

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
Division of Extramural Research and Training

NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL

May 22, 2009

Concept Clearance
For

**Breast Cancer and the Environment Research Program (BCERP)
RFA Concept Program Renewal**

Background

This proposal is to renew the Breast Cancer and the Environment Research Program, a partnership between the National Institute of Environmental Health Sciences (NIEHS) and the National Cancer Institute (NCI). The initial Request for Applications (RFA) on Breast Cancer and the Environment Research Centers (BCERC) was released in November, 2002 as a cooperative agreement (U01). This 7-year initiative, that terminates in July, 2010, has the following goals:

- to compare the molecular changes that occur in normal breast development across the life span to changes that occur when environmental exposures are introduced;
- to conduct an epidemiologic study of the timing of female pubertal events, including the onset of breast development, age at menarche, and environmental and genetic factors that may affect pubertal maturation;
- to integrate scientific information on the development of the mammary gland and exposure-induced changes in order to construct public health messages for young girls and women who are at risk for breast cancer.

To accomplish these goals, a network of teams comprised of scientists, clinicians, and breast cancer advocates was established to work collaboratively on questions related to environmental and genetic factors that may predispose a woman to breast cancer throughout life. The original RFA was developed as a result of workshops held by NIEHS in collaboration with the National Breast Cancer Coalition. This common discussion between scientists and advocates resulted in a program designed to examine the causes of breast cancer from a developmental approach in order to understand the role of the environment on the causes of breast cancer. The resulting BCERC program was designed to address gaps in knowledge about the developmental biology of the mammary gland and the physiology and genetic regulation of sexual maturation. A critical over-arching aspect of the program was collection of data on environmental factors that could impact these processes.

At the time of the BCERC inception, much of the research on the determinants of breast cancer had been conducted on adult women at a point in the lifespan when only a few risk factors may be recalled or that are modifiable through lifestyle choices. However, a considerable body of literature has established the ages at menarche, first full-term pregnancy, and menopause as risk factors, thus indicating that the timing of hormonally related events across the life span is an important consideration in breast cancer risk. The BCERC program focused on the pre-pubertal and pubertal developmental stages in an attempt to determine the environmental influences on early life risk factors. This unique opportunity investigated a window of time in which

undifferentiated breast cells are rapidly proliferating in response to ovarian hormones and may be more susceptible to damage from environmental exposures. Moreover, the hypothesis being tested is that earlier age at breast development and menarche potentially increases the prolonged exposure of the breast to endogenous hormones, thus increasing the risk of breast cancer later in life. Because little progress in identifying environmental risk factors has been made, it remains an area of intense community and scientific interest.

The BCERC program operates within a transdisciplinary framework. It consists of four multidisciplinary centers that include laboratory experimentalists, epidemiologists, clinicians and members of the breast cancer advocacy community, each using skills from their own disciplinary training to address the role that environmental and genetic factors play during early puberty on the etiology of breast cancer. The centers are based at the Fox Chase Cancer Center, Philadelphia; Michigan State University, East Lansing; the University of Cincinnati; and the University of California, San Francisco. The four centers conduct laboratory experiments on rodent and cell culture models to characterize molecular and morphologic changes in the mammary gland over the life span and to determine how environmental exposures affect mammary gland development and susceptibility to carcinogenesis. Three of the centers also conduct focused and coordinated epidemiologic research that examines the independent and interactive impact of environmental, genetic, biologic, lifestyle, and socioeconomic factors on pubertal development in girls. Each center has a Community Outreach and Translation Core (COTC) in which advocates and academicians specializing in outreach, education, and communications work closely with scientists from the biology and epidemiology projects to develop and implement strategies to translate and communicate findings from the laboratory and human studies.

The Centers work collaboratively on two projects, a laboratory-based study using animal models, "Environmental Effects on the Molecular Architecture and Function of the Mammary Gland across the Life span," and an epidemiologic study, "Environmental and Genetic Determinants of Puberty." A major accomplishment across the centers is the detection of over 50 environmental agents and their metabolites in the cohort of girls, including phenols, phthalates, persistent pesticides, flame retardants and perfluorinated compounds many of which had not been previously reported in children(Wolff, MS, et. al. "Pilot Study of Urinary Biomarkers of Phytoestrogens, Phthalates, and Phenols in Girls." *Env Hlth Perspect.* 2007; 115:116-121), . A list of publications by the BCERCs is attached (Attachment A).

The research conducted by the BCERCs has led to significant achievements. For example, investigation of the impact of a select set of exposures and dietary factors on female puberty and tumorigenesis, demonstrated for the first time the presence of select hormonal-influencing chemicals, such as mono(2-ethyl-5-carboxypentyl) phthalate, triclosan, bisphenol A (BPA), and BP3 in children. The overall results of the studies indicate that common exposures, including endocrine disruptors, organochlorines, heavy metals, and dietary fats, may alter the onset and progression of puberty. Among the unexpected findings was the detection of extremely elevated levels of PFOA in a group of individuals localized among the Kentucky-Ohio cohort. The source and physiological potential of this apparent one-time exposure are being followed-up on the girls through a subsequent NIH grant (R21). Moreover, the mechanisms by which PFOA may influence puberty and tumorigenesis are being explored in BCERC laboratory studies. These studies are providing much needed clues on the potential mechanisms of action of these exposures and indicate that low doses of certain agents have effects at the genetic or cellular level that may not be recognized in the overt phenotype for many years.

Gene discovery studies within the BCERC suggest a set of genetic variations that may place individuals at elevated risk for either altered onset of puberty, obesity, or breast cancer risk. Basic studies led to the discovery of GATA-3 as the master gene for mammary gland development and related work in the BCERC indicates that the activity of this gene may be a sensitive predictor of tumor predisposition. Another research direction is providing new information on the distribution of estrogen and progesterone receptors over the female life span. These data could be of great importance in understanding the relative roles of these influential hormones in puberty and cancer and could suggest therapeutic regimens.

The BCERCs are unique in addressing environmental factors and pubertal development. NIEHS supports approximately 30 grants concerning breast cancer and the environment at an annual cost of \$10.9M (FY2009). These include epidemiologic and basic studies of endocrine disruptors, dioxin, organochlorines, diet, phytoestrogens, PFOA, and environmental justice issues. National Cancer Institute (FY2008) supports 170 breast cancer and environment grants funded at \$74.6M. Of these grants, 104 specifically address epidemiology of breast cancer and the environment. The topics of these grants include estrogen and genetic susceptibility, dietary and hormonal determinants, gene-environment interaction, chemical and environmental exposures, role of nutrition, biomarkers and energy balance and breast cancer risk.

Purpose of RFA

The purpose of this RFA is to continue support and to expand upon the Breast Cancer and the Environment Research Program which is the only NIH project supporting transdisciplinary research on the interaction of chemical, physical, biological, and social environmental factors with genetic factors using puberty as a window of susceptibility.

The program was groundbreaking in its transdisciplinary approaches; that is, a methodology and practice that utilizes multiple forms of expertise including community members and activists in an integrated fashion so as to generate new hypotheses and tools. The BCERC optimized involvement of community members and advocates in the research process and to consider the etiology of environmental impact on breast cancer at the genetic, metabolic, cellular, individual, and environmental (physical and social) levels. A manuscript describing the BCERC approach has been submitted for publication. The next phase of the program is intended to complete the initial population study, to expand upon the recent findings of the Breast Cancer and the Environment Research Program in identifying biomarkers of common exposures, the links to genetic polymorphisms, chemical agent-induced changes on mammary gland architecture and cellular phenotypes, and to continue efforts to include and inform the engaged breast cancer community. In addition, efforts will be made to stimulate basic and applied research to exploit the latest concepts in breast cancer pathogenesis and environmental health.

