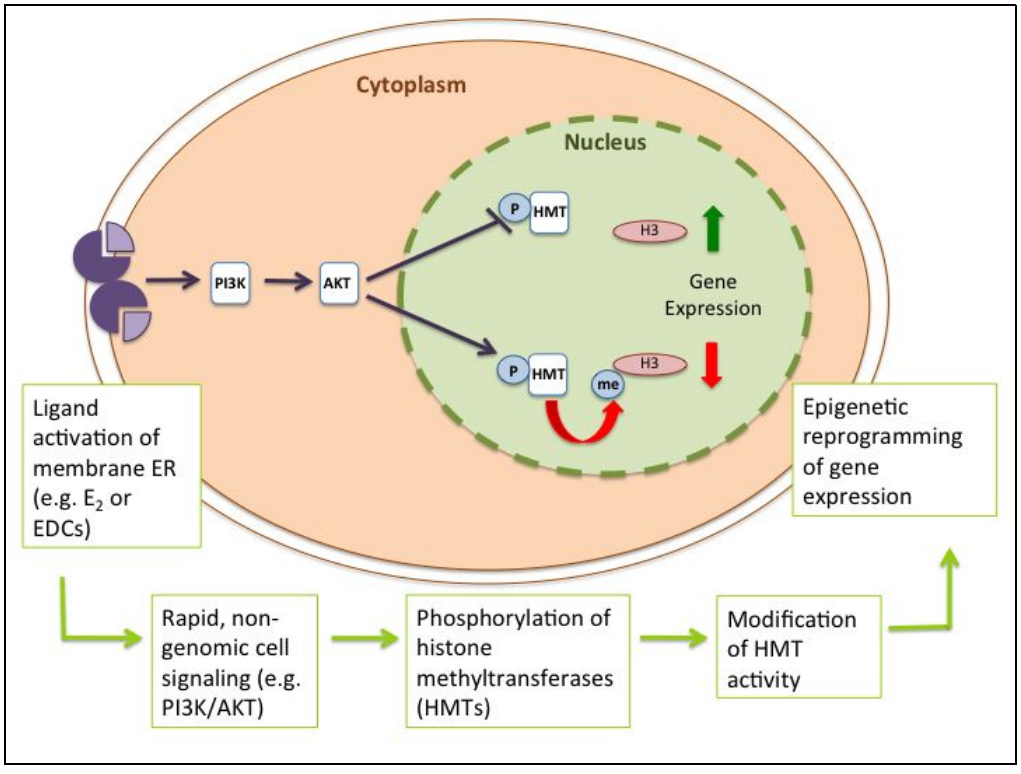
Current project: We are studying how developmental reprogramming by EDCs increase risk of developing uterine and prostate cancer.

Model: Rat and mouse models, human cell lines.

Toxicant: Primarily xenoestrogens including DES, genistein and BPA.

Methods: Animal models (immunohistochemistry), epigenetics (histone and DNA methylation), cell signaling (westerns, IP) and protein-protein interactions (protein domain microarrays).

Endpoints and results: We have developed the following model for how EDCs disrupt the cell's epigenetic machinery to induce developmental reprogramming.



Selected Publications:

Alexander A, Walker CL. Differential localization of ATM is correlated with activation of distinct downstream signaling pathways. Cell Cycle 9(18):3685-6, 9/2010. e-Pub 9/5/2010. PMID: 20890104.

Alexander A, Kim J, Walker CL. ATM engages the TSC2/mTORC1 signaling node to regulate autophagy. Autophagy 6(5). e-Pub 7/28/2010. PMID: 20581436.

McCampbell AS, Broaddus RR, Walker CL. Loss of inhibitory insulin receptor substrate-1 phosphorylation: An early event in endometrial hyperplasia and progression to carcinoma. Cell Cycle 9(14):2698-9, 7/15/2010. e-Pub 7/9/2010. PMID: 20676044.

Bredfeldt TG, Greathouse KL, Safe SH, Hung MC, Bedford MT, Walker CL. Xenoestrogen-induced regulation of EZH2 and histone methylation via estrogen receptor signaling to PI3K/AKT. Mol Endocrinol 24(5):993-1006, 5/2010. e-Pub 3/29/2010. PMCID: PMC2870935.

Alexander A, Cai SL, Kim J, Nanez A, Sahin M, MacLean KH, Inoki K, Guan KL, Shen J, Person MD, Kusewitt D, Mills GB, Kastan MB, Walker CL. ATM signals to TSC2 in the cytoplasm to regulate mTORC1 in response to ROS. Proc Natl Acad Sci U S A 107(9):4153-8, 3/2/2010. e-Pub 2/16/2010. PMCID: PMC2840158.

Dere R, Wilson PD, Sandford RN, Walker CL. Carboxy Terminal Tail of Polycystin-1 Regulates Localization of TSC2 to Repress mTOR. PLoS One 5(2):e9239, 2010. e-Pub 2/16/2010. PMCID: PMC2821926.

Crabtree JS, Jelinsky SA, Harris HA, Choe SE, Cotreau MM, Kimberland ML, Wilson E, Saraf KA, Liu W, McCampbell AS, Dave B, Broaddus RR, Brown EL, Kao W, Skotnicki JS, Abou-Gharbia M, Winneker RC, Walker CL. Comparison of human and rat uterine leiomyomata: identification of a dysregulated mammalian target of rapamycin pathway. Cancer Res 69(15). e-Pub 7/21/2009. PMID: 19622772.

Teresa K. Woodruff, Ph.D. and Cheryl Lyn Walker, Ph.D. Fetal and Early Postnatal Environmental Exposures and Reproductive Health Effects in the Female. Fertil Steril. 2008 February; 89(2 Suppl): e47–e51.

Greathouse KL, Cook JD, Lin K, Davis BJ, Berry TD, Bredfeldt TG, Walker CL. Identification of uterine leiomyoma genes developmentally reprogrammed by neonatal exposure to diethylstilbestrol. Reprod Sci 15(8):765-78, 10/2008. PMID: 19017814.

Session II

Speaker 7

Louis J. Guillette Jr., PhD

Professor of Obstetrics and Gynecology; CoEE
Endowed Chair in Marine Genomics

Medical University of South Carolina
Hollings Marine Laboratory

Overview: Environmental influences (e.g., seasonal variation, contaminants, climate change) on the evolution and development of the reproductive system in vertebrates, including sex determination of the ovary, development and evolution of the female reproductive tract and development of external genitalia in males and females. We use multiple sentinel species (e.g., fish, amphibians and reptiles) as well as humans.

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Current Projects: 1) Ongoing studies of contaminant (e.g., pesticides, PCBs and metals) effects on the development of the endocrine and reproductive systems of wildlife such as the American alligator, with special focus on altered gene expression. **2)** Newly initiated studies examine epigenetic markers. An ongoing study of genital development assessed with ultrasound measurements during human pregnancy, as it relates to urinary and plasma/serum contaminant concentrations (e.g., BPA, phthalates, OCs, metals). In data collection phase, with current pregnancy and babies being born – males and females are receiving well baby checkup and assessment using previously validated procedures (e.g., those used by Swan et al.). **3)** Initiated study examining ovarian follicular fluid (contaminant profiles with lipidomics / proteiomics) and granulosa/thecal cells (transcriptomics and proteiomics, QPCR) obtained during oocyte retrieval in ART patients. Data is then matched with pregnancy establishment and outcomes followed by well baby checkups. **4)** iPS cell and primary cell studies using wildlife (e.g., pig, whale and alligator), mouse and human model systems to understand the influence of contaminants on the fate of cell differentiation.

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Models: Sentinel species (varied including alligators, dolphins) and human – in ovo or in utero environmental exposures.

Toxicant: varied from agricultural (pesticides & fertilizers), industrial (PCBs, metals), dietary (BPA & pesticides) and personal care product (phthalates).

Methods: Both descriptive sampling (during natural pregnancy in humans and wildlife) or experimental treatments. For human samples, collection at multiple points in pregnancy and post partum period. In wildlife, treatment during various critical windows of development and harvest of samples either during embryonic development or either during neonatal or juvenile phases. Samples examined by genomic and functional genetics (QPCR, NexGen sequencing) as well as advanced analytical chemistry (GC or LC/MS/MS; AA; ICP).

Endpoints and Results: Human studies are ongoing but the wildlife studies have documented long term developmental abnormalities at the physiological, morphological and genetic levels. Current studies with the American alligator have shown that the genetic markers displayed by ovaries exposed to contaminant mixtures from agricultural sites are similar to those reported in women experiencing PCOS

and premature ovarian failure. Key genes such as follistatin, aromatase and ESR1 expression are altered.

