WINDOW OF SUSCEPTIBILITY FOR ENVIRONMENTAL EXPOSURES: **PREGNANCY**

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“Translating Research into Action to Reduce Breast Cancer”
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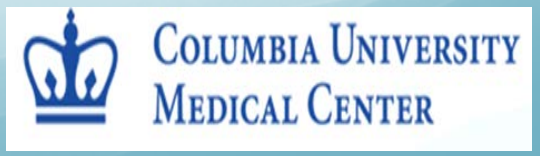

Breast Cancer Incidence: The Environment is a Major Player

- The incidence of breast cancer remains only partially explained by the established risk factors.
- US population-based cancer registry data:
  - Significant increases over time in the incidence of breast cancer in young (ages 25-39 years) women.
  - From 1.53 (95% confidence interval [CI] 1.01-2.21) per 100,000 in 1976 to 2.90 (95% CI 2.31-3.59) per 100,000 in 2009.
  - Average compounded increase of 2.07% per year (95% CI 1.57%-2.58%).

Madigan et. al. J. Natl Cancer Inst 1995
Bouchardy et. al. Br. J. Cancer 2007
Sprauge et. al. Am. J. Epidmeiol. 2008
Johnson et. al. JAMA 2013

Windows of Susceptibility (WOS)

Air pollution
Chemicals
High fat diet

Genetic x environment interactions
Epigenetic regulation
Endocrine disruption

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Why These Key WOS?
Key Periods in Mammary Gland Development

- Pregnancy:
  - Rapid proliferation and full differentiation/lobulo-alveolar development.
  - Increased the number of in utero mutations.
- Prenatally:
  - Fat pad and bud form.
  - Epithelium forms ductal tree.
- Critical developmental processes during both periods can be disrupted by toxic exposures.

Rudel et.al. EHP. 2011
Soto et. Al.J. Mammary Gland Biol Neoplasia 2013

Why These Key WOS?
Plausible Underlying Mechanisms

- Genetic x environment interactions.
  - Altered gene expression
  - Modified endogenous mammary gland signaling
- Epigenetic regulation-posttranscriptional modifications.
  - Reversible?
- Endocrine disruption.
- Genomic imprinting.

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*Rodent studies
*Human cohorts

*Regulation by hormones, growth factors, stromal factors is similar between rodents and humans.

Rodent Studies

- DMBA-challenged rats fed a high-fat diet during later pregnancy.
  - increase in circulating estrogen levels during pregnancy.
  - increased rate of developing subsequent mammary tumors.
- Perinatal isoflavones enhanced mammary gland differentiation in female heterozygous Tg.NK (MMTV/c-neu) mice.
  - palpable mammary tumor onset was not affected.

Hilakivi-Clarke et al. J. Natl Cancer Insti. 1996
Luijten et. al. Nutr Cancer 2004

Human Cohorts

- Child Health and Development Studies (Oakland, CA)
  - Birth cohort from 1950s and 1960s.
  - Approx 20,000 births
  - Increased breast cancer odds associated with:
    - highest tertile of blood p,p'-DDT level measured 1-3 days after birth (OR=5.4, 95% CI 1.7-17.1)
    - higher polychlorinated biphenyl (PCB) congener 203 relative to congeners 167 and 187 (OR=2.98, 95% CI 1.1-7.1).
- Highest quintile sera levels of perfluorooctane-sulfonamide (PFOSA) during pregnancy were associated premenopausal breast cancer.