The program is proposed to undergo some significant changes. The most prominent being disassociation of the Centers into its epidemiological components – that continue to operate with dedicated Community Outreach and Education Cores – and a parallel set of studies focused on gene-environment interactions in breast cancer over more varied periods of the life span. While the program to date has had many outstanding accomplishments, NCI and NIEHS staff have found that the current Center structure - requiring each Center to have both epidemiological and basic biology components and to focus on the same window of susceptibility, namely puberty - may not provide the necessary flexibility to capitalize on recent advances. Providing greater flexibility to broader teams of investigators to examine various windows of susceptibility would seem to be constructive and far-reaching. This strategy is

expected to seed research across a broad spectrum that would then be pursued through the traditional application process.

A major component of the previous project, the epidemiological study of young females, is proposed for continuation. While it is anticipated that adequate data collection on the cohort of girls will take place in the current funding period - at the level of genetic and environmental factors associated with breast and pubic hair development - continued monitoring is essential to maximize research opportunities and to produce a comprehensive model of the pubertal transitional period. Many of the girls will not have achieved menarche, maturation tempo, peak height velocity, or peak adult height by the end of the current funding period. While the program has established that detectable levels of environmental chemicals exist in girls, continued monitoring of the cohort will be necessary to determine if these chemicals are associated with important developmental periods and subsequent breast cancer risk. In addition, continued follow-up provides an opportunity for serial measurement of biomarkers to assess persistence of chemicals of interest and to estimate variation in sex hormone levels and ovulatory cycles. Novel questions will be pursued in animal and cell culture models as results from the epidemiology study materialize. Finally, translation of findings into useful public health messages will be promoted as findings of the BCERC program are published.

Staff oversight and cohesion of the program will be assisted with establishment of the Breast Cancer and the Environment Research Coordinating Center. The Coordinating Center would ensure quality control and standardization as it manages pooled data collected at the three epidemiological study sites. In addition, the Coordinating Center will organize the Steering Committee that will guide operations of the program, organize meetings among the scientists and outreach engineers to achieve enhanced integration across the program, and produce the national meetings that have become a hallmark of the program. Finally, in concert with the Steering Committee, the Coordinating Center will oversee a competitive Pilot Project / Opportunity Fund to exploit special scientific opportunities and to enhance collaborations and emerging concepts.

Project Plan

The Breast Cancer and the Environment Program will be comprised of three FOAs. Total costs for FY10 and for the duration of the projects are indicated and are to be shared by NCI and NIEHS. Costs are also estimated for biomarker studies through a continuing Interagency Agreement with the Centers for Disease Control and Prevention.

Early Environmental Exposures: Continuing Studies of Human Puberty (U01)

This FOA will support a limited competition – open only to the existing, funded epidemiology projects of the Breast Cancer and the Environment Research Centers - to complete the epidemiological studies of the current cohort of girls through menarche. A considerable investment has been made to date in establishing this cohort. In order to maximize the amount of data collected and to have the power to draw significant conclusions regarding environmental determinants on female puberty onset, the next phase of the study will require five additional years in the field to ensure that 95% of the cohort can be monitored through the initiation of menarche. An additional year is necessary to complete biomarkers assays and data analyses for a total of six years. The epidemiological team at each site will partner with a local Community Outreach and Education Core that will assist with recruiting and community relations and concerns, as well as to disseminate messages on novel findings and lifestyle choices.

This component of the program aims to:

- Continue a human longitudinal study focusing on aspects of environmental exposure including nutrition, physical activity, social stress, and pediatric endocrinology.
- Continue data collection on the established cohort of girls including risk factors and biological specimens; assess age at pubertal stages, age at menarche, and length of tempo; measure environmental exposures known to influence either the sex hormone milieu or cellular factors; examine relationships of hormonal determinants with pubertal milestones; and prospectively investigate the relationship between hormonally active exposures and pubertal milestones
- Analyze and validate biomarkers to determine persistence of chemicals in girls and evaluation of the role of these biomarkers on the endpoints (age to menarche, tempo of maturation, trajectory of growth, etc).
- Examine environmental factors that interact with adiposity
- Evaluate the impact of social environment on the pathways (e.g. initial breast development vs. initial pubic hair development) and timing of pubertal onset
- Identify genetic variants associated with pathways

Cost: \$2.9M per year to support three U01s; total project cost: \$17.4M

Environmental Influences during Windows of Susceptibility & Breast Cancer Risk (U01)

This FOA will support novel experimental and clinical studies focusing on the gene – environment interaction and molecular mechanisms of windows of susceptibility over the life span. This arm allows for studies including human subjects, animal models, and/or cellular and molecular studies. Multiple-PI projects are encouraged to promote a multidisciplinary approach. Grantees will be required to partner with breast cancer advocates and/or members of the engaged community. The U01s would be for 5 years and grantees would be encouraged to apply for renewals through the traditional competitive process.

Examples of research goals for this FOA include, but are not limited to:

- Discovery of environmentally sensitive genes identified as involved in windows of susceptibility and their mechanisms of action in breast tumor formation. Further insights into the roles of variation in these genes in development and cancer would also be appropriate.
- Follow-up and expansion on the families of chemical agents that influence gene expression and morphology in the susceptible periods of breast development and function
- Further studies to explore the impact of elevated levels of exposures, such as PFOA, that was detected at high levels in a subset of the initial female BCERC cohort; examination of other potential “windows of susceptibility” such as pregnancy, periods from *in utero* life through early puberty, or post-menopause.
- Investigation of the impact of select agents within the microenvironment as to their effects on the cellular, molecular, and epigenomic states of mammary stem cells.

Cost: \$2.7M per year to support five to six U01s; total project cost: \$13.4M

The Breast Cancer & the Environment Research Coordinating Center (U01)

The Coordinating Center would be a data storage and retrieval management unit for sample and questionnaire results from all the study sites and would support the research among the Epidemiologic and Laboratory Studies. The Coordinating Center would be supported for six

years coincident with the epidemiological study, “Early Environmental Exposures,” to facilitate site-specific and pooled analyses. Among its responsibilities, the Coordinating Center would:

- Act as a central repository and clearinghouse for pooled data; manage, standardize, quality control, and, where appropriate, distribute data collected at the three epidemiologic study sites.
- Facilitate the Steering Committee that evaluates and recommends new opportunities and directions to NIH. Program staff from NIEHS and NCI will manage the BCER program and the Steering Committee, comprised of the Principal Investigator and a COTC member from each epidemiological project, representatives of the supported investigators of the program on “Environmental Influences during Windows of Susceptibility & Breast Cancer Risk” and NIEHS and NCI program staff.
- Organize Business Meetings, Program Integration Meetings, and a National Scientific Meeting for scientists, public health workers, and the public, and other meetings as necessary to promote interactions, collaborations, project planning and analysis, and updates to NIH staff.
- Support the operations of an expert Working Group on Breast Cancer and the Environment in order to obtain independent advice, engage the community, and give voice to breast cancer survivors and their advocates
- Assist NIH staff in overseeing and administering a Pilot Project / Opportunity Fund
- Coordinate evaluation of the program and work with NIH staff in preparing a report

Cost: \$900,000 per year to support one U01; total project cost: \$5.4M

Biomarkers Assays (Interagency Agreement with the Centers of Disease Control and Prevention)

The Breast Cancer and the Environment Program has had a fruitful collaboration with the Division of Laboratory Sciences, National Centers for Environmental Health, CDC to assay biomarkers in the blood and urine of the female cohort. Environmental exposure assessments conducted for the BCERP has facilitated common goals in understanding the biological basis of the effects of environmental factors on the age of onset and progression through puberty of the diverse population of pre-pubertal and pubertal girls. Among the findings was the first report identifying the levels of a number of phthalates and phenols among children in the US. This critical facet of the program is expected to continue and costs will be shared equally by NIEHS and NCI and transferred annually to CDC.