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Selected Recent Publications:

Brandon C. Moore, Satomi Kohno, Robert W. Cook, Ashley L. Alvers, Heather J. Hamlin, Teresa K. Woodruff, Louis J. Guillette. 2010. Altered sex hormone concentrations and gonadal mRNA expression in neonatal alligators from contaminated and control Florida lakes. Journal of Experimental Zoology 313A:218-230. PMID:20166196

Moore BC, Hamlin HJ, Botteri NL, Guillette LJ Jr. 2010. Gonadal mRNA expression levels of TGFβ signaling factors correspond with post hatching morphological development in American alligators. Sexual Development 4: 62-72. PMID:20110644

Cynthia V. Rider, Phillip C. Hartig, Mary C. Cardon, Christy R. Lambright, Kathy L. Bobseine, Louis J. Guillette Jr, L. Earl Gray Jr, Vickie S. Wilson.2010. Are alligators more sensitive to some xenoestrogens than humans? Environmental Toxicology and Chemistry 29: 2064-2071. PMID:20821664

Moore BC, Milnes MR, Kohno S, Katsu Y, Iguchi T, Woodruff TK, Guillette LJ Jr. 2011. Altered gonadal expression of TGFb superfamily signaling factors in environmental contaminant-exposed juvenile alligators. Journal of Steroid Biochemistry and Molecular Biology 127: 58-63. PMID:21251980

Hamlin HJ, Guillette LJ Jr. 2011. Embryos as targets of endocrine disrupting contaminants in wildlife. Birth Defects Res. (Part C) 93: 19-33. PMID:21425439

Speaker 8

Satomi Kohno, PhD

Assistant Professor, Departments of Obstetrics and Gynecology,
Marine Biomedicine and Environmental Sciences Center,
and Hollings Marine Laboratory

Medical University of South Carolina (MUSC)

Overview: To understand the endocrine alterations, the mechanisms need to be investigated. American alligator, Alligator mississippiensis, is one of the top predators in the wild, and environmental contaminants can concentrate in their body by bioaccumulation. Crocodilians including alligator use the unique sex determination system called temperature-dependent sex determination. This sex determination is sensitive to estrogenic compounds, and it can be overwritten by them. Therefore, American alligator is a unique model animal to investigate the influences of environmental contaminants.

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Current project: Sexual plasticity and developmental exposure to endocrine active compounds in American alligators.

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Model: American alligators.

Toxicant: Estrogenic compounds, actual contaminants in Lake Apopka (e.g., DDTs & PCBs).

Methods: American alligator eggs were exposed to an estrogen receptor-alpha or -beta specific agonist, or the eggs were collected at Lake Apopka and incubated at the laboratory. Gonadal tissues were analyzed by histology and Q-PCR.

Endpoint: Morphological characteristics and mRNA expression pattern of gonads were used to see their sexual plasticity. Estrogen receptor-alpha specific agonist induced sex-reversal under male-producing condition, whereas ERβ agonist-treatment or eggs from Apopka did not. However, Apopka eggs produced more females than males under the intermediate condition.

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Selected publications:

M. R. Milnes et al., Increased posthatching mortality and loss of sexually dimorphic gene expression in alligators (Alligator mississippiensis) from a contaminated environment. Biol Reprod 78, 932 (MAY, 2008.

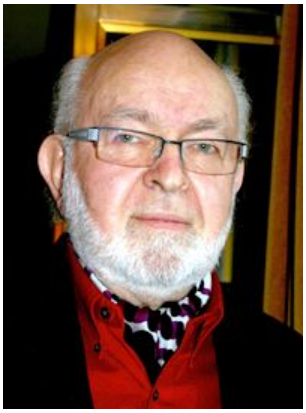
Y. Katsu et al., Molecular cloning, characterization, and chromosome mapping of reptilian estrogen receptors. Endocrinology 151, 5710 (Dec, 2010).

S. Kohno et al., Potential contributions of heat shock proteins to temperature-dependent sex determination in the American alligator. Sexual development: genetics, molecular biology, evolution, endocrinology, embryology, and pathology of sex determination and differentiation 4, 73 (2010).

B. C. Moore et al., Influences of sex, incubation temperature, and environmental quality on gonadal estrogen and androgen receptor messenger RNA expression in juvenile American alligators (Alligator mississippiensis). Biol Reprod 82, 194 (Jan, 2010).

H. Urushitani et al., Molecular cloning of anti-Mullerian hormone from the American alligator, Alligator mississippiensis. Mol Cell Endocrinol 333, 190 (Feb 20, 2011).

Speaker session 9



Ana M. Soto

Department of Anatomy, Tufts University School of Medicine, Boston MA

Carlos Sonnenschein

Department of Anatomy, Tufts University School of Medicine, Boston MA

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Overview: Our research has centered on a) the control of cell proliferation by sex steroids, b) the fetal origins of adult disease, particularly the role of endocrine disruptors on carcinogenesis, reproductive and behavioral disorders, c) the role of stroma/epithelial interactions on organogenesis and carcinogenesis and d) the role of biomechanics on epithelial organization. We are currently using a systems biology approach to investigate and better understand morphogenesis. In the book The Society of Cells (Taylor and Francis, 1999) we posited that the default state of cells in all organisms is proliferation, and proposed the Tissue Organization Field Theory of Carcinogenesis, in which cancer is viewed as development gone awry. We also work on epistemological issues arising from the study of complex biological phenomena and on theoretical biology.

Regarding endocrine disruption, the laboratory developed assays for detecting estrogenicity and androgenicity (E-SCREEN and A-SCREEN assays) and identified novel xenoestrogens. We are currently studying the mechanisms underlying xenoestrogen-induced alterations of the development of the female reproductive system, the neuroendocrine system and the mammary gland. We have shown that in utero exposure to minute, environmentally relevant quantities of xenoestrogens irreversibly alters the development of the female genital tract and the mammary gland. Our findings indicate that environmentally relevant levels of BPA affect the regulation of the estrous cycle probably at the central level (hypothalamic-hypophyseal-gonadal axis), induce early cessation of ovarian cycles, alter the development and histoarchitecture of the mammary gland, and induce preneoplastic and neoplastic lesions in the mammary gland. We are currently exploring the mechanisms underlying these effects.

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Current project: Perinatal Effects of BPA on Female Reproduction and Mammary Neoplasia.

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Models: Wistar Furth Rat, Sprague Dawley Rat, CD-1 mouse and C57Bl6 mouse

Toxicant: Bisphenol A

Methods: In utero exposure of rodents to Bisphenol A via osmotic pumps, morphometric analysis of tissues and organs, transcriptome and methylome analysis, metabolomic analysis, several microscopic

modes (confocal, second harmonic generation, immunohistochemistry), 2 and 3 D- tissue culture, organ culture, biomechanics.

Endpoints: Body weight, mammary gland development (morphometrics, gene expression, protein expression, collagen fiber organization), fertility, fecundity, mammary cancer, alterations of sexually dimorphic brain structures, epigenetic markers, metabolomic markers of exposure.

……

Selected publications:

Bizzarri M, Giuliani A, Cucina A, D'Anselmi F, Soto AM, Sonnenschein C: Fractal analysis in a systems biology approach to cancer. Semin.Cancer Biol. 2011; 21: 175-82.

Cabaton NJ, Wadia PR, Rubin BS, Zalko D, Schaeberle CM, Askenase MH, Gadbois JL, Tharp AP, Whitt GS, Sonnenschein C, Soto AM: Perinatal exposure to environmentally relevant levels of Bisphenol-A decreases fertility and fecundity in CD-1 mice. Environmental Health Perspectives 2011; 119: 547-52.

Saetzler K, Sonnenschein C, Soto AM: Systems biology beyond networks: generating order from disorder through self-organization. Semin.Cancer Biol. 2011; 21: 165-74.

Sonnenschein C, Soto AM: The death of the cancer cell. Cancer Research 2011; 71: 4334-7.

Sonnenschein C, Wadia PR, Rubin BS, Soto AM: Cancer as development gone awry: the case for bisphenol-A as a carcinogen. Journal of Developmental Origins of Health and Disease 2011; 2: 9-16.

Soto AM, Sonnenschein C: The tissue organization field theory of cancer: A testable replacement for the somatic mutation theory. BioEssays 2011; 33: 332-40.

Krause S, Maffini MV, Soto AM, Sonnenschein C: The microenvironment determines the breast cancer cells' phenotype: organization of MCF7 cells in 3D cultures. BMC Cancer 2010; 10: 263-75.