Cohn et. al. EHP 2007
Cohn et.al. Breast Cancer Research and Treatment 2012
Bonefeld-Jorgensen et. al. Cancer Causes Control 2014

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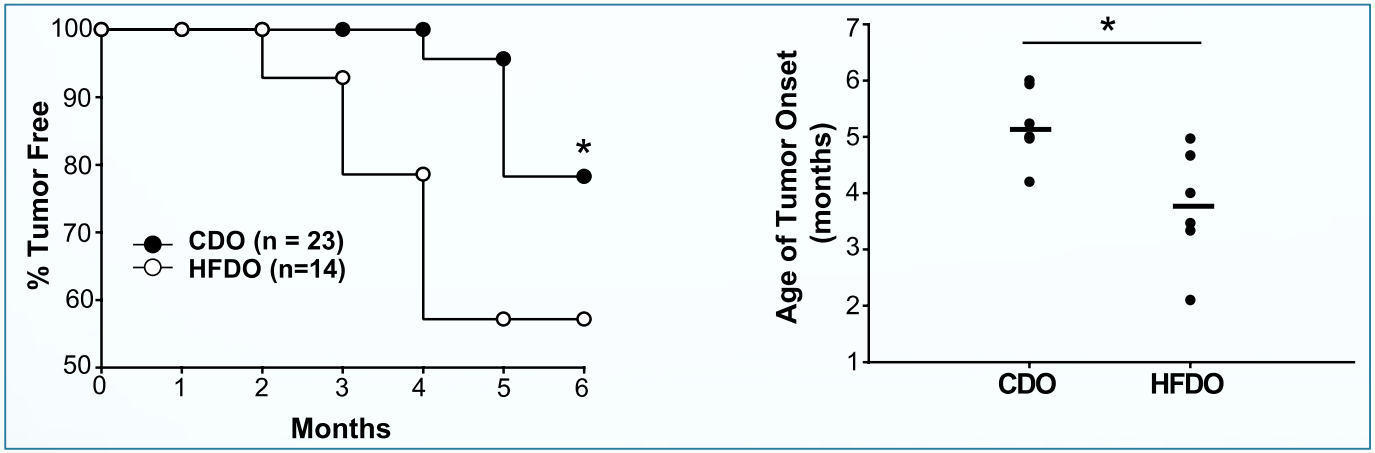
Rodent Studies

- Maternal bisphenol A (BPA) (5.0 mg/kg/d) exposure altered global CpG methylation of the uterine genome in mice.
  - Subsequent effect on gene expression apparent at sexual maturation.
  - Eg. estrogen receptor-α (ERα)-binding genes.
- Maternal metalloestrogen arsenite (5 µg/kg bw ip) days 12, 17 gestation increased the number of mammosphere-forming cells and branching, epithelial cells, and density in rats prior to puberty
  - Overexpression of ERα following puberty.

Parodi et. Al.Reprod Toxicol. 2015
Jorgensen et. al. The Faseb J. 2016
Gomez et. al. Horm Cancer 2017

Rodent Studies: High Fat Diet

- Maternal high fat diet increased mammary tumor incidence and decreased tumor latency in mammary tumor virus-Wnt-1 transgenic mice.



CD: 175 kcal from fat
HFD: 45% kcal from fat

Through pregnancy and lactation

- Tumor risk was associated with:
  - higher TNF-α, insulin and altered oxidative stress biomarkers in sera
  - early changes in mammary expression of genes linked to tumor promotion [IL6] or inhibition (Pten), B-cell lymphoma 2 (Bcl2)]

