HARVARD CATALYST

THE HARVARD CLINICAL AND TRANSLATIONAL SCIENCE CENTER

Addressing Health Disparities in Cancer Through Basic Research

The Harvard Catalyst Health Disparities Research Program and Dana-Farber/Harvard Cancer Center co-sponsored this Pilot Grant opportunity to encourage basic scientists to conduct innovative research into the biology underlying racial, ethnic and socioeconomic disparities in cancer. The goal of this Pilot Grant Opportunity was to generate new insights about basic mechanisms contributing to health disparities that could improve the prevention, diagnosis or treatment of cancer, and ultimately reduce the unequal burden of cancer in society.

This funding opportunity was open to any faculty member holding a Harvard University faculty appointment. Three Pilot Grants were awarded in amounts of up to $50,000 for each one-year project.

Funding decisions for the Addressing Health Disparities in Cancer through Basic Research Pilot Grants were made in June, 2012.

Small Molecule Screen to Identify Compounds Targeting HPV Positive Cervical Cancers and Precancers

Principal Investigator: Peter Howley, MD, Harvard Medical School

Co-Investigator: Nathanael Gray, PhD, Dana-Farber Cancer Institute

There is a need for novel therapies to treat HPV associated cervical cancer and the precursor preneoplastic lesions. Cervical cancer is a particular burden among black and Hispanic women who are more at risk for cervical cancer and are diagnosed later in the disease. Despite the development and approval of highly effective preventive vaccines for the high-risk HPV types associated with cancer risk, there are eleven other cancer associated HPV types that account for 30% of anogenital cancers. Furthermore the current HPV vaccines have no therapeutic value. Thus individuals already infected by either HPV16 or HPV18 do not benefit from vaccination and remain at risk for cancer. The benefit of the vaccine will therefore not be fully realized for decades. HPVs encode two oncoproteins (E6 and E7). The major activity of E6 is to counter the pro-apoptotic activity of E7 by targeting the ubiquitylation and proteolysis of p53. The pathway involving the E6-mediated degradation of p53 involving the E6AP ubiquitin protein ligase was identified in the Howley laboratory and has been validated as a potential therapeutic target; cellular depletion of E6 by siRNA is cytotoxic through the induction of p53 mediated apoptosis. This proposal will combine Peter Howley's expertise on HPV and cervical cancer with that of Nathanael Gray on discovering and developing small molecule modulators for protein targets in conducting a pilot small molecule screen at the ICCB-Longwood facility.

Genomic Profiling of Uterine Papillary Serous Carcinoma in African American Women

Principal Investigator: Larissa Lee, MD, Brigham and Women's Hospital

Co-Investigators: Suzanne Dahlberg, PhD, Dana-Farber Cancer Institute
Ursula Matulonis, MD, Dana-Farber Cancer Institute
Andrea Myers, MD, PhD, Dana-Farber Cancer Institute
Akila Viswanathan, MD, MPH, Brigham and Women's Hospital
Alexi Wright, MD, Dana-Farber Cancer Institute

The disparities in clinical outcomes between African American and Caucasian women with endometrial cancer are marked, with a 24% absolute difference in overall survival. Studies suggest that biological differences may contribute to the higher cancer-specific mortality. African Americans are more likely to be diagnosed with uterine papillary serous histology (UPSC), a less common, more aggressive, and poorly understood subtype of endometrial cancer. The purpose of this study is to explore the biological underpinnings of UPSC with the following specific aims:

1. To molecularly characterize a cohort of clinically annotated UPSC tumors from the DF/HCC archives using mutational and copy number analysis of candidate genes.
2. To explore molecular differences of UPSC between tumors from African Americans and Caucasians.
3. To explore the association between copy number alterations and somatic mutation rates by disease stage, recurrence rate and overall survival in UPSC.

Validating Epigenetic Markers for Studies of Disparities in ER-Negative Breast Cancer

Principal Investigator: Andrea Baccarelli, MD, MPH, Harvard School of Public Health

Co-Investigator: Alexandra Shields, PhD, Massachusetts General Hospital

This pilot will generate preliminary data to support investigations to understand epigenetic mechanisms activated by stress that may increase risk of estrogen receptor-negative (ER-) cancer, an aggressive subtype of breast cancer that disproportionately affects black women and contributes to their higher mortality rates. Prior studies examining stress and breast cancer risk have yielded mixed results, but none has distinguished cancer subtypes. One emerging hypothesis is that stress, through chronic activation of cortisol and subsequent dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, decreases risk of ER+ cancer (through reduced endogenous estrogen), but increases risk of ER- cancer. The association between stress and dysregulation of the HPA axis and increased mammary tumor burden of ER- cancers has been confirmed in animals, but no studies have been conducted in humans. We propose to conduct a proof-of-concept pilot validating self-reported measures of psychosocial stress in epigenetic markers in the HPA axis. Pilot data will support the first national study assessing the role of psychosocial stress in risk of ER- breast cancer. Study aims are to: (1) assess epigenetic changes (specifically, DNA-methylation) at three HPA-related genes; (2) assess the relationship between four measures of psychosocial stress and DNA-methylation for selected genes; and (3) use study results to develop an analysis plan for an R01 to be submitted to NCI in February 2013. This pilot will provide essential preliminary data to support research aimed at generating new insight into risk factors for ER- cancer and guide development of novel interventions to reduce breast cancer disparities.