Maffini MV, Sonnenschein C, Soto AM: Breast, Environmental Impacts on Reproductive Health and Fertility. Edited by Woodruff TJ, Janssen SJ, Guillette LJ, Jr., Giudice LC. Cambridge, Cambridge University Press, 2010, pp 36-47.

Soto AM, Sonnenschein C: Environmental causes of cancer: endocrine disruptors as carcinogens. Nat.Rev.Endocrinol. 2010; 6: 363-70.

vom Saal FS, Akingbemi BT, Belcher SM, Crain DA, Crews D, Guidice LC, Hunt PA, Leranth C, Myers JP, Nadal A, Olea N, Padmanabhan V, Rosenfeld CS, Schneyer A, Schoenfelder G, Sonnenschein C, Soto AM, Stahlhut RW, Swan SH, Vandenberg LN, Wang HS, Watson CS, Welshons WV, Zoeller RT: Flawed experimental design reveals the need for guidelines requiring appropriate positive controls in endocrine disruption research. Toxicological Sciences 2010; 115: 612-3.

Aubert ML, Nef S, Soto AM: Special issue on the topic: Role of endocrine disruptors from the environment in the aetiology of obesity and diabetes. Mol.Cell Endocrinol. 2009; 304: 1-2.

Speaker 10

Shuk-Mei Ho, PhD

Department of Environmental Health
Center for Environmental Genetics,
and Cancer Institute
University of Cincinnati Medical Center;
and Cincinnati Veteran Affairs Medical Center

Overview:
Dr. Ho's research focus on (1) hormonal carcinogenesis of the prostate, breast, ovaries and endometrium; (2) the developmental bases of disease susceptibility by applying epigenetics to endocrine-related cancers and other complex diseases such as asthma, and (3) the development and validation of molecular biomarkers for the measurement of toxic exposure and various disease states in clinical and epidemiological studies. She uses a host of "omics" discovery platforms to address two of the important challenges in environmental exposure and human health – interactions among multiple exposures with various developmental stages, and the trans-generational effects of exposure.

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Current project: The developmental effects of in utero exposure to bisphenol A with high fat diet in mammary cancer risk in later-life.

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Model: Rat

Toxicant: Bisphenol A, high fat (life style modifier).

Methods: Prenatal exposure, DMBA-induced mammary carcinogenesis, disruption of female reproductive function, identification of epigenetic and transcriptional disruption.

Endpoints and results: Dams reproductive capacity, pre-pubertal mammary gland development, susceptibility to DMBA-induced mammary carcinogenesis.

……

Selected publications:

Ho SM, Lee M-T, Lam H-M, Leung YK. (2011) Estrogens and prostate cancer: etiology, mediators, prevention, and management. Endocrinol Metab Clin North Am. 40:591-614. PMID: 21889723.

Wu T, Giovannucci E, Welge J, Mallick P, Tang WY, Ho SM. (2011) Measurement of GSTP1 promoter methylation in body fluids may complement PSA screening: a meta-analysis. Br J Cancer. 105:65-73. PMID: 21654682

Hu WY, Shi G-B, Lam H-M, Hu D-P, Ho SM, Madueke IC, Kajdacsy-Balla A, and Prins GS. (2011) Estrogen-initiated transformation of prostate epithelium derived from normal human prostate stem-progenitor cells. Endocrinology, 152:2150-2163. PMID: 21427218

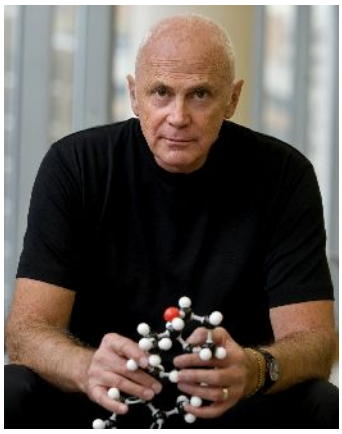
Zhang X and Ho SM. (2011) Epigenetics meets endocrinology. J Mol Endocrinol. 46:R11-32. PMID: 21106863

Ouyang B, Leung YK, Wang V, Chung E, Levin L, Bracken B, Cheng L, and Ho SM. (2011) Alpha-methylacyl-CoA racemase spliced variants and their expression in normal and malignant prostate tissues. Urology 77:249.e1-7. PMID: 21195844

Tarapore P, Shu Y, Guo P, and Ho SM. (2011) Application of Phi29 motor pRNA for targeted therapeutic delivery of siRNA silencing metallothionein-IIA and survivin in ovarian cancers. Molecular Therapy 19:386-394, PMID: 21063391

Tam NN, Szeto CY, Freudenberg JM, Fullenkamp AN, Medvedovic M, Ho SM. (2010) Research Resource: Estrogen-Driven Prolactin-Mediated Gene-Expression Networks in Hormone-Induced Prostatic Intraepithelial Neoplasia. Mol Endocrinol 24:2207-2217, PMID: 20861223

Scientific Session B: Developmental Estrogenization Syndrome



John McLachlan, PhD

Department of Pharmacology
Department Ecology and Evolutionary Biology
Tulane University, New Orleans

Overview: McLachlan studies the estrogenic chemical induction of differentiation defects in the reproductive system. Cell signaling and transcriptional regulation with an emphasis on epigenetic change underlie the work. McLachlan worked at NIEHS/NIH for twenty years, before moving to Tulane University in 1995 as the Weatherhead Distinguished Chair of Environmental Studies.

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Current project: Understanding induction of differentiation defects through non-coding RNAs.

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Model: Cell culture with human reproductive tract and breast cells.

Toxicant: EDCs with emphasis on BPA, DDT, genestein, DES.

Methods: Cellular, molecular and functional.

Endpoint: Understand the initial steps in EDC induced misprogramming.

……

Selected publications:

McLachlan JA, Tilghman SL, Burow ME, Bratton MR. Environmental signaling and reproduction: A comparative biological and chemical perspective. Mol Cell Endocrinol. 2011 Dec 8. [Epub ahead of print].

Jiang Q, Payton-Stewart F, Elliott S, Driver J, Rhodes LV, Zhang Q, Zheng S, Bhatnagar D, Boue SM, Collins-Burow BM, Sridhar J, Stevens C, McLachlan JA, Wiese TE, Burow ME, Wang G. Effects of 7-O substitutions on estrogenic and anti-estrogenic activities of daidzein analogues in MCF-7 breast cancer cells. J Med Chem. 2010 Aug 26;53(16):6153-63.

Bratton MR, Duong BN, Elliott S, Weldon CB, Beckman BS, McLachlan JA, Burow ME. Regulation of ERalpha-mediated transcription of Bcl-2 by PI3K-AKT crosstalk: implications for breast cancer cell survival. Int J Oncol. 2010 Sep;37(3):541-50.

Tilghman SL, Nierth-Simpson EN, Wallace R, Burow ME, McLachlan JA. Environmental hormones: Multiple pathways for response may lead to multiple disease outcomes. Steroids. 2010 Aug-Sep; 75(8-9):520-3. Epub 2010 May 11. Review.

Myers JP, vom Saal FS, Akingbemi BT, Arizono K, Belcher S, Colborn T, Chahoud I, Crain DA, Farabollini F, Guillette LJ Jr, Hassold T, Ho SM, Hunt PA, Iguchi T, Jobling S, Kanno J, Laufer H, Marcus M, McLachlan JA, Nadal A, Oehlmann J, Olea N, Palanza P, Parmigiani S, Rubin BS, Schoenfelder G, Sonnenschein C, Soto AM, Talsness CE, Taylor JA, Vandenberg LN, Vandenbergh JG, Vogel S, Watson CS, Welshons WV, Zoeller RT. Why public health agencies cannot depend on good laboratory practices as a criterion for selecting data: the case of bisphenol A. Environ Health Perspect. 2009 Mar;117(3):309-15. Epub 2008 Oct 22.

Nierth-Simpson EN, Martin MM, Chiang TC, Melnik LI, Rhodes LV, Muir SE, Burow ME, McLachlan JA. Human uterine smooth muscle and leiomyoma cells differ in their rapid 17beta-estradiol signaling: implications for proliferation. Endocrinology. 2009 May;150(5):2436-45. Epub 2009 Jan 29.

Crain DA, Janssen SJ, Edwards TM, Heindel J, Ho SM, Hunt P, Iguchi T, Juul A, McLachlan JA, Schwartz J, Skakkebaek N, Soto AM, Swan S, Walker C, Woodruff TK, Woodruff TJ, Giudice LC, Guillette LJ Jr. Female reproductive disorders: the roles of endocrine-disrupting compounds and developmental timing. Fertil Steril. 2008 Oct;90(4):911-40. Review.