Montales et. al. Carcinogenesis. 2014

Rodent Studies: DES

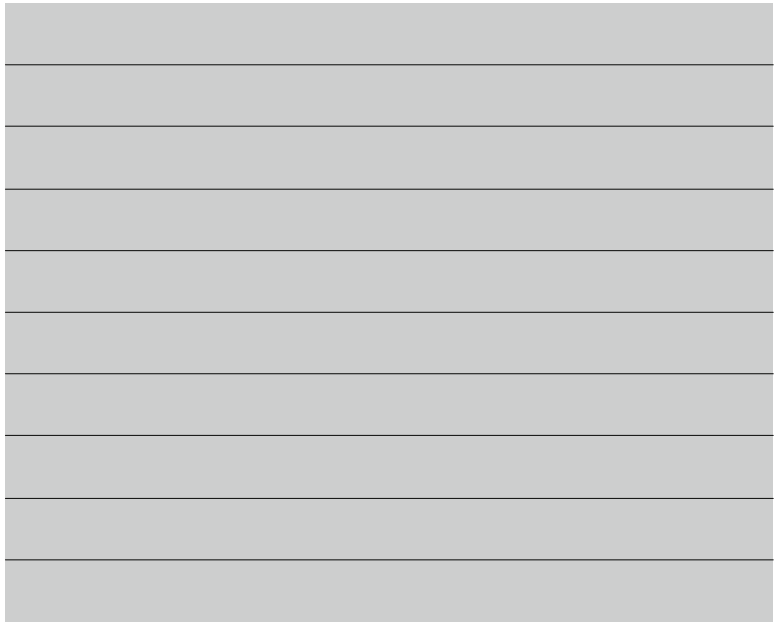
- Several studies in rats showed that maternal diethylstilbestrol (DES) at multiple doses and multiple days during gestation increased mammary cancer risk in female offspring.

- Perinatal exposure to DES followed by estrogen replacement therapy in middle aged rats increased the number of cysts and induced the formation of fibroadenoma and ductal carcinoma in situ.