Cost: \$250,000 per year for six years; total project cost: \$1.5M

Program Management

The BCERP will support a network of cooperative agreements (U01) comprised of research teams that will work within and across the program on targeted biological and epidemiologic research projects. These complex projects require NIH staff oversight and involvement at multiple levels in order to oversee the program, promote collaborations and partnerships, and to ensure proper operation of special components such as the Pilot Project / Opportunity Fund. Program staff from NIEHS and NCI will oversee the BCER program, the Steering Committee, and the Working Group on Breast Cancer and the Environment. The Steering Committee will be comprised of the Principal Investigator and a COTC member from each epidemiological project, investigators and community partner representatives from the program on “Environmental Influences during Windows of Susceptibility & Breast Cancer Risk” and NIEHS and NCI

program staff. Staff will be advised by the Breast Cancer and the Environment Working Group, an independent panel of breast cancer researchers, advocates, and survivors (see below). Program evaluation is described briefly, below.

NIH staff will also take part in the planning and oversight of all activities organized by the Coordinating Center, such as data management, National Scientific Sessions, and message dissemination. Finally, NIH staff will interact with the project investigators and outreach experts on a major goal of the program: constructing and disseminating public health messages on the impact of environmental stressors on the development and life span of the mammary gland.

This program will include evaluation components in order to monitor and assess the performance of the BCER Program in achieving its goals. Criteria include evaluating the quality and innovation of the conducted science as well as assessing critical intermediate indicators of success such as infrastructure development and capacity building; career development; linkages and resource sharing arrangements within and among Centers; and the interdisciplinary and multilevel nature of the research.

In the previous project period, the project evaluation was performed largely by staff of NIEHS and NCI assisted by the Breast Cancer and the Environment (BCE) Working Group, composed of approximately ten multidisciplinary scientists and advocates together with an independent panel composed of scientific and outreach experts. The primary role of the BCE Working Group is to assess the progress of the BCERC program, suggest opportunities to enhance its work, communicate BCERC program findings to broad scientific and public audiences, and provide annual reports to NIH program officials to guide program needs and development. The criteria for evaluation include an assessment of BCERC program performance on the RFA goals: comparing the molecular changes that occur in normal breast development across the life span to changes that occur when environmental exposures are introduced, conducting a coordinated epidemiologic study of the timing of pubertal events, like the onset of breast development, age at menarche, and environmental and genetic factors that may affect pubertal maturation, and integrating scientific information on the development and life span of the mammary gland so that public health messages can be developed for young girls and women who are at risk for breast cancer. The BCE Working Group Report (2008) is attached (Attachment B).

The evaluation goals will be expanded in the forthcoming renewal period of the BCERP to include a set of objective criteria such as: 1) the overall capacity to study the mechanisms underlying the associations between exposures, breast cancer development, or risk factors; 2) the ability to study relationships among diet and chemical exposures, genetic variability and breast cancer risk; 3) collaborative relationships within and among the study participants have been established and institutionalized; 4) achievement of “transdisciplinary research culture;” and 5) successful competition for R01 and R21 funding.

In October 2008, Congress enacted the “Breast Cancer and Environmental Research Act of 2008” that establishes an Interagency Breast Cancer and Environmental Research Coordinating Committee. It also authorizes funding – but does not provide appropriations for 2009 - for research activities aimed at determining the genomic and environmental etiology of breast cancer. Prior to this legislation, NIEHS and NCI have supported initiatives designed to determine the environmental etiology of breast cancer and will be leading the Committee in developing future research agendas in this field.

Budget

The total cost of all three FOAs will be \$37.7M over six years and will be shared between NIEHS and NCI.

FY10 cost of entire initiative:	\$ 6.7M	Total cost of entire initiative (6 years):	\$37.7M
FY10 cost to NCI:	\$ 2.6M	Total cost to NCI:	\$15.3M
FY10 cost to NIEHS:	\$ 4.1M	Total cost to NIEHS:	\$22.5M

Attachment A
BCERC List of Publications 2004 - 2008
2004
Cases S, Zhou P, Schillingford J, Wiseman BS, Fish J-D, Hennighausen L, Werb Z & R. V. Farese, Jr RV. Development of the mammary gland requires DGAT1 expression in stromal and epithelial tissues. Development 2004 Jul; 131(13):3047-55. Epub 2004 May 26
Claudio L. Translation: Breast Cancer Takes Center Stage. Environmental Health Perspectives 2004; 112: A92-A94
Whitten, P. (2004). Evidence regarding patient and provider perceptions and health indicators for telehome health. Public Policy & Aging Report, 14(1), 19-21
2005
Atabai K., R. Fernandez, X. Huang, A. Ueki, A. Kline, Y. Li, S. Sadatmansoori, C. Smith-Steinhart, W. Zhu, R. Pytela, Z. Werb & D. Sheppard (2005). Mfge8 is critical for mammary gland remodeling during involution. Mol. Biol. Cell. 16:5528-5537. PMID: 16195353
Mark D. Aupperlee, Kyle T. Smith, Anastasia Kariagina and Sandra Z. Haslam. Progesterone Receptor Isoforms A and B: Temporal and Spatial Differences in Expression During Murine Mammary Gland Development. 2005 Endocrinology 146:3577-88. doi: 10.1210/en.2005-0346
Barcellos-Hoff MH. Integrative radiation carcinogenesis: Interactions between cell and tissue responses to DNA damage. Sem. Cancer Biol. 2005; 15(2):138-147
Barcellos-Hoff, M.H., and Medina, D. (2005). New highlights on stroma-epithelial interactions in breast cancer. Breast Cancer Res 7, 33-36. PMID: 15642180
Barcellos-Hoff, M.H., Park, C.C., and Wright, E.G. (2005). Radiation and the microenvironment: Tumorigenesis and therapy. Nat Cancer Rev 5, 867-875. PMID: 16327765
Frank M. Biro, Phillip Khoury, and John A. Morrison, Influence of Obesity on Timing of Puberty: Intl J of Andrology, 2005
Fernandez-Gonzalez, R., Barcellos-Hoff, M.H., and Ortiz de Solorzano, C. (2005). A tool for the quantitative spatial analysis of complex cellular systems. IIEEE Trans Image Process 14, 1300-1313. PMID: 16190466
Galvez MP, Forman JA and Landrigan PJ. Chapter 28: Children's Environmental Health in Environmental Health: From Local to Global. Eds: Frumkin H. 2005
Grimm, S.L., Contreras, A., Barcellos-Hoff, M.H., and Rosen, J.M. (2005). Cell cycle defects contribute to a block in hormone-induced mammary gland proliferation in C/EBP beta-null mice. J. Biol. Chem 280(43):36301-36309. PMID: 16120603
Sandra Z. Haslam : Monograph Writing Group IARC: Carcinogenic Risk Assessment of Oral Contraceptives and Combined Estrogen Progestin Menopausal Hormone Therapy. Lyon, France. June 2005(Review)
Heissig, B., S. Rafii, Y. Ohki, Y. Sato, T. Rafael, Z. Zhu, D. J. Hicklin, H. Ogawa, Z. Werb & K. Hattori (2005). Low-dose irradiation promotes tissue revascularization through Kit-ligand mediated release of VEGF from mast cells and MMP-9 mediated progenitor cell mobilization. J. Exp. Med. 202:739-750. PMID: 16157686
Hiatt, RA. The Breast Cancer and the Environment Research Centers. Essays on the Future of Environmental Health Research. Ed. Goehl TJ. Env Health Persp 2005: 16-23.
Rodier, F., S-H. Kim, T. Nijjar, P. Yaswen, & J. Campisi (2005). Cancer and aging: The importance of telomeres in genome maintenance. Int. J. Biochem. Cell Biol.: 37 :977-990.PMID: 15743672
Rowell, C., Carpenter, D.M., and Lamartiniere , C.A. Chemoprevention of Breast Cancer, Proteomic Discovery of Genistein Action in the Rat Mammary Gland. J Nutrition Sci, 135:2953S-2959S, 2005

