Breast Cancer and the Environment Research Centers

Biology Projects

Fox Chase Cancer Center (FCCC)

Michigan State University (MSU)

Bay Area (BA)

University of Cincinnati (UC)

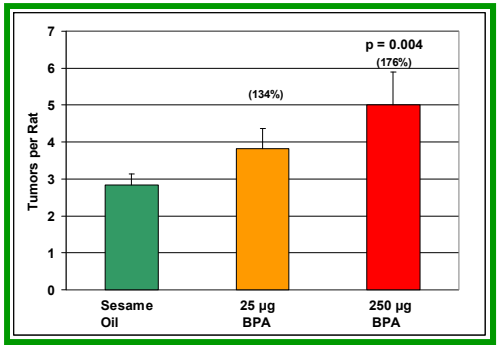
Cross-Center Interactions and Integration: Epidemiology and Biology Studies

Epidemiology Studies
Identify relevant exposures; effects on pubertal development

Exposures
Chemicals
Endocrine Disruptors
Hormones, Diet

Biology Studies
Normal mammary development; effects of exposures

Risk Assessment
Mammary cancer susceptibility



Mechanisms

Biomarkers, Genes

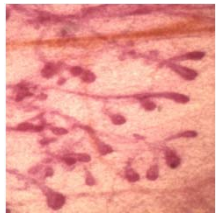
Breast Cancer Prevention Public Health Messages

Normal Mammary Gland Development

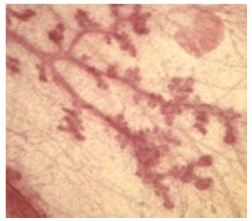
Define the cellular and molecular architecture of the normal mammary gland in experimental models — focus on puberty

Key Findings: Rat and Mouse Models

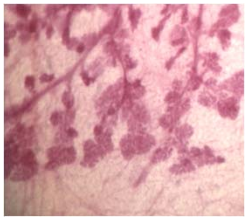
1. **Mechanisms of hormone action: estrogen and progesterone**
2. **Key mammary gland regulators: GATA-3**
3. **Mammary stem cells: distribution mapped in the architecture of the mammary gland**



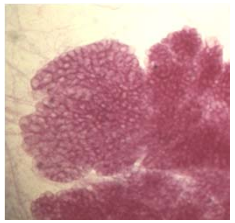
Puberty



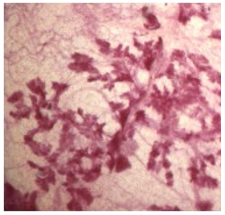
Sexual maturity



Pregnancy



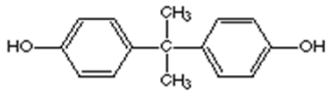
Lactation



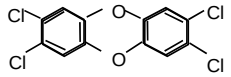
Involution

Exposure-Induced Changes

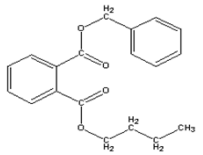
Endocrine disruptors: bisphenol A (BPA), butyl benzyl pthalate (BBP), 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) — Rat Model



Bisphenol A



2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)


Butyl benzyl phthalate (BBP)

Key Findings

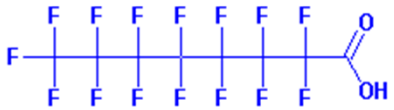
1. **BPA, BBP, or TCDD treatments generate unique gene expression signatures relevant to mammary gland development and susceptibility to carcinogenesis.**

2. **Risk Assessment:**
   Prepubertal exposure to BPA increases susceptibility to mammary carcinogenesis.

3. **Relationship to human studies:**
   SNPs associated with either BMI or breast stage in girls (Bay Area cohort) are associated with the same genes dysregulated by BPA, BBP, or TCDD in rats.

Perfluorooctanoic Acid (PFOA) Exposure
Human Studies/Mouse Model

Industrial pollutant in contaminated water and food



Key Findings

Findings from human studies: BCERCs and CDC

1. **Subgroup of girls had high PFOA levels (Cincinnati and Bay Area studies).**
2. **Positive association with early pubertal maturation and lower LDL cholesterol; altered liver function?**

Findings from animal studies: to identify mechanisms
Genetic background determines effect of pubertal exposure:

1. **Stimulation or inhibition of mammary gland and uterine development.**
2. **Degree of liver toxicity.**

Relationship to human studies: common hypothesis
PFOA may produce liver-mediated effects that disrupt the normal hormone profile.

This may explain early pubertal maturation in girls and stimulatory effects on mammary gland and uterine development in mice.

Diet Studies

1. Specific types and amounts of dietary fats — Rat
2. High-fat diet-induced pubertal obesity — Mouse

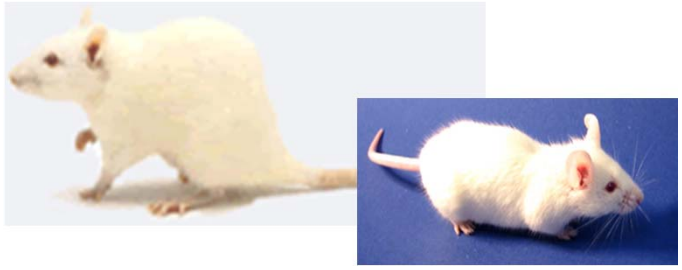
Key Findings

1. **All dietary fats cause a "mitotic cell cycle" gene expression signature and increase cell proliferation.**

   Risk assessment: Most high-fat diets increase mammary tumor susceptibility.