Session III – Fertility & Fetal Outcomes

Speaker 11

Shanna H. Swan, PhD

Mount Sinai School of Medicine
Department of Preventive Medicine

Overview: Early life exposures and sexually dimorphic reproductive tract development. Exposures of particular interest: phthalates, BPA, stress. Outcomes of particular interest: testicular dysgenesis (including anogenital distance), play behavior and other neurodevelopmental outcomes, growth (growth rate and obesity); risk factors for impaired fertility and semen quality, PCOS.

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Current projects: The Study for Future Families (SFF) (children now 5-10 years); The Infant Development and the Environment Study (TIDES) currently enrolling; children now being born; Rochester Young Men's Study, Spanish Young Men and Women Studies.

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Model: Human prenatal, infant, early childhood (multicenter pregnancy cohort, prospective); population-based samples of adult men and women.

Toxicant: Phthalates, BPA, pesticides, stress.

Methods: For pregnancy cohort studies; Urine and blood in collected in pregnancy, assayed for chemicals and hormones, multiple questionnaires, birth exams, follow-up for later developmental endpoints; Recruitment of fertile and healthy men and women for genital measures, semen quality and PCOS; recruitment of testicular cancer cases and controls.

Endpoints: Anogenital distance, testes volume and other genital measures, anthropometry, play behavior, gender identity, games and activities and food preference, asthma and allergy-related symptoms, CBCL, BRIEFS; semen quality, PCOS, testicular cancer.

……

Selected publications:

Gaskins AJ, Colaci D, Mendiola J, Swan SH, Chavarro J. Dietary Patterns and Semen Quality in Young Men. Fertility and Sterility. 2011 Sep;96(3):S8-S.

Mendiola J, Jorgensen N, Andersson AM, Calafat AM, Silva MJ, Redmon JB, et al. Associations between urinary metabolites of di(2-ethylhexyl) phthalate and reproductive hormones in fertile men. International Journal of Andrology. 2011 Aug;34(4):369-78.

Mendiola J, Stahlhut RW, Jorgensen N, Liu F, Swan SH. Shorter Anogenital Distance Predicts Poorer Semen Quality in Young Men in Rochester, New York. Environ Health Persp. 2011 Jul;119(7):958-63.

vom Saal FS, Akingbemi BT, Belcher SM, Crain DA, Crews D, Guidice LC, et al. Flawed Experimental Design Reveals the Need for Guidelines Requiring Appropriate Positive Controls in Endocrine Disruption Research. Toxicological Sciences. 2010 Jun;115(2):612-3.

Swan SH, Liu F, Hines M, Kruse RL, Wang C, Redmon JB, et al. Prenatal phthalate exposure and reduced masculine play in boys. International Journal of Andrology. 2010 Apr;33(2):259-67.

Swan SH, Hunt P and Giudice L. "Conclusions – what does this all mean, and where are we going?" Environmental Impacts on Reproductive Health and Fertility. Tracey J Woodruff, Sarah J Janssen, Louis J Guillette Jr, and Linda C Giudice. Cambridge: Cambridge University Press, 2010. 240 – 242. (Not subject to PubMed Central Policy).

Mendiola J, Jorgensen N, Andersson AM, Calafat AM, Ye XY, Redmon JB, et al. Are Environmental Levels of Bisphenol A Associated with Reproductive Function in Fertile Men? Environ Health Persp. 2010 Sep;118(9):1286-91.

Jørgensen N, Liu F, Andersson AM, Vierula M, Irvine DS, Auger J, et al. Serum inhibin-b in fertile men is strongly correlated with low but not high sperm counts: a coordinated study of 1,797 European and US men. Fertility and Sterility. 2010 Nov;94(6):2128-34.

Speaker 12

Michael S. Bloom, PhD

Department of Environmental Health Sciences
Department of Epidemiology and Biostatics
School of Public Health, University at Albany
State University of New York

Overview: Our group is interested in the effects of long-term, 'background' exposures to widespread environmental pollutants on in vitro fertilization (IVF); including organic compounds and elements.

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Current project: The Study of Metals and Assisted Reproductive Technologies (SMART).

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Model: A cohort of IVF patients and their male partners receiving infertility treatment at the University of California at San Francisco Center for Reproductive Health.

Toxicants: Bisphenol A (BPA), mercury (Hg0), cadmium (Cd), lead (Pb) and other elements.

Methods: Prospective epidemiologic study of 58 couples completing a 1st cycle of IVF at UCSF with collection of bio-specimens from women and men on the day of oocyte retrieval (blood, urine, follicular fluid, seminal fluid).

Endpoints and results: Inverse association between female serum unconjugated BPA and estrogen synthesis in response to controlled ovarian stimulation; inverse association between female serum unconjugated BPA and oocyte maturity following hCG 'trigger' in Asian women; inverse association between female and Asian male serum unconjugated BPA and oocyte fertilization; association between male BPA and embryo quality indicators; inverse association between female blood Pb and oocyte maturity; inverse association between male urine Cd and oocyte fertilization; association between female blood Pb and embryo quality indicators; association between male blood Hg and Pb and embryo quality indicators; inverse association between female blood Hg and embryo implantation. Associations for female blood Hg and Pb, and serum unconjugated BPA with DNA methylation at GSTM1/5, COL1A2 and TSP50, respectively.

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Selected publications:

Bloom MS, Kim D, vom Saal FS, Taylor JA, Cheng G, Lamb JD, Fujimoto VY. Bisphenol A exposure reduces the estradiol response to gonadotropin stimulation during in vitro fertilization. Fertil Steril 2011;96(3):672-677.

Fujimoto VY, Kim D, vom Saal FS, Lamb JD, Taylor JA, Bloom MS. Serum unconjugated bisphenol a concentrations in women may adversely influence oocyte quality during in vitro fertilization. Fertil Steril 2011;95(5):1816-1819.

Bloom MS, Parsons PJ, Kim D, Steuerwald AJ, Vaccari S, Cheng G, Fujimoto VY. Toxic trace metals and embryo quality indicators during in vitro fertilization (IVF). Reprod Toxicol 2011;31(2):164-170.

Bloom MS, vom Saal FS, Kim D, Taylor JA, Lamb JD, Fujimoto VY. Serum unconjugated bisphenol a concentrations in men may influence embryo quality indicators during in vitro fertilization. Environ Toxicol Pharmacol 2011;32(2):319-323.

Kim K, Steuerwald AJ, Parsons PJ, Fujimoto VY, Browne RW, Bloom MS. Biomonitoring for exposure to multiple trace elements via analysis of urine from participants in the study of metals and assisted reproductive technologies (SMART). J Environ Monit 2011;13(9):2413-2419.

Bloom MS, Parsons PJ, Steuerwald AJ, Schisterman EF, Browne RW, Kim K, Coccaro GA, Conti GC, Narayan N, Fujimoto VY. Toxic trace metals and human oocytes during in vitro fertilization (IVF). Reprod Toxicol 2010;29(3):298-305.

Kim K, Fujimoto VY, Parsons PJ, Steuerwald AJ, Browne RW, Bloom MS. Recent cadmium exposure among male partners may affect oocyte fertilization during in vitro fertilization (IVF). J Assist Reprod Genet 2010;27(8):463-468.

Speaker 13

Vasantha Padmanabhan, PhD

Professor of Pediatrics
Professor of Obstetrics and Gynecology
Professor of Molecular & Integrative Physiology
Director of Pediatric Endocrine Research
University of Michigan

Overview: Our research focus is on the effects of BPA on developmental programming.

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Current projects:

NIH ES016541 Bisphenol A and reproductive dysfunction

Hypothesis: prenatal exposure to BPA at levels similar to what human fetuses are exposed to, will disrupt adult reproductive function by disrupting the mechanisms controlling postnatal neuroendocrine feedback controls of LH secretion and ovarian sensitivity to gonadotropins. Further, postnatal adiposity would exacerbate severity of reproductive disruptions in prenatal T-treated sheep. In parallel, insulin sensitivity is being monitored.

NIH ES016541 Bisphenol A and reproductive dysfunction (ARRA supplement)

Hypothesis: prenatal exposure to BPA at levels found in humans disrupts free fatty acid (FFA) balance and induces oxidative stress at the systemic and adipose tissue level. Four species (mouse, rat, sheep and human) are used to assess the impact of prenatal BPA exposure on oxidative-stress marker and FFA profiles. Mouse samples are provided by Dana Dolinoy and rat samples by Heather Patisaul.