Rowell, C., Carpenter, D.M., and Lamartiniere, C.A. Modeling Biological Variability in 2-D gel Proteomic Carcinogenesis Experiments. <i>Journal of Proteome Research</i> , 4:1619-1627, 2005.
Sternlicht, M.D., S.W. Sunnarborg, H. Kouros-Mehr, Y. Yu, D.C., Lee & Z. Werb (2005). Mammary ductal morphogenesis requires paracrine activation of stromal EGFR via ADAM17-dependent shedding of epithelial amphiregulin. <i>Development</i> . 132:3923-3933. PMID: 16079154
Wetmur, J.G., Kumar, M., Zhang, L., Palomeque, C., Wallenstein, S. & Chen, J. Molecular haplotyping by linking emulsion PCR: Analysis of PON1 haplotypes and phenotypes. <i>Nucleic Acids Res.</i> 33, 2615-2619 (2005).
Whitten, P., Doolittle, G., & Mackert, M. (2005). Providers' Acceptance of Telehospice. <i>Journal of Palliative Medicine</i> , 8 (4): 730-735.
Wolff MS, Britton JA, and Russo J. TCDD and Puberty in Girls. <i>Environmental Health Perspectives</i> 2005; 113: A17
Wolff MS, Britton JA, Russo, J. Letter regarding Serum Dioxin Concentrations and Age at Menarche, <i>Environ Health Perspect</i> , 113:A17, 2005.
Mark D. Aupperlee, Anastasia Kariagina, Janet Osuch and Sandra Z. Haslam. Progestins and Breast Cancer. <i>Breast Disease</i> 24: 38-58.
2006
Atkin, C.K., Smith, S.W., Ferguson, V. & McFeters, C. A Comprehensive Analysis of Breast Cancer, News Coverage in Leading Media Outlets. <i>Journal of Health Communication</i> (In Press)
M Aupperlee, S Haslam. "Differential hormonal regulation and function of PR isoforms in normal adult mouse mammary gland." <i>Endocrinology</i> 148(5):2290-2300 (2007). doi:10.1210/en/2006-1721
Mark D. Aupperlee, Anastasia Kariagina, Janet Osuch and Sandra Z. Haslam. Progestins and Breast Cancer. <i>Breast Disease</i> 24: 38-58.
Claudio, L. Making progress on breast cancer. <i>Environ Health Perspect.</i> 2006 Feb; 114(2):A98-9.
Claudio L. RTP leaders unite to advance environmental health. <i>Environ Health Perspect.</i> 2006 Sep;114(9):A524-5.
D Clegg, S Heffelfinger. Obesity: its influence on breast cancer susceptibility. <i>Women's Health</i> 2006. 2: 1-9
R Fernandez-Gonzales, A Munoz-Barrutia, MH Barcellos-Hoff, and C Ortiz-de-Solorzano. Quantitative in vivo Microscopy: the return from the 'omics'. <i>Current Opinion in Cell Biology</i> , 2006. 17(5): 501-510.
Fleisch, M.C., Maxwell, C.A., and Barcellos-Hoff, M.H. (2006). The pleiotropic roles of transforming growth factor beta in homeostasis and carcinogenesis of endocrine organs. <i>Endocr Rel Cancer</i> 13, 379-400.
Glass, RI, Bridbord K, Rosenthal J., Claudio L. Global perspective on environmental health. <i>Environ Health Perspect.</i> 2006 Aug;114(8):A454-5.
Jenkins S, Rowell C, Wang J, and Lamartiniere CA. Prenatal TCDD Exposure Predisposes for Mammary Cancer in Rats. <i>Reproductive Toxicology</i> (2006) doi:10.1016/j.reprotox.2006.10.004
Sandra Z. Haslam. Experimental Mouse Model of Hormonal Therapy Effects on the Postmenopausal Breast. 2006 <i>Breast Disease</i> 24:71-78
Kouros-Mehr, H., E.M. Slorach, M.D. Sternlicht & Z. Werb (2006). GATA-3 maintains the differentiation of the luminal cell fate in the mammary gland. <i>Cell</i> , 127:1041-1055.

Kouros-Mehr, H., Werb, Z. (2006). Candidate regulators of mammary branching morphogenesis identified by genome-wide transcript analysis. <i>Dev Dyn.</i> 235:3404-3412.
Lu, P., M.D. Sternlicht & Z. Werb (2006). Comparative mechanisms of branching morphogenesis in diverse systems. <i>J. Mamm. Gland Biol. Neoplasia</i> 11:213-228. PMID: 17120154
D Lum, J Tan, S Rosen, Z Werb. "Gene trap disruption of the mouse heparan sulfate 6-O-endosulfatase, Sulf2." <i>Mol. Cell. Biol.</i> 27:678-688 (2006) PMID: 17116694
Silk, K.J., Bigsby, E., Volkman, J., Kingsley, C., Atkin, C., Ferrara , M., & Goins, L.A. (2006) Formative Research on Adolescent and Adult Risk Factors for Breast Cancer. <i>Social Science and Medicine</i> , 63, 3124-3136
Sternlicht, M.D. (2006). Branching morphogenesis: the cues that regulate mammary ductal development. <i>Breast Cancer Res.</i> 8:201[doi:10.1186/bcr1368]. PMID: 16524451
Sternlicht, M.D., H. Kouros-Mehr, P. Lu & Z. Werb (2006). Hormonal and local control of mammary branching morphogenesis. <i>Differentiation</i> 74: 365-381. PMID: 16916375
Wallenstein, W Chan, J Wetmur. "Comparison of statistical models for analyzing genotype, inferred haplotype and molecular haplotype data ." <i>Mol. Genet. Metab.</i> 89(3):270-3 (2006)
Whitten, P., Kreps, G., & Eastin, M. (Eds.) (2006, in-progress). <i>Advances in Cancer Online Information Services</i> . Cresskill, NJ: Hampton Press.
Wolff, M.S., Endocrine disruptors: Challenges for Environmental Research in the 21st Century, <i>Ann NY Acad Sci</i> , 1076: 228-38.
Wolff, M.S., Teitelbaum, S.L., Windham , G., Pinney, S.M., Britton, J.A., Chelimo, C., Godbold, J., Biro, F., Kushi, L.H., Pfeiffer, C.M., Calafat, A.M. "Pilot Study of Urinary Biomarkers of Phytoestrogens, Phthalates, and Phenols in Girls." <i>Env Hlth Perspect</i> Jan. 115(1):116-21 (2007) (article: doi:10.1289/ehp.9488) (online 19 October 2006)
2007
M Aupperlee, S Haslam. "Differential hormonal regulation and function of PR isoforms in normal adult mouse mammary gland." <i>Endocrinology</i> 148(5):2290-2300 (2007). doi:10.1210/en/2006-1721
Chace R: Growing up healthy in East Harlem and the Bronx, New York. <i>The Ribbon</i> 12: 9-12, 2007
L. Claudio. Centered on Breast Cancer. <i>Environ Health Perspect.</i> 2007 Mar; 115(3):A132-33.
Fata, H Mori, A Ewald, H Zhang, E Yao , Z Werb, M Bissell. "The MAPKERK-1,2 pathway integrates distinct and antagonistic signals from TGFa and FGF7 in morphogenesis of mouse mammary epithelium." <i>Dev. Biol.</i> Epub 16 March (2007). PMID: 17448457
Fernandez-Gonzalez, R., I. Ille-Bochaca, C. Ortiz de Solorzano & M.H. Barcellos-Hoff (2007). In Situ Analysis of Mammary Progenitors. In <i>Protocols for Stem Cells</i> . I.M. Conboy and M. Conboy, editors. Humana Press, Totowa, N.J
Galvez MP, Morland K, Siskind J, Raines C, Kobil J, Britton JA, Brenner B, Godbold J. Race and Food Store Availability in an Inner City Neighborhood. <i>Public Health Nutr.</i> Oct 2007.
RB Gear, M Yan, J Schneider, P Succop, SC Heffelfinger, DJ Clegg. Charles River SPrague Dawley Rats Lack Early Age-Dependent Susceptibility to DMBA-Induced Mammary Carcinogens. <i>Int. J Biol Sci</i> 2007, 3(7)408-416.
S Jenkins, C Rowell, J Wang, C Lamartiniere. "Prenatal TCDD Exposure Predisposes for Mammary Cancer in Rats." <i>Reproductive Toxicology</i> , 23(2007) 391-396.
A Kariagina, M Aupperlee, S Haslam. "Progesterone Receptor Isoforms and Proliferation in the Rat Mammary Gland During Development." <i>Endocrinology</i> 148(6):2723-2736 (2007) doi:

10.1210/en.2006-1493.
Raquel Moral, Richard Wang, Irma H. Russo, Coral A. Lamartiniere, Julia Pereira, Jose Russo. Effect of prenatal exposure to the endocrine disruptor bisphenol A on mammary gland morphology and gene expression signature. <i>Journal of Endocrinology</i> 196:1-13, 2007.
Moral, R., Wang, R., Russo, I.H., Mailo, D.A Balogh, G.A., Lamartiniere, C.A., and Russo, J. The plasticizer butyl benzyl phthalate induces genomic changes in rat mammary gland after neonatal/prepubertal exposure", <i>Journal: BMC Genomics</i> (2007). 8: 453
Oketch-Rabah, H.A.& M.H. Barcellos-Hoff. (2007) Stroma, microenvironment and radiation carcinogenesis. In <i>Reviews in Cancer Biology & Therapeutics</i> . V.N. U. N. Kasid, A. Haimovitz-Friedman and M. Bar-Eli, editor. Transworld Research Network, Kerala , India
A Page-McCaw, A Ewald, Z Werb. "Matrix Metalloproteinases and the Regulation of Tissue Remodeling ." <i>Nat. Rev. Mol. Cell Biol.</i> 8:221-233 (2007) PMID: 17318226
S J Santos, S Haslam, S Conrad. Estrogen and Progesterone are Critical Regulators of Stat5a Expression in the Mouse Mammary Gland. <i>Endocrinology</i> . doi:10.1210/en.2007-0594. E-publish 09/20/07
Teitelbaum, SL, J.A. Britton, A.M. Calafat, X. Ye, M.J. Silva, J.A. Reidy, M.P. Galvez, B.L. Brenner and M.S. Wolff. Temporal variability in urinary concentrations of phthalate metabolites, phytoestrogens and phenols among minority children in the United States. <i>Environmental Research</i> 106, 257-269 Epub 2007 Oct 31.
2008
Atkin, C. K., Smith, S. W., Ferguson , V. & McFeters, C., (2008). A comprehensive analysis of breast cancer news coverage in leading media outlets. <i>Journal of Health Communication</i> , 13, 3-17.
Britton,J.A., Boguski,L., Hochman,S., Maloney,N., Tully, N-S., Berkowitz, G., Larson,S., Forman, J.Wolff.M.S. Environmental Exposures and Puberty in Inner-City Girls. <i>Environmental Research</i> 2008. 107:393-400.
Brenner, BB and Galvez MP. Chapter 14: Community Interventions to Reduce Exposure to Chemicals with Endocrine Disrupting Properties. In <i>Endocrine-disrupting Chemicals: From Basic Research to Clinical Practice</i> , ed. Andrea C. Gore. Humana Press.
Egeblad M, Ewald AJ, Askautrud HA, Truitt ML, Welm BE, Bainbridge E, Peeters G, Krummel MJ, Werb Z (2008). Visualizing Stromal Cell Dynamics in Different Tumor Microenvironments by Spinning Disk Confocal Microscopy. <i>Disease Models & Mechanisms</i> 1:155-167.
Ford K, Khoury J, Biro FM. Early Markers of Pubertal Onset: Height and Foot Size. <i>J Adolesc Health</i> . 2009 May;44(5):500-1.
Kariagina, M Aupperlee, S Haslam. "Progesterone Receptor Isoform Functions in Normal Breast Development and Breast Cancer ." <i>Crit Rev in Eucaryotic Gene Ex</i> , 2008. 18(1): 11-33.
Kouros-Mehr, H, SK Bechis, EM slorach, LE Littlepage, M Egeblad, AJ Ewald, S-Y Pai, I-C Ho, & Z Werb. GATA-3 Links Tumor Differentiation and Dissemination in a Luminal Breast Cancer Model. <i>Cancer Cell</i> (2008), 13; 141-152.
Kouros-Mehr H, JW Kim, S Bechis, Z Werb. GATA-3 and the regulation of the mammary luminal cell fate, <i>Curr Opin Cell Biol</i> (2008), doi:10.1016/j.ceb.2008.02.003
Pinney SM, Biro FM, Yaghjyan L, Calafat A, Windham G, Brown MK, Hernick A, Sucharew H, Succop P, Ball K, Kushi LH, Bornschein RL. Pilot Study of Serum Biomarkers of Polyfluoroalkyl Compounds in Young Girls. Submitted to <i>Environmental Science & Technology</i> , April 2008.
Teitelbaum SL, Britton JA, Calafat AM, Ye X, Silva MJ, Reidy JA, Galvez MP, Brenner BL, Wolff MS. Temporal variability in urinary concentrations of phthalate metabolites, phytoestrogens and phenols among minority children in the United States. <i>Environ Res</i> . 2008

Feb;106(2):257-69.
Volkman, J., and Silk, K. "Adolescent females and their mothers: Examining perceptions of the environment and breast cancer," Journal of Health Psychology. 2008 Nov;13(8):1180-9.
Welm, B.E, G. J. P. Dijkgraaf, A. S. Bledau, A. L. Welm & Z. Werb (2007). Lentiviral transduction of stem cells for genetic analysis of mammary development and breast cancer. Cell Stem Cell 2008. 2; 90-102.
Wetmur, J.G., & Chen, J. An emulsion of PCR-based method for molecular haplotyping. Methods in Molecular Biology. Environmental Genomics, Martin C, ed, Humana Press, Totowa, NJ, 410:351-361 (2008).
2009
Biro FM, Wolff MS, Kushi LH. Impact of yesterday's genes and today's diet and chemicals on tomorrow's women. J Pediatr Adolesc Gynecol. 2009 Feb;22(1):3-6.
Biro FM, Galvez MP, Greenspan LC, Vangeepuram N, Pinney SM, Kushi LH, Wolff MS. Pubertal Assessment Methodology and Baseline Pubertal Characteristics in the BCERC Cohort. <i>Submitted for publication</i>
Britton, JA, Wetmur J, Kadlubar FF, Teitelbaum SL, Moshier EL, Wolff MS. CYP19 and Breast Pubertal Prevalence (submitted)

Attachment B: Report of the Breast Cancer and the Environment Working Group

To: National Institute of Environmental Health Science (NIEHS) / National Cancer Institute

From: BCERC Working Group

Date: February 25, 2009

Subject: EVALUATION REVIEW: Breast Cancer and the Environment Research Centers (BCERC)

SUMMARY

The Breast Cancer and the Environment Research Centers (BCERC) was launched in 2003 in response to RFA-ES-03-001. The current funding for BCERC will expire June 2010.

