

Bankhead-Coley Cancer Research Program

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Bridge (1-year project)*

Project Title: Genetic Mechanisms of Anthracycline Cardiotoxicity in Pediatric Cancer Survivors

Project Summary: Anthracycline chemotherapy has been used in more than 50 percent of patients with childhood cancer and has helped contribute to 5-year survival rates of over 77 percent. This therapeutic success is tempered by the well-recognized and clinically significant late cardiotoxicity associated with these therapies. Anthracycline chemotherapy has been associated with rates of cardiac death more than 8-fold higher than those found in a healthy control population. While the exact mechanism of anthracycline cardiotoxicity is not yet known, both mitochondrial DNA and hemochromatosis gene mutations have been implicated in cardiomyopathy in other populations and animal models. In this grant, we will extend our understanding of anthracycline-based cardiotoxicity through the study of mitochondrial DNA mutations (mtDNA) and genetic mutations of the hemochromatosis genes (HFE) as potential causes/mechanisms of the increased cardiovascular risk in survivors of childhood acute lymphoblastic leukemia (ALL). We will also examine whether dexrazoxane, which has been seen to protect the hearts of children receiving chemotherapy, reduces late anthracycline cardiotoxicity and whether it acts through a reduction in the frequency of mtDNA mutations. The Bankhead Coley Bridge Grant funding supports study activation as well as preliminary patient enrollment from the long-term survivor cohort of the Dana-Farber Cancer Institute Acute Lymphoblastic Leukemia Consortium (DFCI ALL Consortium) and analysis of the cardiac function and HFE and mtDNA mutation status of those individuals enrolled. We anticipate a first year enrollment of 40 long-term survivors of childhood ALL, all previously treated with anthracyclines and with approximately half having received dexrazoxane as a cardioprotective agent. We will measure heart status and function via the blood proteins proBrain Natriuretic Peptide (proBNP) and highly sensitive C-Reactive Protein (hsCRP), both of which are well validated indicators for subsequent cardiovascular disease, as well as echocardiographic studies, a diagnostic tool for assessing heart function. We will also perform assays for the type and frequency of mtDNA mutations and the presence of HFE mutations on patient blood samples. Cardiac and mutations data will be used to determine whether cardiovascular toxicity is related to the frequency of mtDNA mutations or to the presence of HFE mutations. We will determine if there is a reduction in late cardiovascular toxicity in response to an early free-radical scavenger treatment during anthracycline chemotherapy and whether this reduction is related to a reduced frequency of mtDNA mutations. Knowledge of mtDNA mutations and mutations of the hemochromatosis genes in long-term pediatric cancer survivors has the potential to identify patients who are at risk for developing clinically significant cardiovascular disease. Targeting such patients for clinical intervention will result in a decreased risk of developing late cardiovascular complications. Further, identifying patients at a lower risk for cardiovascular complication may permit increased doses in therapy, thereby increasing overall survivorship.