THE HARTWELL FOUNDATION

2024 Nominee Individual Biomedical Research Award

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Optimizing the Cytokine Microenvironment for CAR T Cell Therapy in Acute Myeloid Leukemia

Over 80% of children with acute myeloid leukemia (AML) who receive the current standard of care have no detectable residual AML after initial therapy. However, for the 40-50% of patients with persistent AML or who later recur, the prognosis is dismal. While there is no consensus among experts on the best treatment for relapsed AML, it generally includes chemotherapy with toxic side effects. By contrast, children with B cell acute lymphoblastic leukemia (B-ALL), have benefitted greatly from the introduction of a therapy called chimeric antigen receptor (CAR) T cell therapy. Unfortunately, AML-specific CAR T cells have not worked well in early-phase clinical trials. CAR T cells harness the power of the immune system to kill cancer cells without harming healthy cells. They are modified T cells that express a synthetic receptor designed to bind to a target antigen on the surface of tumor cells, while propagating T cell signaling that culminates in cytotoxicity that kills the cancer cells. In this context, tumor cells and T cells secrete important cell signaling proteins in the surrounding microenvironment that enhance or inhibit CAR T cell function. The combination of pro- and anti-inflammatory cytokines, chemokines, and growth factors regulate CAR T cell expansion and related toxicities (e.g., cytokine release syndrome). My hypothesis is that the tumor-specific "signature" created by these signaling proteins will inform strategies to better target AML cells with CAR T cell therapy. I have already shown that interferon-gamma (IFNγ), one of the most important secreted proteins associated with CAR T cell activity, is necessary for optimal CAR T cell activity against AML but not against B-ALL. My lab has generated a model system in which AML and B-ALL can be targeted by the same CAR T cells, which will uniquely enable examination of IFNγ dependence while delineating its role in each tumor type. Next, I will modify CAR T cells to express a protein called interleukin 12 (IL-12) to increase local IFNγ production and boost CAR T cell activity against AML. This in turn should render AML cells more susceptible to CAR T cell recognition, especially when CAR T cells attack a specific protein called CD123, because its expression increases with IFNγ exposure. Finally, I will disrupt cell signaling that normally inhibits CAR T cell function with drugs to test whether such interventions enhance AML CAR T cell efficacy. If I am successful, these results will provide the foundation for early-phase clinical trials for implementation of AML CAR T-cell therapy. A positive outcome will dramatically transform the treatment of children affected with relapsed or refractory AML, which will greatly extend and improve their quality of life.