EVALUATION REVIEW: Breast Cancer and the Environment Research Centers

Introduction

The Working Group (WG) is composed of scientists in the fields of toxicology, cancer biology, environmental health research, epidemiology, risk communication, and risk assessment, as well as breast cancer advocates who bring a broad range of interdisciplinary perspectives to NIEHS/NCI on the progress of the Centers program and opportunities to enhance its work, and can communicate the work of the Centers to broader scientific and public audiences. The WG meets twice annually with BCERC investigators, participates in conference calls, and reviews progress reports.

The WG congratulates NIEHS/NCI and the Centers on the development of a valuable, innovative approach to the urgent public health need to identify modifiable risk factors for breast cancer. We have been honored to contribute to this process.

The goal of this memorandum is to provide a summary evaluation to NIEHS/NCI for consideration in decisions about the future of the Centers during the next 18 months and at the close of the program's 7-year funding period. We do not aim to comprehensively report on the accomplishments of each of the contributing centers within BCERC. For that, we refer readers to reports by the investigators.

This report responds to questions posed to the WG by NIEHS/NCI, which are shown below in *italics*.

[1] How well has the BCERC performed in regard to the following goals of the original RFA?

A. OVERALL SCIENTIFIC GOALS:

- *Fill gaps in the regulation of normal mammary gland development*
- *Fill gaps related to how environmental exposures impact the development of the mammary gland.*
- *Integrate time, susceptibility and exposure to more fully appreciate the changes that occur in the mammary gland early in life that may predispose a woman to breast cancer.*

- *Define specific periods of susceptibility of the breast when environmental stressors may change the molecular architecture of the gland, conferring increased risk of future breast cancer.*

The Epidemiology Project (P2) is well-designed to provide important information on these topics but has not yet reached the point in data analysis where the contribution to overall scientific goals can be assessed. The project's preliminary data on biomarkers of exposures to hormonally active environmental chemicals indicates young girls are exposed to a number of potentially health-related environmental stressors during the pre-pubertal phase of breast development. For many of these chemicals, this was the first report of an exposure in this age group in American girls and thus represents an important scientific and public health milestone.

Regarding the Biology Project (P1, animal and cell studies), several major contributions have been achieved directly addressing the overall scientific goals. Some basic scientific data gaps have been filled using both animal and cell line models. For instance, the identification of which progesterone receptor isoform is present in the mammary gland in different species at various times in development and their specific roles in mammary gland development has been clarified by the Michigan State (MSU) laboratories, and multiple genes controlling branching morphogenesis have been identified by the group. *GATA-3* is one recent example that was identified by a University of California-San Francisco (UCSF) laboratory. The BCERC P1 scientists have characterized mammary gland developmental effects stemming from exposure to the environmental contaminants bisphenol A (BPA), benzyl butyl phthalate (BBP), perfluorooctanoic acid (PFOA), and specific dietary fats in terms of species and dose. These animal studies have been careful to consider the dose and route of exposures so that the relevance to human exposures and potentially health effects can be interpreted across species. The timing of exposure, the importance of critical periods of development, and variations in response due to genetic differences in rodent strains has been addressed. The finding that oral administration of BPA at low, environmentally relevant doses during critical time periods, results in dose-dependent increase in the number of mammary tumors and in reduced tumor latency, is an important finding by the Fox Chase/University of Alabama-Birmingham laboratories (FCCC/UAB). Other researchers have not administered BPA at these low levels, and frequently not by an oral route, which is the most relevant route for human exposure.

Specific biomarkers related either to changes in developmental endpoints or tumor formation have been identified by FCCC/UAB and are being characterized further for use in human studies. Numerous aspects of these studies are still on-going and productive. The P1 PFOA (MSU) and BBP (FCCC/UAB) studies in animals have been conducted in close collaboration with P2 (epidemiology) investigators evaluating those particular end points in adolescent girls and this collaboration has helped both the P1 and P2 investigators to further their research.

B. TARGETED SCIENTIFIC GOALS

- *Conduct collaborative experiments using relevant animal and cell culture models of mammary gland development over the lifespan integrating endpoints such as gene expression, proteomics, and metabolomics, in order to understand the effects of selected chemicals or other environmental exposures on mammary gland pathology (Project 1).*

The P1 studies have investigated regulation of normal mammary gland development and have evaluated early life environmental exposures (focused so far primarily on the pubertal period)

and identified specific genes and proteins of interest for further study. Using targeted gene array analyses, both the FCCC/UAB and University of Cincinnati (UC) labs have identified a small number of genes that are associated with phenotypic changes in the mammary gland. The FCCC/UAB group has confirmed these gene changes by RT-PCR and their protein counterpart has been characterized using proteomic approaches, work that has been recently published. The genomic and proteomic changes identified by the FCCC/UAB group appear to be dependent on the timing of exposure (pre-vs. postnatally) and when changes were measured (21 vs 50 days postnatally), suggesting these signatures depend on critical windows of exposure and are expressed at different times during mammary development. The studies are evaluating early life genomic and proteomic markers as predictors of adverse outcome (tumor development).

They have also identified a novel inflammatory gene pathway whose expression is dysregulated following early life exposures and they are following up on this discovery in multiple P1 labs (UAB, UC., and MSU). Evaluating the role of inflammation and obesity (lipid metabolism) in the susceptibility of the mammary gland to changes instigated by environmental contaminants is a challenge that has brought the several P1 laboratories together, and an area in which they will make a strong contribution in the near future.

- *Conduct collaborative multi-site epidemiologic study of the young girls experiencing physiologic changes of thelarche and sexual maturation and their exposures that can impact on their future risk of breast cancer. All study sites will use standardized methodologies to collect data on markers of breast development and other physiologic changes of sexual maturation, assessment of environmental stressors of importance to future breast cancer risk, including lifestyle behaviors, nutrition and dietary supplements, anthropometry, chemical and physical exposures at home, and school, and social factors. DNA specimens will be collected, stored, and analyzed for relevant polymorphic variation related to pathways of interest in defining susceptibility (Project 2).*

The Centers successfully recruited diverse groups of young girls from different geographic areas in the US (east and west coast and the Midwest) with varied racial/ethnic and socioeconomic backgrounds. The Centers have collected extensive information on markers of pubertal development, anthropometry, nutrition, and relevant aspects of lifestyle. This trans-disciplinary study will provide substantial information about dietary factors and is unique in that it incorporated environmental pollutants, the built environment and social factors. The Centers have collected blood and urine samples that have generated novel information on pollutants and provide a resource for additional study. In recent studies, the UCSF P2, in collaboration with Fox Chase/Roswell Park Cancer Center, have identified single-nucleotide polymorphisms associated with either BMI or breast stage in their cohort. Similar types of studies are on-going in the P1 studies and this is seen as an area in which these scientists can collaboratively make major contributions in the coming years.