2. **Pubertal obesity is dependent upon genetic background.**
   High-fat diet with obesity: inhibits mammary development; insulin resistance.
   High-fat diet without obesity: normal/increased mammary development.

   Risk assessment: High-fat diet without obesity increases mammary tumor susceptibility.



Ionizing Radiation Studies — Mouse

(prototype for other putative carcinogens)

Key Findings

Mechanism(s) of increased mammary tumorigenesis:

1. **Alters the mammary gland tissue microenvironment (activation of TGFβ; extracellular matrix remodeling).**

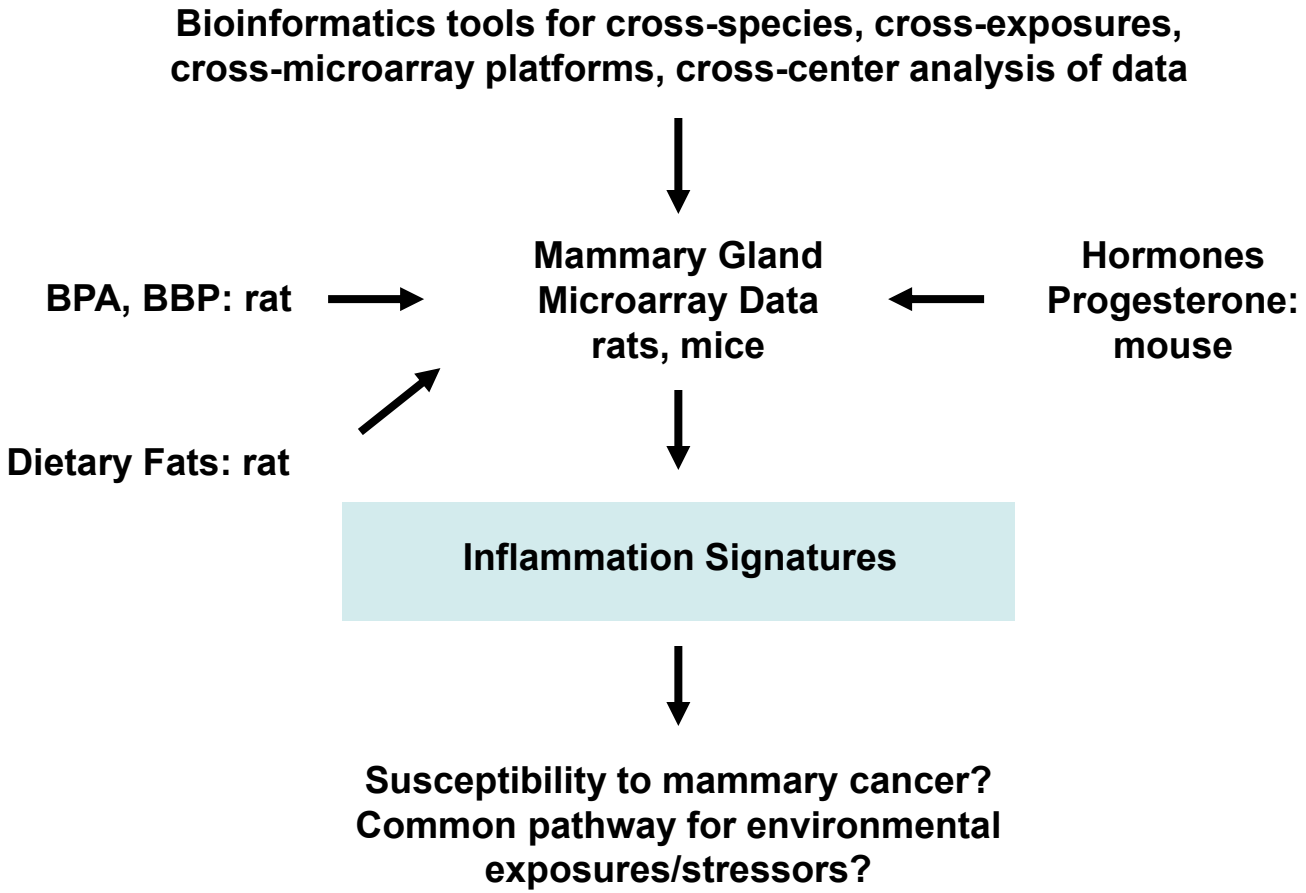
2. **Causes deregulation of stem cell number.**

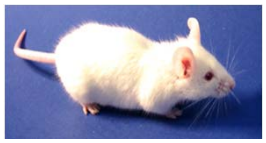
3. **These effects of radiation are distinct from those on genomic integrity.**

Paradigm shift from the theory that radiation works directly to damage DNA. True for other putative carcinogens?

Novel Findings — Cross-Center Collaborations

Microarray Studies





Future Scientific Opportunities

1. Inflammation
2. Lipid metabolism alterations
3. Key mammary gland regulators
4. Interactions between multiple relevant exposures
5. Biomarkers of exposure and susceptibility
6. Mammary stem cells
7. Specific mechanisms of gene action
8. Application of tools across species and models; bioinformatics
9. Molecular engineering to generate models and test hypotheses

Potential Biomarkers:

Relevant to Human Breast Cancer Risk

Other Public Health Concerns:

Adolescent obesity, Type II diabetes