Hilakivi-Clarke Breast Cancer Res 2014

Cohort Studies

- Meta-analyses: Heavier birth weights were associated with increased breast cancer risk.
- Higher measures of prenatal PCB exposure in women with subsequent breast case vs control (n=112 age matched pairs):



Childrens Health and Development Studies Cohort

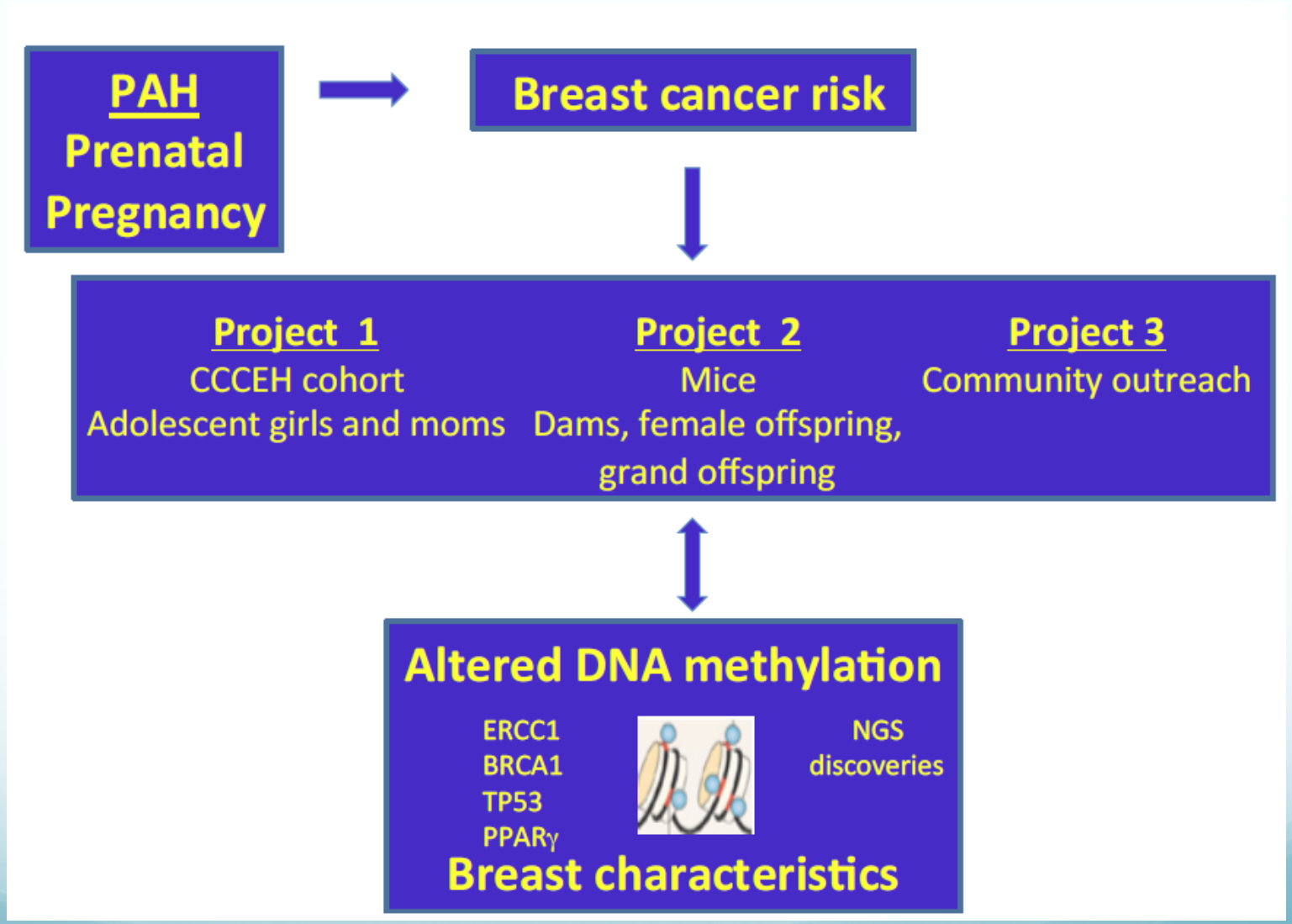
Hilakivi-Clarke Breast Cancer Res 2014
Park et. al. Breast Cancer Res. 2008
Cohn et. al. Breast Cancer Res Treat 2012

