THE HARTWELL FOUNDATION

2023 Nominee Individual Biomedical Research Award

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Targeting Bone Marrow Fibrosis in Cellular Immunotherapy for Acute Leukemia

B-cell acute lymphoblastic leukemia (B-ALL) is the most common diagnosis of blood cancer in U.S. children and adolescents, representing 20% of all cancers diagnosed in those less than 20 years of age. With more than 3000 new cases per year, B-ALL originates from abnormal growth and overproduction of immature white blood cells in bone marrow that spreads into blood. The usual treatment is chemotherapy but new cellular immunotherapies, like chimeric antigen receptor modified T cell therapy(CAR T cell therapy) are also being used to harness the power of patient immune cells to eliminate the cancer. The 5-year survival following such immunotherapy is near 90%, but 10-20% of B-ALL patients do not achieve a complete remission (absence of all detectable cancer) and may require additional treatments with significant risk of side effects, including death. Unfortunately, among those patients achieving complete remission, a third undergo relapse, creating an unmet need to overcome resistance or relapse following CAR T cell therapy. Based on my observations that bone marrow derived from primary biopsies of B-ALL had an increased stiffness and reduction in fluid-like properties compared to what normally is a soft, viscous tissue, I hypothesize that an immunosuppressive or inflammatory microenvironment in bone marrow may actively regulate the ability of T cells to mount an anti-leukemic response. In effect, physical changes in the bone marrow may be acting to suppress engineered immune cells in CAR T cell therapy. To investigate this phenomena, I propose in vitro experiments that will examine the impact of fibrosis on engineered immune cells using a hydrogel material that mimics the solid-like properties of fibrotic bone marrow and will enable independent examination of the impact of stiffness and viscoelasticity on the cells. To examine the effectiveness of CAR T cell therapy in the treatment of leukemia with human engineered immune cells, I will also analyze the impact of fibrosis in vivo by targeting mechanical regulation of bone marrow with an inhibitor of inflammation in a humanized mouse model. To modulate the bone marrow microenvironment in leukemia and improve responses to CAR T-cell therapy, I will target the bone marrow's environmental cues. If successful, the proposed research will lay the foundation for clinical translation to improve immune cell therapy and prolong the lives of children affected by recurrent or refractory leukemia.