CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180166

Project Title:
Molecular mechanisms of anthracycline response in cardiomyocytes and link to genetic susceptibility to cardiotoxicity in long-term childhood cancer survivors

Award Mechanism:
Individual Investigator Research Awards for Cancer in Children and Adolescents

Principal Investigator:
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Entity:
The University of Texas M.D. Anderson Cancer Center

Lay Summary:

Anthracyclines are highly effective chemotherapeutic drugs that improve survival for many types of childhood cancers, but are known to cause irreversible and progressive cardiac damage that often manifests decades following treatment. These late cardiotoxic effects are a serious complication of cancer treatment and are the third most common cause of premature death in long-term survivors of childhood cancer. The underlying mechanisms for the development of late cardiotoxicity remain unclear due to lack of human model systems to explore the effect of anthracyclines on the cardiomyocyte. With the emergence of pluripotent stem cell (iPSC)-derived cardiomyocytes as a model system, this study was designed with the motivation to elucidate the molecular mechanisms underlying the development of anthracycline-dependent cardiotoxicity in the human cardiomyocyte and to then use this knowledge to identify genetic predictors of cardiotoxicity in long-term childhood cancer survivors. Our study leverages the patient populations of the two largest childhood cancer hospitals in Texas – MD Anderson Cancer Center and Texas Children's Hospital – to create a cohort of long-term survivors who were exposed to anthracyclines and followed-up to assess cardiac function. Targeted gene sequencing of the key biological mediators of anthracycline response will be performed in this population to identify cardiotoxicity susceptibility genes. The success of anthracyclines has created a large population of cancer survivors that have previously been exposed to these agents and limiting use of these successful agents in the treatment of childhood cancer is unlikely. Therefore, if genetic susceptibility to cardiotoxicity is known, this can inform how childhood cancer patients are treated in the future to reduce the long-term adverse effects of anthracyclines on their heart, as well as guide the design of risk stratified, cost-effective surveillance programs in survivors tailored to individual risk.