Polycyclic Aromatic Hydrocarbons (PAH)

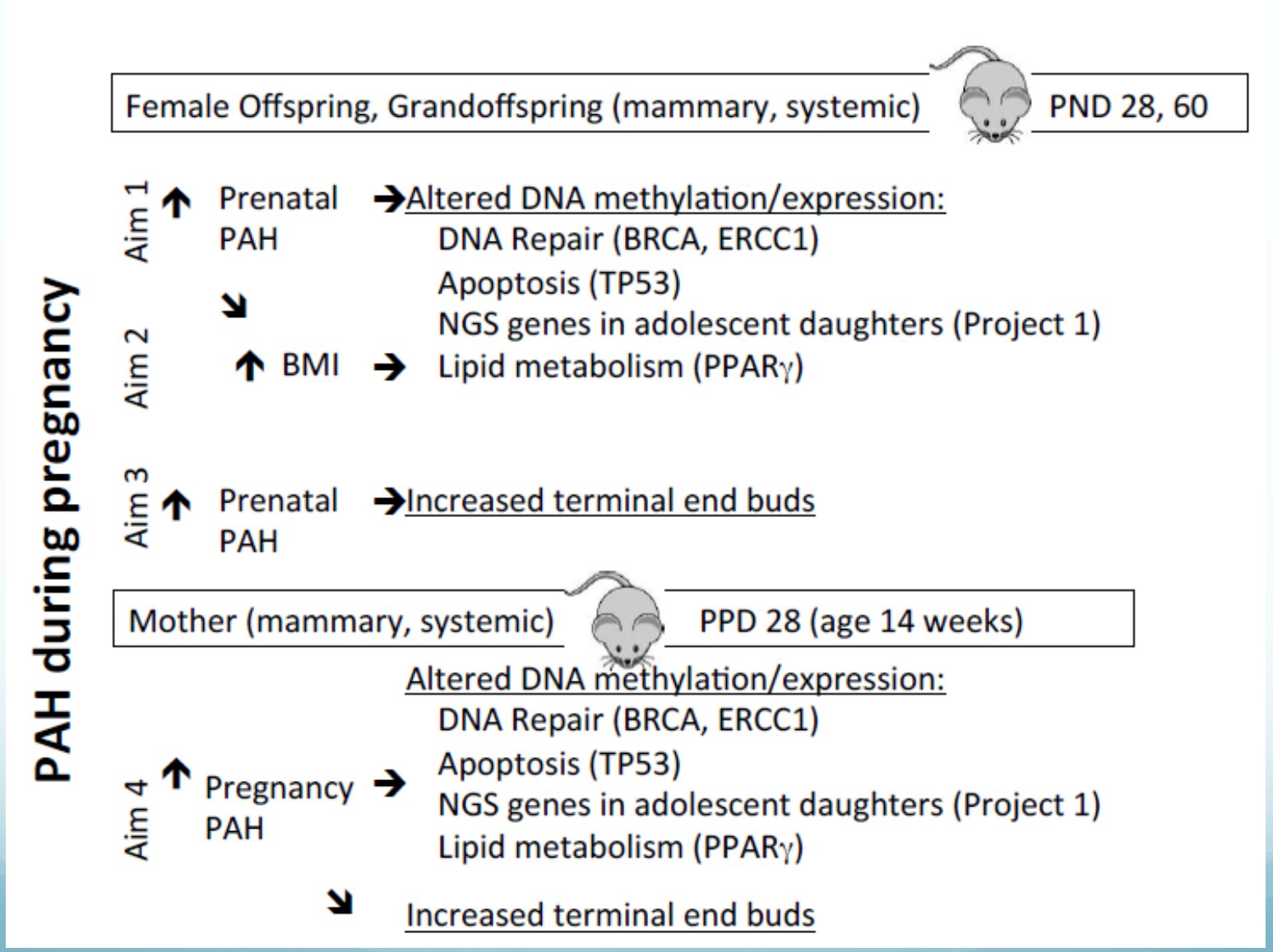
- Combustion by-product
- Multiple sources:
  - gasoline and diesel-fueled engines, coal
  - oil burners
  - grilled and smoked meats
  - cigarettes
- Lipophilic; also stored in the fat tissue of the breast.
- Weakly estrogenic.
- Human and animal carcinogens as cited by IARC and possible breast carcinogens by EPA.
- Prenatal exposure to the PAH has been associated with multiple harmful effects on offspring: adiposity, and several cancers.
  - Epigenetically mediated

Castro et. al. Toxicol. Appl. Pharmacol. 2008
Rundle et. al. Carcinogenesis 2000
Yan et. al. PloSOne 2014
Rundle et. al. Am. J. Epidemiol. 2012

