

Early Detection Research Network

Paul F. Engstrom, M.D., *Senior Member, Senior Vice President, Population Science (until December 2005), Senior Vice President for Extramural Research Programs*

Mary B. Daly, M.D., Ph.D., *Senior Member, Senior Vice President, Population Science, Timothy R. Talbot Jr. Chair in Cancer Research*

Paul Cairns, Ph.D., *Member*

Andrew K. Godwin, Ph.D., *Member*

Eric A. Ross, Ph.D., *Associate Member*

The Early Detection Research Network (EDRN) was established in 2000 by the National Cancer Institute to foster a highly collaborative, multi-disciplinary research venue to improve the early detection of cancer. The network is focused on translating new molecular knowledge into practical clinical tests that identify cancer at the earliest stages of normal cellular transformation into a cancer cell and to identify individuals at risk of developing cancer. The EDRN was established to help expedite the translation of discovery into medical practice. This network is based on the premise that integration of discovery, evaluation, and clinical validation phases of medical research are more likely to success when they are carried out in a concerted and systematic effort.

There are five phases to early detection research. Phase I is preclinical and relies on exploratory studies to identify potentially useful markers. In phase II, studies are carried out to determine the capacity of biomarkers to distinguish between people with cancer and those without (clinical assessment and validation). In phase III, scientists determine how well biomarkers detect preclinical disease by testing the markers in tissues collected longitudinally from research cohorts. Phase IV utilizes prospective screening to identify the extent and characteristics of disease detected by the test and to determine the false positive rate. Markers that have successfully moved through the four phases arrive at phase V, cancer control. At this level, investigators evaluate both the role of the biomarkers for detection of cancer and overall impact of screening on the population through large-scale population studies.

Clinical Epidemiology

Fox Chase Cancer Center (FCCC) is a designated Clinical Epidemiology and Validation Center for the early detection of breast and ovarian cancer. In 1999, FCCC established the Biosample Repository under the direction of A. Godwin. The Biosample Repository is a CAP accredited and CLIA-approved facility whose major function is to identify participants, administer informed consent for blood and tissue use, and to collect blood samples and information on personal and family history of cancer, clinical interventions, clinical outcomes, and lifestyle factors. The Biosample Repository has accrued blood samples from more than 7,000 unaffected and cancer-affected individuals, which have been processed and stored as over 180,000 vials. Subcollections in the Repository include over 1,500 women diagnosed with breast cancer and another 1,600 women with no cancer history, but age and ethnically matched to the cancer patients. In addition, there are samples from more than 700

individuals whose blood was collected prior to breast cancer surgery at FCCC. As part of our ovarian cancer SPORE program, blood samples have been collected from 613 individuals with ovarian cancer family history and over 914 blood samples from 145 unaffected women with a hereditary pattern of breast/ovarian cancer.

Gil Mor, M.D., Ph.D., Director of Reproductive Immunology Unit, Yale University School of Medicine, has requested specimens from the FCCC Biosample Repository. Mor has isolated four proteins in the serum of patients with epithelial ovarian cancer that shows significant differences in expression between controls and cancer patients by ELISA assays. The combination of the four analyses exhibited the following: sensitivity 95% positive predictive value, 95% specificity, 95% negative predictive value, 94% considerable improvement over current methodology. In order to validate his findings, Mor has requested additional samples from the FCCC Repository. In the initial phase I pretest, five controls at usual risk and five ovarian

cancer patients with advanced disease matched on age will be tested. An additional 50 controls to include 10 high-risk women (BRCA1, BRCA2 carriers) and 50 ovarian cancer patients to include 25% early stage, 60% late stage, and 15% non-serous cancers will be tested. The analysis will be accomplished in Mor's laboratory and the data and statistical review will be performed by the Data Management Core.

The Breast/Ovarian collaborative group in the EDRN has proposed to develop a breast cancer reference set. The purpose is to assemble a well-characterized set of blood specimens to test biomarkers that can detect and discriminate breast cancer. These samples will be divided to provide sets of specimens that can be tested in a number of different laboratories with results that can be directly comparable. Each of the EDRN epidemiology sites will assemble a cohort of women undergoing diagnosis for breast cancer. These will encompass two groups, one accrued in diagnostic radiology where lesions detectable by imaging are sampled, and a second group from surgical oncology where non-imaged masses are often

found and biopsied in the examining room. Cancer found via these two approaches may have biological properties and associated biomarkers that differ. The collection will include incident cases of breast cancer and benign breast disease (200 invasive cancer and 200 benign). In addition, 100 cases of DCIS and at least 40 invasive lobular carcinomas will be in the collection. Blood will be collected, separated, and aliquoted into 3 ml. samples that will be frozen and stored at -80° . Buffy coat will be stored as two dried pellets, one from each tube also at -80° . These samples will be forwarded to an NCI-sponsored storage facility for distribution to approved investigators.

In addition to the Epidemiology and Validation Center, P. Cairns has a biomarker developmental laboratory project to determine the diagnostic utility of methylation specific PCR in serum from patients at high risk for breast cancer. Cairns proposes to study 100 tumor/serum pairs to include early disease such as DCIS and Stage I patients. The breast cancer control samples are available in the Biosample Repository and the Tissue Bank at FCCC.