NIH ES17005 Endocrine disruptors and fetal development

The goal of this is to determine if poor pregnancy outcomes and low birth weight offspring in humans are correlated with increased exposure to BPA and consequent epigenetic modifications. Maternal and cord blood samples are being collected during first trimester at the time of birth.

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Model: NIH ES016541: Sheep

NIH ES016541 (ARRA supplement): Sheep, rat, mouse and human

NIH ES17005: human

Toxicant: Bisphenol A

Methods:

NIH ES016541: Exposure of pregnant sheep to bisphenol A from days 30-90 of gestation.

NIH ES016541 (ARRA supplement): Measures of FFA and oxidative markers in blood samples from prenatal BPA-treated female fetuses of mouse, rat and sheep, plus cord samples from subjects with high and low maternal BPA levels.

NIH ES17005: Collect first trimester maternal and term maternal and cord samples for measures of BPA and epigenetic modifications (cord only)

Endpoints:

NIH ES016541: Cycle disruption, neuroendocrine feedback, ovarian disruptions and insulin resistance

NIH ES016541 (ARRA supplement): Measures of FFA and oxidative stress.

NIH ES17005: BPA measures, epigenetics and birth weight.

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Selected publications:

Padmanabhan V, Veiga-Lopez A. Developmental origin of reproductive and metabolic dysfunctions: androgenic versus estrogenic reprogramming. Semin Reprod Med. 2011 May;29(3):173-86. Epub 2011 Jun 27.

Mahoney MM, Padmanabhan V. Developmental programming: impact of fetal exposure to endocrine-disrupting chemicals on gonadotropin-releasing hormone and estrogen receptor mRNA in sheep hypothalamus. Toxicol Appl Pharmacol. 2010 Sep 1;247(2):98-104. Epub 2010 Jun 4.

Padmanabhan V, Sarma HN, Savabieasfahani M, Steckler TL, Veiga-Lopez A. Developmental reprogramming of reproductive and metabolic dysfunction in sheep: native steroids vs. environmental steroid receptor modulators. Int J Androl. 2010 Apr;33(2):394-404. Epub 2010 Jan 12.

Savabieasfahani M, Kannan K, Astapova O, Evans NP, Padmanabhan V. Developmental programming: differential effects of prenatal exposure to bisphenol-A or methoxychlor on reproductive function. Endocrinology. 2006 Dec;147(12):5956-66. Epub 2006 Aug 31.

Speaker 14

Hugh Taylor, MD

Section Chief, Reproductive Endocrinology and Infertility; Director, Yale Center for Endometrium and Endometriosis; Director, Yale Center for Reproductive Biology

Overview: Homeobox genes, embryo implantation, endometriosis, stem cells, menopause, uterine development, endocrine disruption, developmental programming.

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Current project: Effect of DES/BPA on HOX Gene Expression

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Model: Mouse.

Toxicant: DES, BPA.

Methods: ChIP analysis.

Endpoint: Alteration of the HOX code, *In utero* alterations in uterine HOXA10 Methylation induced by BPA, Reporter activity driven by the methylated and unmethylated ERE.

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Selected publications:

Cakmak H and Taylor HS. Implantation failure: molecular mechanisms and clinical treatment. Human Reproduction Update 2011, 17(2):242-253.

Doherty LF, Bromer JG, Zhou Y, Aldad TS, Taylor HS. In utero exposure to diethylstilbestrol (DES) or bisphenol-A (BPA) increases EZH2 expression in the mammary gland: an epigenetic mechanism linking endocrine disruptors to breast cancer. Horm Cancer. 2010 Jun;1(3):146-55.

Bromer JG, Zhou Y, Taylor MB, Doherty L, Taylor HS. Bisphenol-A exposure in utero leads to epigenetic alterations in the developmental programming of uterine estrogen response. FASEB J. 2010 Jul;24(7):2273-80. Epub 2010 Feb 24.

Speaker 15

Carmen J. Williams, PhD, MD

Reproductive Medicine Group
Reproductive and Developmental Toxicology
NIEHS Intramural

Overview: We use a mouse model to study the effects on female reproductive health of neonatal exposure to the phytoestrogen genistein or to DES. Female mice treated neonatally with genistein are completely infertile even after superovulation. Defects in both the oviduct and uterus contribute to this phenotype. We are currently examining how genistein or DES exposure leads to these defects in the female reproductive tract environment. Overall, this project has direct relevance to understanding how endocrine disrupting chemicals or other environmental factors can impact early reproductive events and potentially lead to reproductive failure in women.

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Current project: Effects of environmental chemical exposures on early reproduction.

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Model: Mouse.

Toxicant: Genistein and DES.

Methods: Immunohistochemistry, microarrays, qPCR, ChIP.

Endpoint: Alterations in gene expression or chromatin modifications.

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Selected publications:

Padilla-Banks E, Jefferson WN, Myers PH, Goulding DR, Williams CJ. Neonatal phytoestrogen exposure causes hypospadias in female mice. Mol Reprod Dev. 2012 Jan;79(1):3. doi: 10.1002/mrd.21395. Epub 2011 Oct 11. No abstract available.

Jefferson WN, Padilla-Banks E, Phelps JY, Gerrish KE, Williams CJ. Permanent oviduct posteriorization after neonatal exposure to the phytoestrogen genistein. Environ Health Perspect. 2011 Nov;119(11):1575-82. Epub 2011 Aug 2.

Jefferson WN, Williams CJ. Circulating levels of genistein in the neonate, apart from dose and route, predict future adverse female reproductive outcomes. Reprod Toxicol. 2011 Apr;31(3):272-9. Epub 2010 Oct 15. Review.

Jefferson WN, Padilla-Banks E, Goulding EH, Lao SP, Newbold RR, Williams CJ. Neonatal exposure to genistein disrupts ability of female mouse reproductive tract to support preimplantation embryo development and implantation. Biol Reprod. 2009 Mar;80(3):425-31. Epub 2008 Nov 12.

Research Summaries

of Scientists Not Presenting

Donna Baird, PhD

Principal Investigator, Epidemiology
NIEHS Intramural

Overview: Research on female fecundability, early pregnancy, reproductive hormones, menopause, and uterine fibroids.

Current project: Examining menstrual-cycle-specific BPA levels and time to pregnancy, early pregnancy loss, and events of early pregnancy such as time to implantation and corpus luteum rescue.

Model: Human study.

Toxicant: BPA.

Methods: Epidemiology.

Endpoints: Multiple.

Selected publications:

Peddada, SD, Laughlin, K, Miner, K, Guyon, J-P, Haneke, K., Vahdat, HL, Semelka, RC, Kowalik, A, Armao, D, Davis, B, and Baird, DD. Growth of uterine leiomyomata among pre-menopausal black and white women. Proceedings National Academy of Sciences USA, 105:19887-92, 2008.

Baird DD, Weinberg CR, McConnaughey DR, Wilcox AJ. Rescue of the corpus luteum in normal human pregnancy. Biol Reprod 2003 68:448-456.

Wegienka G, Baird DD, Hirtz-Picciotto I, Harlow SD, Steege JF, Hill MC, Schectman JM, Hartmann KE. Self-reported heavy bleeding associated with uterine leiomyomata. Obstet Gynecol 2003 101:431-437.

Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: Ultrasound evidence. Am J Obstet. Gynecol 2003 188:100-107.

Katherine (Katie) Burns, PhD
Post Doctoral Scholar

NIEHS Intramural

Overview: I am a postdoctoral fellow working with Dr. Ken Korach in the Receptor Biology Group on the Stimulation of Estrogenic Responses. Our research focus has been to study the development of endometriosis-like lesions in an estrogen receptor mediated manner. We use a mouse model of endometriosis to examine both host genotype and lesion genotype on the initiation and progression of disease.

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Current project: Project focus will move to the treatment of mice with BPA and access the progression of endometriosis-like disease in this mouse model.

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Model: Mouse model of endometriosis.

Toxicant: BPA.

Methods: Mouse model of endometriosis, ELISA, real time-PCR, histology, immunohistochemistry.

Endpoint: The focus will be on the development and growth of endometriosis-like lesions after treatment of environmental toxicants to determine the potential relevance of these toxicants on human disease.

…….

Selected publications:

Burns, K. A., Y. Li, et al. Selective mutations in estrogen receptor alpha D-domain alters nuclear translocation and non-estrogen response element gene regulatory mechanisms. The Journal of biological chemistry 286(14): 12640-12649. 2011.