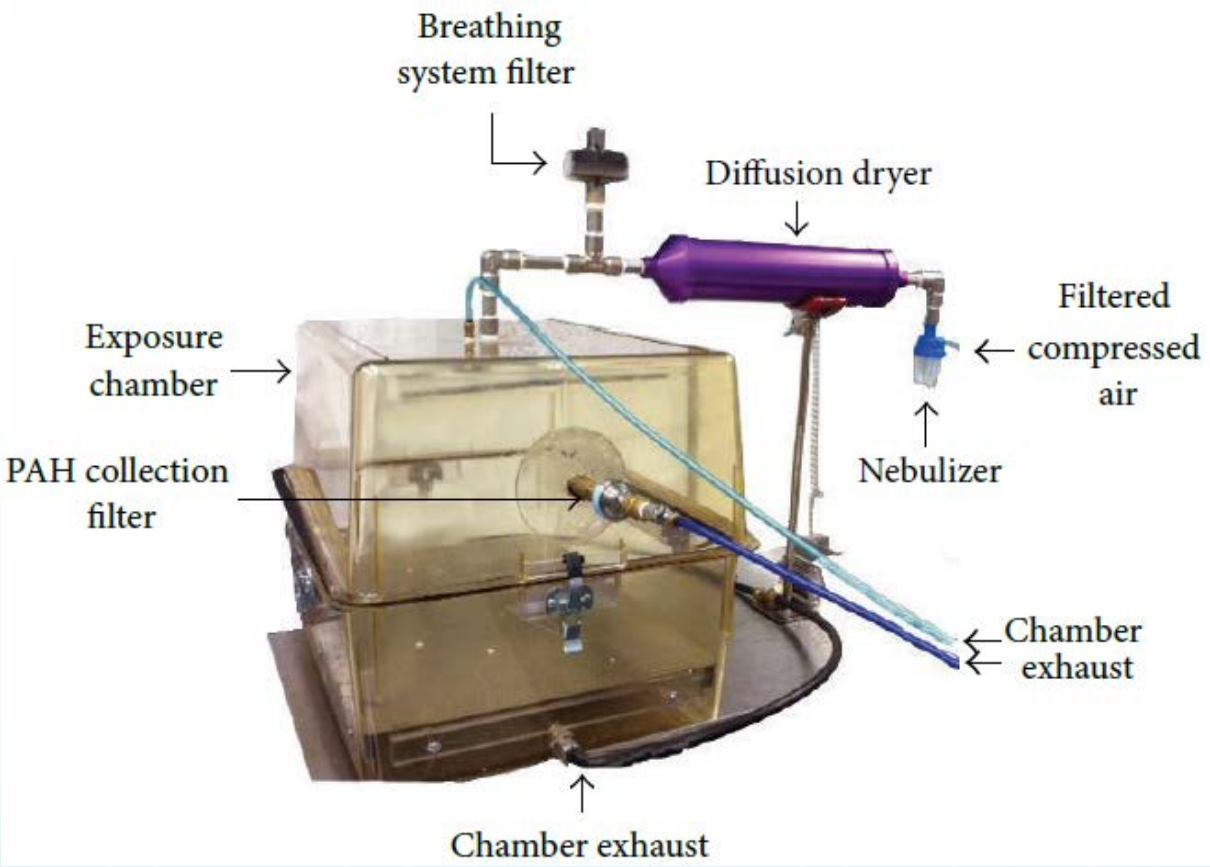
3 Columbia Projects: Human, Mouse, Community Correlates



Columbia BCERP Mouse Study: Aims and Approach



Delivering Ambient PAH to Mice



PAH mixture – Lovelace Respiratory Research Institute
PAH solution to yield a final concentration of 7.29 ng/m3 (3.69 ng/m3 pyrene, plus 3.60 ng/m3 from 8 other individual PAH)

Emerging Concepts: Transgenerational effects

- Reprogramming may leave a permanent biochemical footprint on the genome of the offspring F1 generation germ cells that may be inherited by the grandoffspring F2 generation germ line and beyond.

- Recent example:
  - Prenatal ethinyl estradiol changed methylation patterns of 351 genes of the rat mammary glands in three generations.
    - Increased mammary tumorigenesis, number of terminal end buds in daughters, granddaughters and great granddaughters.

De Assis Nat. Communi 2012

Future Directions

- Fill research gaps:
  - Obtain environmental data collected during the key WOS for breast cancer.
  - Assess and apply proxy measures of the pregnancy environment to cohort studies to identify those at higher risk in advance of disease.
- Resolve dose effects (by WOS).
- Test interventions.
  - Remediation of environment-inside, outside home
  - Behavior changes
  - Development of new therapeutics to administer during WOS and prior to onset of disease

Take Home Points For Our Community

- **Prevention** can occur during pregnancy with the following:
  - More science, more dissemination of findings, feasible interventions.
  - Multifactorial/shared approaches.
    - Involve doctor, family; examine home environment
  - Remediation, even against air pollution. It's feasible.
    - Advocacy, public policy
      - Eg. Zone more green spaces near homes, schools
    - Reducing outdoor traffic emissions and indoor gas-fired boilers
    - Changing individual behaviors (reduce smoking, alter cooking methods, avoid smoked meat and fish; adjust outdoor travel routes to reduce traffic exposure)