THE HARTWELL FOUNDATION

2024 Nominee Individual Biomedical Research Award

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Characterizing Autoantibodies Underlying the Late Effects of Cancer Treatment on the Heart

After decades of progress, treatments for certain childhood cancers can now achieve a remarkable 90% survival rate. Unfortunately, the same treatments that help these children beat their cancer can cause life-threatening toxicity. It has long been assumed that these side effects are similar regardless of age, but growing evidence shows that cancer treatments affect children differently from adults. Adults exhibit a high incidence of acute complications, whereas children often experience late effects from the same treatments. Among the most common and problematic late effects are those that impact the heart. Despite dose-sparing and diligent monitoring, cardiac late effects remain the leading cause of non-relapse mortality amongst survivors. As the field continues to improve the survival rates of children with cancer, there is a growing clinical need to prevent the late effects of curative cancer treatments on the heart. However, the molecular drivers of cardiac late effects are incompletely understood, and thus, remain untreated. Emerging research from my lab and others implicates antibodies. Antibodies are a component of the immune system that recognizes and eliminates foreign substances called antigens. Each person's antibody repertoire is comprised of 1013 unique sequences, of which only 0.022% are shared with others. With such a large and diverse repertoire of antibody sequences, a person can react, in their own unique way, to almost any antigen they may encounter in life. These antigens are typically derived from pathogens but can also come from one's own cells in settings of immense tissue destruction, such as during cancer treatment. While tolerance mechanisms prevent the body from producing self-reactive antibodies, or autoantibodies, these processes are imperfect and do arise. Depending on their antigen specificity, autoantibodies may stay dormant or become life-threatening years later. Unfortunately, the specificity of most autoantibodies remains a mystery because the necessary tools to reliably and comprehensively screen antigens do not exist. Leveraging recent technological advances, this proposal aims to develop a platform to identify autoantibodies generated in children after cancer treatment predictive of life-threatening complications in their adulthood. I hypothesize that there are meaningful differences in autoantibodies between those who do and do not develop late-effect cardiac toxicity but that these autoantibodies cannot be unbiasedly profiled due to the limitations of current techniques. The platform and findings generated by this proposal will inspire a distinct shift in current perspectives and open opportunities for better strategies to monitor, stratify, and treat pediatric patients. With this investigation, the goal of ensuring a healthy future for all survivors of childhood cancer will likely be one step closer.