Hewitt, S.C., Korach, K.S. Estrogenic Activity of Bisphenol A and 2,2-bis(p-hydroxyphenyl)-1,1,1-trichloroethane (HPTE) Demonstrated in Mouse Uterine Gene Profiles. Environmental health perspectives 119(1):63-70, 2011.

Ribas, V., Drew, B.G., Le, J.A., Soleymani, T., Daraei, P., Sitz, D., Mohammad, L., Henstridge, D.C., Febbraio, M.A., Hewitt, S.C., Korach, K.S., Bensinger, S..J, Hevener, A.L. Myeloid-specific estrogen receptor alpha deficiency impairs metabolic homeostasis and accelerates atherosclerotic lesion development. Proceedings of the National Academy of Sciences of the United States of America 108(39):16457-16462, 2011.

Barbara Cohn, PhD, MPH, MCP

Director Child Health and Development Studies
Public Health Institute

Overview: Early life predictors of health over the life-span and across generations.

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Current project: Multiple endpoints: 50 year follow-up of 20,000 pregnancies, continuing active follow-up of 2nd and 3rd generation females, with male follow-up and 4th generation follow-up planned.

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Model: Human, epidemiological studies.

Toxicant: Multiple-environmental chemicals including pops, pharmaceuticals, tobacco, caffeine, alcohol.

Methods: Prospective epidemiological studies.

Endpoints and results: Pregnancy complications and outcome, placenta characteristics, infant and child health, growth and development, neurodevelopment, social development, reproduction (e.g. PCO, pre-eclampsia), semen quality, time to pregnancy, obesity, aging (menopause) cancer, cardiovascular disease and risk factors for these, mental health and mental health symptoms.

……

Selected publications:

Cohn, B.A., et al., Polychlorinated biphenyl (PCB) exposure in mothers and time to pregnancy in daughters. Reproductive Toxicology, 2011. 31(3): p. 290-6..

Cohn, B.A. Developmental and Environmental Origins of Breast Cancer: DDT as a Case Study. Reproductive Toxicology 2011 Apr;31(3):302-11.

Cohn, B.A., P.M. Cirillo, and R.E. Christianson, Prenatal DDT Exposure and Testicular Cancer: A Nested Case-Control Study. Archives of Occupational and Environmental Health, 2010. 65(3): p. 127-134.

Mongraw-Chaffin, M.L., P.M. Cirillo, and B.A. Cohn, Preeclampsia and Cardiovascular Disease Death: Prospective Evidence From the Child Health and Development Studies Cohort. Hypertension, 2010. 56(1): p. 166-171.

Barbara Davis, VMD, PhD, DACVP

Tufts Cummings School of Veterinary Medicine

Overview: Dr. Davis's longstanding research interests are in the discovery of gene-environment interactions that contribute to cancer over the lifespan of an individual. She is internationally recognized for her expertise in female reproductive pathology and oncology having spent a significant portion of her career at the National Institutes of Environmental Health Sciences, NIH, as Head of the Female Reproductive Pathology group and Acting Chief of the Laboratory of Women's Health. Current research initiatives focus on multigenerational effects on female endocrine systems and the reproductive tract, including toxicity and cancer.

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Current project: Effects of Multigenerational Exposure to BPA on Female Endocrine Systems and Reproductive Tract, in collaboration with Ana Soto.

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Model: Rat

Toxicant: BPA

Methods: Reproductive assessment, histopathology

Endpoint: Toxicity, cancer

……

Selected publications:

Davis BJ, Haneke KE, Miner K, Kowalik, A, Barrett JC, Peddada S, Baird DD. The Fibroid Growth Study: Determinants of therapeutic intervention. Journal of Women's Health , 18(5):725-32, 2009.

Peddada, SD, Laughlin, K, Miner, K, Guyon, J-P, Haneke, K., Vahdat, HL, Semelka, RC, Kowalik, A, Armao, D, Davis, B, and Baird, DD. Growth of uterine leiomyomata among pre-menopausal black and white women. Proceedings National Academy of Sciences USA, 105:19887-92, 2008.

Cook JD, Davis BJ, Goewey JA, Berry TD, Walker CL. Identification of a sensitive period for developmental programming that increases risk for uterine leiomyoma in Eker rats. Reproductive Sciences, 14:121-36, 2007

Atanassov, B, Barrett, JC, Davis, BJ. Homozygous germ line mutation in exon 27 of murine Brca2 isrupts the Fancd2-Brca2 pathway in the homologous recombination mediated DNA inter-strand cross-links repair but does not affect meiosis. Genes, Chromosomes and Cancer, 44: 429-437, 2005.

Cook, JD, Davis, BJ, Cai, S-L, Barrett, JC, Conti, CJ, Walker, CL. Interaction between genetic susceptibility and early life environmental exposure determines tumor suppressor gene penetrance. Proceedings National Academy of Sciences USA, 102: 8644-9, 2005.

Darlene Dixon, DVM, PhD, DACVP
Molecular Pathogenesis Group
National Toxicology Program (NTP) Laboratories
NIEHS Intramural

Overview: Our research focuses on understanding molecular mechanisms of tumor cell proliferation/inhibition, and delineating the role of growth factor receptor signaling and signaling pathway interactions in uterine fibroids. We evaluate the effects of environmental chemicals on tumor cell growth and disease progression. Our lab also studies the molecular mechanisms of toxicity and carcinogenicity of chemicals evaluated by the NTP testing program.

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Current project: Molecular pathogenesis of female reproductive tract diseases and the role of environmental chemicals.

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Model: Cell Cultures, Tissue samples (human, rats, mice).

Toxicant: Genistein, Fenvalerate

Methods: RNA and protein analyses, FACS, gene transfection, immunoprecipitation, immunohistochemistry/fluorescence, and light/confocal microscopy, histopathology

Endpoint: Identifying and understanding signaling pathways/novel signaling proteins that regulate disease processes and how environmental chemicals interact with these pathways/proteins.

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Selected publications:

Di X, Andrews DM, Tucker CJ, Yu L, Moore AB, Zheng X, Castro L, Hermon T, Xiao H, Dixon D. A high concentration of genistein down-regulates Activin A, Smad3 and other TGF-beta pathway genes in human uterine leiomyoma cells. Exp Mol Med. 2012 Jan 6. [Epub ahead of print]

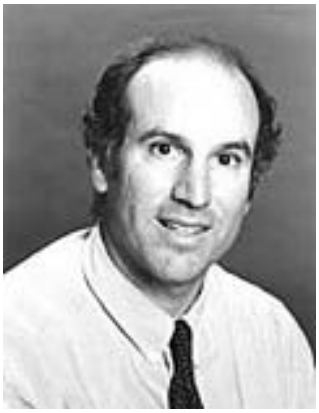
Gao X, Yu L, Castro L, Moore AB, Hermon T, Bortner C, Sifre M, Dixon D. An endocrine-disrupting chemical, fenvalerate, induces cell cycle progression and collagen type I expression in human uterine leiomyoma and myometrial cells. Toxicol Lett. 2010 Jul 15;196(3):133-41.

Moore AB, Yu L, Swartz CD, Zheng X, Wang L, Castro L, Kissling GE, Walmer DK, Robboy SJ, Dixon D. Human uterine leiomyoma-derived fibroblasts stimulate uterine leiomyoma cell proliferation and collagen type I production, and activate RTKs and TGF beta receptor signaling in coculture. Cell Commun Signal. 2010 Jun 10;8:10.

Yu L, Moore AB, Dixon D. Receptor tyrosine kinases and their hormonal regulation in uterine leiomyoma. Semin Reprod Med. 2010 May;28(3):250-9. Review.

Di X, Yu L, Moore AB, Castro L, Zheng X, Hermon T, Dixon D. A low concentration of genistein induces estrogen receptor-alpha and insulin-like growth factor-I receptor interactions and proliferation in uterine leiomyoma cells. Hum Reprod 2008 Aug;23(8):1873-83.

Moore AB, Castro L, Yu L, Zheng X, Di X, Sifre MI, Kissling GE, Newbold RR, Bortner CD, Dixon D. Stimulatory and inhibitory effects of genistein on human uterine leiomyoma cell proliferation are influenced by the concentration. Hum Reprod. 2007 Oct;22(10):2623-31. Epub 2007 Aug 27.