- *Integrate the basic biological, toxicological, and epidemiologic data on the development and lifespan of the mammary gland in a way that public health messages can be designed to educate young girls and women who are at high risk of breast cancer on the role of specific environmental stressors in breast cancer development and how to reduce exposure to those agents (COTC)*

Much of the COTCs' efforts have been devoted to recruitment and retention activities during the data collection phases for P2. COTCs also have developed web sites with information about BCERC and about breast cancer and girls' health and development more generally, and they have conducted a variety of community meetings. The Cincinnati web site is a particularly valuable gateway to information on BCERC and resources outside the program (<http://www.eh.uc.edu/growingupfemale/>). Other examples of COTC activities include the Bay Area town-hall meetings on environmental chemicals and breast cancer and the Mt. Sinai "Growing up Healthy Fact Sheets" and a wallet card on types of plastics to avoid. COTCs contributed to developing fact sheets on environmental chemicals being studied by P2 and P1, providing carefully-reviewed information in areas of scientific uncertainty and controversy; and they provided novel opportunities for breast cancer advocates to visit laboratories and learn about laboratory science. The Cincinnati COTC worked with investigators to develop and implement methods for communicating unanticipated study results back to participants, and additional consideration of reporting individual results to participants is underway in the Cincinnati and San Francisco Bay Area Centers. COTC resources were limited in the initial proposals and have benefited from NIH supplements and Avon Foundation support. Three of the COTCs practice grassroots participatory communications, while the MSU project is an academic-based model charged with formative research to guide dissemination of BCERC results. MSU findings have confirmed broader health communications research and a variety of advocates' observations (for example, that survivor stories and early detection dominate breast cancer messages). MSU studies of mothers and daughters are relevant to the BCERC approach.

Given that scientific publication from BCERC is just beginning to accelerate, much of the work of translation lies ahead. The COTCs have developed an outline for a "dissemination plan" for overall study results that includes future activities, such as developing message content, identifying target audiences, and identifying channels of dissemination. The activities proposed within the outlined plan will need to be prioritized and benefit from additional planning.

C. GOALS FOR COLLABORATION

- *Work within and across centers on targeted biological and epidemiologic research projects.*

The Centers made progress in working within and across centers. These collaborations represent a significant change from "research as usual," requiring time and energy commitments from participants. The development of collaboration was initially slow, as would be expected, given that this type of collaboration was not anticipated during proposal development and investigators typically lack experience and established methods for working this way. Early on in this grant period, the P2s began a communication line to enhance their ability to gather consistent data from their geographically diverse study participants. Several P1:P1 collaborations, noted above, are underway and although slower to develop, there are now 2 P1:P2 collaborations underway, focused on PFOA health effects and environmentally-induced genomic profile changes that may be associated with changes in puberty morphology or tumorigenicity. Additional integration of biology, epidemiology, and outreach/translation and across the Centers remains a goal.

- *Engage participation of the community and national breast cancer advocacy groups and other community or faith based, especially in activities that translate research findings into useful information for the public.*

Each of the COTCs developed unique approaches to its community constituencies. These programs have been successful in recruiting and retaining a diverse study population. COTCs also have provided public health resources (for example, informational programs) for the study's host communities. In addition, COTCs provide community connections that are essential resources to draw upon in the event that a Center must respond to unexpected issues, as occurred with the discovery of higher levels of perfluorinated compounds (PFC) exposure in one community.

National awareness of the BCERC program and its progress to date has been limited and has not met its potential. Translation of findings has been limited in part because there have been few publications from the epidemiology project yet. In addition, P1 investigators have not provided guidance to COTCs on the public messages that should be disseminated from their work. Given that the forthcoming scientific findings will be of national importance, a cross-site processes will be needed that brings together scientific investigators (who must ultimately define the important, accurate messages to communicate) and outreach/communications leaders for national communications to complement regional COTC work.

- *Participate in multiple planning and implementation meetings of each collaborative project during the first year. Methods and approaches will be decided upon by consensus. Less frequent meetings are envisioned after the collaborative projects are launched, but there will be a minimum of two such meetings a year for each collaborative project committee in years two to seven.*

Investigators have generally developed successful processes for meetings and decision-making across the Centers. A majority of the research updates and decision-making within and across Centers/projects are done by monthly conference calls that are open to P1, P2, COTC and WG. The independence of the Centers makes efficient decision-making and management challenging.

- *Planning one scientific workshop/conference on emerging issues in breast cancer and the environment.*

The annual public conference hosted by the Centers at various locations around the country is the primary venue for communicating the Centers' progress to the national breast cancer advocacy network. These conferences have been excellent in recent years as results began to emerge from the BCERC studies. The conference has been well attended by breast cancer advocates in the host area with some additional advocate leaders traveling from other regions. Realistically, a relatively small number of advocates can travel to attend these meetings because of the cost and conflicting time commitments, such as family and employment. The focus of the meetings is on presenting the results of BCERC studies in a lay-accessible way and there is less opportunity for discussion or presentation by other researchers. To date there has not been a large attendance by other scientists working on cancer and environmental risk factors. Scientific audiences have had some opportunities to learn about specific aspects of the study through symposia and presentations at scientific conferences, including the 2008 Society of Toxicology annual meeting and others. However, these forums do not match the transdisciplinary, scientist-advocate context of BCERC. Knowing this BCERC model is unique, focusing on environmental pollutants, the built environment and social factors, consideration should be made to encourage a larger scientific and medical audience to attend the culminating

annual BCERC meetings to build on this valuable resource and enrich the stream of scientific dialogue and productivity coming from the projects.

2] Overall Exemplary Findings

Conceptualization of the BCERC program. The NIEHS/NCI conceptualization of the BCERC program in the RFA remains one of the program's key achievements and contributions. The program was inspired by dialogue among the leadership of NIEHS and consumer advocates. Many of the innovative aspects of the program emerged from that dialogue, and it is commendable that the Institute embraced this collaborative and multidisciplinary model. Beginning with the difficult problem of designing a research program to identify modifiable environmental risk factors for breast cancer, the RFA defined a study of the factors influencing development at puberty, given that age at menarche was an established breast cancer risk factor. Scientific developments both within the Centers and elsewhere strengthen the basis for the research approach defined in the RFA and underline the public health importance of research questions about environmental factors in girls' development at puberty. New evidence has added support to the conceptualization of breast cancer risk as a function of critical events at particular stages in the life cycle. In addition, evidence has continued to accumulate confirming environmental pollutants, nutrition, family social environments, and physical environments influence puberty. The public health importance of understanding these effects extends beyond breast cancer, particularly because of the inter-relationship with obesity, which has rapidly become a national epidemic.

The formative process of convening multi-perspective, multi-stakeholder workshops to discuss the best approaches to research aimed at breast cancer prevention through identification of environmental factors was exemplary. NIH staff incorporated insights from this process in an innovative RFA that addressed these needs:

- to better understand the developmental biology of the mammary gland
- to integrate knowledge from animal and cell studies as well as human studies, given the limitations and cost of relevant epidemiologic research
- to look for early life determinants of breast cancer.
- to encourage and require effective translation of information back to the public.

The integration of animal/cell and human research and the participation of community leaders could not have occurred through traditional NIH grants.

Response to unexpected PFOA findings. BCERC blood samples of limited volume were used in an analytical feasibility study (UC P2 pilot study) at the Centers for Disease Control (CDC) laboratory, leading to the unanticipated discovery of higher exposures to perfluorooctanoic acid (PFOA) in the girls from one community. After some initial hesitation and further evaluation of serum PFOA levels in Cincinnati and other BCERC sites, the P1, P2 and COTC components at this Center worked together to evaluate the cause and implications of the exposure, disseminate information to study participants and the community, and incorporate relevant scientific questions into the on-going P2 projects. The MSU P1 in collaboration with the UC P2 undertook a series of animal model studies to assess the effects of PFOA on pubertal development, mammary gland development, and subsequent susceptibility to mammary carcinogenesis. The resulting analysis will become one of the important scientific contributions of BCERC, and the Centers' response also supported the integrity of relationships between the researchers and participants.

