DKMS Stiftung Leben Spenden

Project Summary

John Hansen Research Grant 2026

Viral Mimicry–Induced Maladaptive Inflammation as a Targetable Driver of CAR T-Cell Resistance in Large B-cell Lymphoma

Sandeep Raj, MD

Memorial Sloan Kettering Cancer Center, New York, USA

Chimeric antigen receptor T-cell (CAR-T) therapy is a cancer treatment in which a patient's own immune cells are engineered to recognize and attack cancer. It has revolutionized the treatment of large B-cell lymphoma (LBCL), an aggressive blood cancer. However, over half of patients with LBCL treated with CAR-T experience disease progression with poor survival, underscoring the need to identify targetable pathways of treatment resistance. Recent discoveries have identified that certain types of inflammation in the tumor microenvironment (TME) and blood shape CAR-T resistance. Immune activation through tumor interferon (IFN) signaling may provide a link between molecular lesions in the tumor and adverse-risk inflammation. IFN signaling induces inflammation and anti-tumoral immunity. However, chronic IFN signaling and inflammation lead to autoregulation that dampens immune activation to prevent sustained tissue injury. Recent work showed that tumor cells exploit this susceptibility by co-opting repetitive non-coding DNA, such as LINE1 endogenous retroelements. Tumor cells activate LINE1, normally repressed by the gene TP53, to mimic chronic viral infection in the tumor while suppressing immunostimulatory effects. In this proposal, I hypothesize that this "maladaptive" inflammation in LBCL is driven by LINE1 activity and TP53 dysfunction and can be targeted to improve CAR-T cell function. In the first aim of my study, I will test this hypothesis using multi-omic profiling of pre-CAR-T tumor biopsies in patients with LBCL. Using causal inference methodology, I will study the effect of LINE1 on systemic inflammation and CAR-T treatment failure while accounting for confounding molecular interactions, with the goal of validating its use as a clinical biomarker. In the second aim of this proposal, I will measure the impact of systemic inflammation on CAR-T cell function with longitudinal immune profiling of patient biospecimens from observational studies of CAR-T cells infused into patients with or without systemic inflammation. I will also model the effect of systemic inflammation on CAR-T function in live, humanized mouse models of patient-derived LBCL tumors, and then study whether this inflammation can be pharmacologically targeted. This proposal will provide me with dual mentorship in computational and experimental research to promote my development into an independent investigator in translational and computational immunology.