Russ Hauser, ScD, MPH, MD

Professor of Obstetrics, Gynecology and Reproductive Biology
Harvard School of Public Health

Overview: My research focuses on the impact of environmental chemicals on development and reproductive function, specifically chemicals that disrupt endocrine signaling. These chemicals include persistent chlorinated compounds, pesticides, phthalates and bisphenol A. My study population consists of couples using assisted reproductive technologies (ART) for infertility. This provides an innovative model for studying embryo-fetal development as it relates to both paternal and maternal exposure to environmental chemicals. ART allows for the identification of the biological mechanisms underlying infertility and early pregnancy loss, including disruption of gametogenesis, oocyte fertilization, and pre- and post-implantation embryonic development.

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Current project: BPA, phthalates, fertility and pregnancy outcomes.

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Model: Humans (ART).

Toxicant: BPA, phthalates.

Methods: Prospective Pre-conception Cohort Study of couples undergoing ART.

Endpoints and results: Ovarian response to hyperstimulation, ovarian reserve, IVF outcomes, implantation, pregnancy loss. Specific endpoints of interest:

1. Male endpoints: conventional semen parameters, reproductive hormones, and sperm DNA damage.
2. Pregnancy endpoints: failure of pre-implantation development, implantation failure, pre-clinical pregnancy loss, spontaneous miscarriage, stillbirth, and altered fetal growth.

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Selected publications:

Humblet O, Williams PL, Korrick SA, Sergeyev O, Emond C, Birnbaum LS, Burns JS, Altshul L, Patterson DG Jr, Turner WE, Lee MM, Revich B, Hauser R. Dioxin and polychlorinated biphenyl concentrations in mother's serum and the timing of pubertal onset in sons. Epidemiology. 2011 Nov;22(6):827-35.

Missmer SA, Pearson KR, Ryan LM, Meeker JD, Cramer DW, Hauser R. Analysis of multiple-cycle data from couples undergoing in vitro fertilization: methodologic issues and statistical approaches. Epidemiology. 2011 Jul;22(4):497-504.

Chavarro JE, Furtado J, Toth TL, Ford J, Keller M, Campos H, Hauser R. Trans-fatty acid levels in sperm are associated with sperm concentration among men from an infertility clinic. Fertil Steril. 2011 Apr;95(5):1794-7. Epub 2010 Nov 11.

Adibi JJ, Whyatt RM, Hauser R, Bhat HK, Davis BJ, Calafat AM, Hoepner LA, Perera FP, Tang D, Williams PL. Transcriptional biomarkers of steroidogenesis and trophoblast differentiation in the placenta in relation to prenatal phthalate exposure. Environ Health Perspect. 2010 Feb;118(2):291-6.

Adibi JJ, Hauser R, Williams PL, Whyatt RM, Thaker HM, Nelson H, Herrick R, Bhat HK. Placental biomarkers of phthalate effects on mRNA transcription: application in epidemiologic research. Environ Health. 2009 Apr 23;8:20.

Sylvia C. Hewitt
Biologist, Receptor Biology Section
Laboratory of Reproductive and Developmental Toxicology
NIEHS Intramural

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Current project: Linking Mouse Uterine Estrogenic Transcriptional, Cistromic and Biological Endpoints.

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Model: Ovariectomized mouse uterus.

Toxicant: BPA, HPTE.

Methods: In Vivo Microarray, RT-PCR, ChiP seq, ChIP PCR_following acute dosing (0-72 hours).

Endpoint: Changes is transcription, ER and Pol2 interaction sequences, cell proliferation, apoptosis.

……

Selected publications:

Hewitt, S. C., G. E. Kissling, et al. 2010. Biological and biochemical consequences of global deletion of exon 3 from the ER alpha gene. Faseb J 24(12): 4660-4667.

Hewitt, S. C. and K. S. Korach; 2011. Estrogenic Activity of Bisphenol A and 2,2-bis(p-Hydroxyphenyl)-1,1,1-trichloroethane (HPTE) Demonstrated in Mouse Uterine Gene Profiles. Environ Health Perspect 119(1): 63-70.

Winuthayanon, W., S. C. Hewitt, et al. 2010. Uterine epithelial estrogen receptor alpha is dispensable for proliferation but essential for complete biological and biochemical responses. Proc Natl Acad Sci U S A 107(45): 19272-19277.

Hewitt, S. C., Y. Li, et al. 2010. Estrogen-mediated regulation of Igf1 transcription and uterine growth involves direct binding of estrogen receptor alpha to estrogen-responsive elements. J Biol Chem 285(4): 2676-2685.

Patricia Hunt, PhD

Meyer Distinguished Professor
School of Molecular Biosciences
Washington State University

Overview: Fertility studies in male and female mice, meiotic analyses of human fetal oocytes.

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Current project: Meiotic Studies of Chemicals with Estrogenic Activity.

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Model: Mouse and human.

Toxicant: Bisphenol A and ethinyl estradiol.

Methods: a) Mouse: Oral or time release pellet implants during fetal and perinatal development.

b) Human: collection of maternal serum, urine and amniotic fluid, fetal ovaries, liver and placenta from intentional terminations of pregnancy.

Endpoints: a) Mouse: fertility studies in males and females, meiotic analyses, and assessment of aneuploidy levels b) Human: meiotic analyses of fetal oocytes

……

Selected publications:

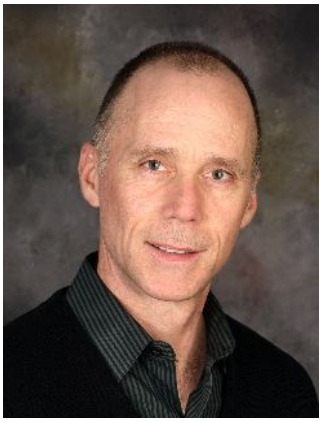
Nagaoka, S. I., C. A. Hodges, et al. 2011. Oocyte-specific differences in cell-cycle control create an innate susceptibility to meiotic errors. Current Biology: CB 21(8): 651-657.

Taylor, J. A., F. S. Vom Saal, et al. 2011. Similarity of bisphenol A pharmacokinetics in rhesus monkeys and mice: relevance for human exposure. Environmental Health Perspectives 119(4): 422-430.

Lawson, C., M. Gieske, et al. 2011. Gene expression in the fetal mouse ovary is altered by exposure to low doses of bisphenol A. Biology of Reproduction 84(1): 79-86.

vom Saal FS, Akingbemi BT, Belcher SM, Crain DA, Crews D, Guidice LC, Hunt PA, Leranth C, Myers JP, Nadal A, Olea N, Padmanabhan V, Rosenfeld CS, Schneyer A, Schoenfelder G, Sonnenschein C, Soto AM, Stahlhut RW, Swan SH, Vandenberg LN, Wang HS, Watson CS, Welshons WV, Zoeller RT: Flawed experimental design reveals the need for guidelines requiring appropriate positive controls in endocrine disruption research. Toxicological Sciences 2010; 115: 612-3.

Swan SH, Hunt P and Giudice L. "Conclusions – what does this all mean, and where are we going?" Environmental Impacts on Reproductive Health and Fertility. Tracey J Woodruff, Sarah J Janssen, Louis J Guillette Jr, and Linda C Giudice. Cambridge: Cambridge University Press, 2010. 240 – 242. (Not subject to PubMed Central Policy).



Matthew P. Longnecker, PhD, MD

Epidemiology Branch, NIEHS Intramural

Overview: Our research program focuses on the health effects of early-life exposure to environmental contaminants. He has ongoing projects to examine the effects of DDT, bisphenol A, and organophosphate pesticides. These projects are being conducted in Africa, Mexico, the Netherlands, and Norway.

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Current project: Perfluorinated compounds and preeclampsia

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Model: Norwegian Mother and Child Cohort Study

Toxicant: Perfluorooctane sulfate, perfluorooctanoate.

Methods: Observational, biomarker-based measures of exposure, prospective design.

Endpoint: Preeclampsia.

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Selected publications:

Cupul-Uicab LA, Skjaerven R, Haug K, Melve KK, Engel SM, Longnecker MP. In Utero Exposure to Maternal Tobacco Smoke and Subsequent Obesity, Hypertension, and Gestational Diabetes Among Women in The MoBa Cohort. Environ Health Perspect. 2011 Nov 29. [Epub ahead of print]

Whitworth KW, Haug LS, Baird DD, Becher G, Hoppin JA, Skjaerven R, Thomsen C, Eggesbo M, Travlos G, Wilson R, Longnecker MP. Perfluorinated Compounds and Subfecundity in Pregnant Women. Epidemiology. 2011 Nov 10. [Epub ahead of print]

Trabert B, Longnecker MP, Brock JW, Klebanoff MA, McGlynn KA. Maternal Pregnancy Levels of Trans-Nonachlor and Oxychlordane and Prevalence of Cryptorchidism and Hypospadias in Male Offspring. Environ Health Perspect. 2011 Oct 5. [Epub ahead of print]

Zhou H, You J, Qin G, Longnecker MP. A Partially Linear Regression Model for Data from an Outcome-Dependent Sampling Design.J R Stat Soc Ser C Appl Stat. 2011 Aug;60(4):559-574.