Biology Project. One of the biggest contributions from P1 is the identification of susceptibility factors in the responses to environmental stressors. As mentioned previously, the investigators have identified specific genes that are associated with time- and morphology-dependent changes in the mammary gland. They have confirmed the peri-pubertal period of development as a critical period for the effects of environmental contaminants of interest. Finally, they have identified the importance of dietary fat and obesity in mammary gland development and susceptibility to tumors. Additionally, an inflammation signature has been identified across species and across exposures to hormones, dietary fat and environmental contaminants that may be highly relevant to susceptibility to tumors. Genomic and proteomic signatures associated with specific stages of pubertal development (both P1 and P2) or susceptibility to mammary tumorigenesis are both novel and important findings. These are important areas of pursuit for the future.

Epidemiology Project. The Centers have collected extensive exposure and puberty outcome data on a large, ethnically diverse group of girls, providing a unique resource for understanding a health outcome of importance for breast cancer, other health outcomes, and social development. The design of the project allowed for flexible expansion to include additional environmental chemical biomarkers in response to new scientific interests and availability of analytical methods. Both the scale and flexibility of the project would have been difficult (or impossible) to achieve under traditional grant mechanisms.

Community Outreach and Translation Cores. The COTCs developed a variety of novel approaches in their communities. We particularly congratulate the COTCs for their sustained commitment to engaging with study participants, community members, and BCERC investigators, including the biology projects' laboratory research. The Bay Area COTC's independent evaluation of its approach will help develop and disseminate this model.

3] Recommendations for Improvement

Publications. The pace of publication has picked up from a slow start. Mechanisms to support sustained momentum are important. Publication delays have slowed access to emerging results that could inform other research. Delay of a foundation paper describing the BCERC approach slowed the opportunity to contribute to development of models of transdisciplinary research and models for understanding complex diseases that develop from multiple factors across the life course. The MSU COTC prepared an annotated bibliography of potential outlets for peer-reviewed publications about the COTCs, and COTCs are beginning to publish their work. In addition, it would be valuable for the P1 and P2 PI's to assist their COTCs (or find appropriate others to assist) in publishing aspects of COTC work that provide national models and messages.

Progress in the biology project. There has been a great deal of change in leadership in the dietary fat project (UC). PIs in the other sites helped to support that project to keep it moving. Currently it is seen as needing strong leadership that is knowledgeable in mammary gland development and cancer. The model, looking at offspring following gestational exposure, is a valuable one and should be able to progress within the project's timeframe.

Secondly, there is a need to encourage those that have been very successful in their own areas of expertise to collaborate more with others in the P1 group (especially those in the Bay Area),

adding environmental exposures (identified in the P2 projects) and/or dietary stressors that will hasten progress in the P1. We understand that some plans are underway in this regard.

Progress in the epidemiology project. Development of a working dataset to allow for baseline description and analysis of the cohort across all Centers should have been completed earlier. We commend investigators who developed work-around analyses of Center-specific data. We expect that this problem has been remedied, and results and publications will be forthcoming from the epidemiology project. Oversight strategies that identify and remedy schedule and /or data entry and verification bottlenecks are needed.

Working Group. The Working Group (WG) provided expertise that facilitated a number of concrete improvements in both P1 and P2; and it provided helpful support and translation for COTCs. In addition, the WG provides transparency for the project and communication on behalf of the project with outside stakeholders. Working Group members were frequently asked by breast cancer advocates, elected officials, and researchers, “how’s it going?” The ability to respond to these questions as informed outsiders has contributed to the project’s credibility. However, the Steering Committee has been largely unresponsive to WG requests. In particular, the Steering Committee never provided a spreadsheet showing exposure measurements to be collected at each time point by each Center – a tool that has now been prepared for the BSA and would have been of earlier use to the investigators in planning analyses as well as to the WG in understanding the detailed aims of the project. In the future, NIEHS/NCI should take responsibility for accountability of the Centers to the WG.

4] Improvements that need to be made

Improved management. The semi-independence of the Centers and coordinating center has made it difficult to manage situations in which performance of an investigator is lagging and situations in which one Center is dependent on progress at another or at the coordinating center. We recommend that NIEHS/NCI develop new controls that allow for adjustments in funding and investigator assignments in mid course if performance is hindering the program as a whole.

Translation of results. We do not see a structure currently in place to adequately and efficiently translate and disseminate BCERC results to audiences beyond regional study communities. Translation includes (a) prompt scientific publication and dissemination to researchers, (b) development of public communications reporting the results (e.g., lay summaries, press releases, news media outreach, reports to participants, outreach to breast cancer advocates, online resources), and (c) development of initial recommendations for public health policies and programs. We believe translation should be considered a shared responsibility of NIEHS/NCI and the Centers.

We do not think that redirecting existing funding from research to translation would be wise, so additional resources will be needed for translation, dissemination, and evaluation of outreach efforts, particularly as a large volume of findings emerges at the end of the study. Public communications must be accurate, highlight what is scientifically important, be accessible, and generate attention. We see value in communicating how BCERC specifically, as an innovative public investment, has contributed to environmental public health. With these goals in mind, we believe public communications will require collaboration of NIEHS/NCI, senior investigators, COTCs, and skilled environmental science/public health writers. The current dissemination plan provides a useful framework, but it will be necessary to focus on feasible priorities and develop

a coordinated, collaborative process involving investigators and COTCs and incorporating skill sets appropriate to national translation. In addition, public health translation will ultimately extend beyond the BCERC program

5] Working Group recommendations

Continuation of the study: Following girls through puberty. Many of the girls in the study will not have attained menarche at the end of the 7-year funding period. Thus, we believe that continuing the study is critical in order to realize the benefits from investments already made in developing this cohort. Further, we believe that the biology projects have already been productive, and we expect that the recently initiated collaborative studies, as well as the planned stand-alone projects would continue to elucidate mammary gland development and cancer mechanisms in a future funding cycle. In addition, as epidemiology results begin to emerge, further biology questions will be raised. Community outreach and translation will continue to be important to the success of this research and its public health impact.

DATA SOURCES USED BY THE REVIEW PANEL

The observations, assessment and recommendations presented in the preceding sections are based on the following:

- Attendance at the BCERC Interim 2008 and Annual Meeting 2008.
- Meeting summary from the 2008 BCERC Interim Meeting
- Selected publications and Project Presentations
- Conference calls and working group meetings
- Annual reports of the Centers
- Consultation with investigators from multiple participating BCERC

EVALUATION COMMITTEE:

Names and Affiliations listed:

- Karen Joy Miller, BCE WG Chair; Huntington Breast Cancer Action Coalition, Inc.
- Julia Brody, PhD, Silent Spring Institute
- Diana T. Chingos, Univ. of Southern California, Kenneth J. Norris Cancer Survivorship Advisory Council
- Dale Eastman, Alamo Breast Cancer Foundation
- Suzanne Fenton, PhD, US EPA, Reproductive Toxicology Division
- Maria Carolina Hinestrosa, M.A., M.P.H., National Breast Cancer Coalition
- Marc Hurlbert, PhD, Avon Foundation Breast Cancer Crusade
- Marion (Mhel) Kavanaugh-Lynch, PhD, University of California, Office of the President, California Breast Cancer Research Program
- Suzanne Snedeker, PhD, Cornell University, Sprecher Institute for Comparative Cancer Research
- Bruce Trock, PhD, Johns Hopkins University