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Multi-Antigen Specific CAR T Cells as a Novel Therapy for Relapsed/Refractory Acute Myeloid Leukemia (AML)

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AML is a cancer of the blood and bone marrow. “Acute” denotes its rapid progression and “myeloid leukemia” refers to the white blood cells, called myeloid cells, that are affected by the disease. “Refractory” indicates the AML does not respond to treatment, and “relapsed” means that it returns after treatment and remission. Pediatric patients with relapsed/refractory AML often survive fewer than 6 months once the cancer returns. Devastatingly, for affected families, the average 5-year overall survival for these patients is only 13%.

AML occurs when myeloid cells that usually mature into red blood cells, white blood cells, and platelets are mutated so that they remain immature and non-functional then accumulate, replacing healthy blood cells. Improvements in the treatment of pediatric leukemia over the last several decades has greatly enhanced the survival of children with leukemia. However, new life-saving therapies are needed for the significant number of patients with relapsed/refractory AML who have poor outcomes with conventional therapies.

Dr. Kohler’s research seeks to advance new immunotherapy treatments for children with relapsed/refractory AML. If successful, Dr. Kohler also intends to expand the applicability of CAR T cells to other forms of childhood cancers with poor prognoses. Dr. Kohler hypothesizes that the development of CAR T cells for the treatment of AML must utilize multi-specific antigen targeting allowing the response to be broadened or narrowed based on the antigen(s) (malignant cell surface proteins) of interest. With multi-specific antigen targeting, CAR T cells either:

> (1) require the concurrent recognition of two different antigens at the same time for activation (AND-CAR), decreasing the potential for the CAR T cells to identify and destroy normal tissues that may express one of the antigens or
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> (2) can detect either one antigen or another, reducing the ability of tumor cells to escape the CAR T cell therapy by decreasing expression of one of the antigens on its surface.

The development of these technologies is essential to safely target AML cells in a way that minimizes relapses due to changes in antigen expression and reduces off-tumor toxicities.

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“CAR T-cells have revolutionized the treatment of pediatric patients with relapsed acute lymphocytic leukemia or ALL,” said Dr. Kohler. “Through this award from the SebastianStrong Foundation, we have the opportunity to reimagine CAR T-cell therapies to meet the needs of children and young adults with AML.”

The goal of the project is to adapt CAR T-cell therapy to the unique characteristics of AML through the simultaneous targeting of multiple antigens to prevent relapse. Success will be directly translatable to clinical trials for pediatric AML, as well as opening new opportunities for the development of CAR T-cell therapies against malignancies that are currently un-targetable through a single antigen, such as brain tumors and sarcomas.

“We are excited and proud to partner with Dr. Kohler. We’ve seen the results CAR-T cell approaches have had on ALL (Acute Lymphoblastic Leukemia) and are very excited about the potential of bringing similar successes to AML,” said Oscar Ortiz, Executive Director of SebastianStrong. “Our ultimate goal is to create more potential treatments for kids facing a cancer diagnosis. We want the research that we fund to provide hope so that parents don’t have to hear the devastating words that so many parents hear every day, “we’re out of options”.

The successful end-product of this work would be used as data for the FDA for a Phase I clinical trial to evaluate the safety of the CAR T cells at various doses. For families facing the grim outcomes of relapsed/refractory AML, this research seeks to improve long-term survival rates which currently remain low.