Zhou H, You J, Qin G, Longnecker MP. Associations between brominated flame retardants in human milk and thyroid-stimulating hormone (TSH) in neonates. Eggesbø M, Thomsen C, Jørgensen JV, Becher G, Odland JØ, Longnecker MP.

Trabert B, Longnecker MP, Graubard BI, Klebanoff MA, Stanczyk FZ, McGlynn KA. Placental characteristics as a proxy measure of serum hormone and protein levels during pregnancy with a male fetus. Environ Res. 2011 Aug;111(6):737-43. Epub 2011 May 20.

Hazel Nichols, PhD
Epidemiology Branch, NIEHS Intramural

Brief bio: Hazel Nichols joined the Epidemiology Branch as a Research Fellow in 2011. She completed her PhD in Cancer Epidemiology at Johns Hopkins University in 2011 and a MS in Reproductive Epidemiology at the Harvard School of Public Health in 2003.

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Current project: Hormonal factors associated with breast cancer risk & survival in the Sister Study.

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Model: Humans

Toxicant: N/A

Methods: Epidemiology

Endpoint: Breast cancer incidence, chronic disease among breast cancer survivors.

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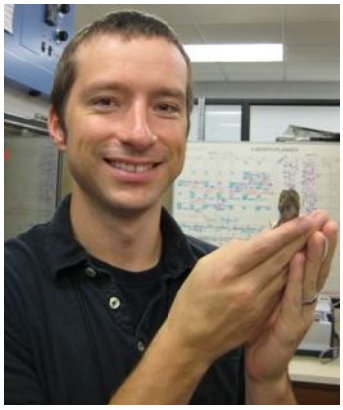
Selected publications:

Nichols HB, Visvanathan K, Newcomb PA, Hampton JM, Egan KM, Titus-Ernstoff L, Trentham-Dietz A. Bilateral oophorectomy in relation to risk of postmenopausal breast cancer: confounding by nonmalignant indications for surgery? Am J Epidemiol. 2011 May 15;173(10):1111-20. Epub 2011 Mar 23.

Nichols HB, Berrington de González A, Lacey JV Jr, Rosenberg PS, Anderson WF. Declining incidence of contralateral breast cancer in the United States from 1975 to 2006. J Clin Oncol. 2011 Apr 20;29(12):1564-9. Epub 2011 Mar 14.

Nichols HB, Trentham-Dietz A, Egan KM, Titus-Ernstoff L, Holmes MD, Bersch AJ, Holick CN, Hampton JM, Stampfer MJ, Willett WC, Newcomb PA. Body mass index before and after breast cancer diagnosis: associations with all-cause, breast cancer, and cardiovascular disease mortality. Cancer Epidemiol Biomarkers Prev. 2009 May;18(5):1403-9. Epub 2009 Apr 14.



Ben B. Parrott, PhD

Post Doctoral Scholar
Medical University of South Carolina (MUSC)

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Overview: Our research focuses on elucidating the cellular and genetic mechanisms by which contaminants in the environment affect the reproduction of wildlife and humans. Our lab has previously shown that alligators living in environments contaminated with EDCs are characterized by the alteration of sexually dimorphic gene expression. This perturbation of sexually dimorphism appears to have origins in early development, as eggs removed from contaminated environments and placed in the lab yield juveniles in which these abnormalities still persist. Currently, we are investigating sexually dimorphic epigenetic signatures in alligators to identify pathways affected by early exposure to endocrine disrupting contaminants. The aim of these studies is to provide insights into the mechanisms by which EDCs negatively affect reproduction in a long-lived sentinel species.

…….

Selected publications:

Parrott, B.B., Chiang, Y., Hudson, A., Sarkar, A., Guichet, A., Schulz, C. 2011. Nucleoporin98-96 Function is Required for Transit Amplification Divisions in the Germline of Drosophila melanogaster. PLoS One, In Press.

Hudson A, BB Parrott, Qian Y, Schulz C. Dose Dependent Effects of EGFR signaling in Drosophila Testes. 2011. Submitted.

Gubbels MJ, Lehman M, Muthalagi M, Jerome ME, Brooks CF, Szatanek T, Flynn J, Parrott BB, Radke J, Striepen B, White MW. 2008. Forward Genetic Analysis of the Apicomplexan Cell Division Cycle in Toxoplasma gondii. PLoS Pathogens 4(2): e36.

Heather B. Patisaul, PhD

Department of Biology
North Carolina State University

Overview: Brain sexual differentiation, hormone-dependent organization of GnRH signaling pathways, pubertal timing, sexually dimorphic behavior (including reproductive behavior) and estrous cycle quality.

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Current project: Impact of BPA on neuroendocrine development and behavior

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Model: Rats (Wistar or Long Evans).

Toxicant: BPA and soy phytoestrogens.

Methods: Neuroanatomy, behavioral analysis, ovarian histology, in situ hybridization and immunohistochemistry.

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Selected publications:

Jefferson WN, Patisaul HB, Williams C. Reproductive consequences of developmental phytoestrogen exposure. Reproduction. 2012 Jan 5. [Epub ahead of print]

Cao J, Mickens JA, McCaffrey KA, Leyrer SM, Patisaul HB. Neonatal Bisphenol A exposure alters sexually dimorphic gene expression in the postnatal rat hypothalamus. Neurotoxicology. 2011 Nov 9;33(1):23-36. [Epub ahead of print]

Cao J, Patisaul HB. Sexually dimorphic expression of hypothalamic estrogen receptors α and β and Kiss1 in neonatal male and female rats. J Comp Neurol. 2011 Oct 15;519(15):2954-77.

Dickerson SM, Cunningham SL, Patisaul HB, Woller MJ, Gore AC. Endocrine disruption of brain sexual differentiation by developmental PCB exposure. Endocrinology. 2011 Feb;152(2):581-94. Epub 2010 Dec 29.

Losa SM, Todd KL, Sullivan AW, Cao J, Mickens JA, Patisaul HB. Neonatal exposure to genistein adversely impacts the ontogeny of hypothalamic kisspeptin signaling pathways and ovarian development in the peripubertal female rat. Reprod Toxicol. 2011 Apr;31(3):280-9. Epub 2010 Oct 15.

Adewale HB, Todd KL, Mickens JA, Patisaul HB. The impact of neonatal bisphenol-A exposure on sexually dimorphic hypothalamic nuclei in the female rat. Neurotoxicology. 2011 Jan;32(1):38-49. Epub 2010 Aug 7.

Gore AC, Patisaul HB. Neuroendocrine disruption: historical roots, current progress, questions for the future. Front Neuroendocrinol. 2010 Oct;31(4):395-9. Epub 2010 Jul 16.

Wipawee (Joy) Winuthayanon, PhD

Research Fellow
NIEHS Intramural

Overview: I am a research fellow in Dr. Ken Korach Lab at laboratory of reproductive and developmental toxicology. Our research interests are the effects of xenoestrogenic compounds on reproductive function as well as the roles of tissue specific estrogen receptor (ER) α in reproduction.

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Current project: The roles of tissue specific ERα (and its ligands) in the female reproductive tract on fertility and preimplantation embryo development.

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Model: Tissue specific ERα knockout mouse model.

Toxicant: Estrogen, phytoestrogens.

Methods: IVF, oviduct/uterine embryonic transfer, preimplantation embryo collection.

Endpoint: Fertilization rate and number of preimplantation embryos compared between control and conditional knockout mice.

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Selected publications:

Winuthayanon, W., S. C. Hewitt, et al. 2010. Uterine epithelial estrogen receptor alpha is dispensable for proliferation but essential for complete biological and biochemical responses. Proc Natl Acad Sci U S A 107(45): 19272-19277.

Winuthayanon, W., Piyachaturawat, P., Suksamrarn, A., Ponglikitmongkol, M., Arao, Y., Hewitt, S.C., Korach, K.S. 2009. Diarylheptanoid phytoestrogens isolated from the medicinal plant Curcuma comosa: Biological actions in vivo and in vitro indicate ER-dependent mechanisms. Environmental health perspectives 117(7):1155-1161.

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