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Research Description:

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Project title: A gene therapy strategy to enhance the persistence of antitumor efficacy of human chimeric antigen receptor (CAR)-modified NK cells for childhood cancer.

Although chemotherapy has greatly improved outcomes for children with cancer, its benefits are plateauing and new targeted therapies are needed. In 2017 the Federal Drug Administration (FDA) approved utilization of chimeric antigen receptor (CAR) T cells for childhood leukemias and lymphomas. This therapy involves harvesting patients' own immune cells (T-cells) and genetically modifying them to target specific proteins on tumor cells and destroy them. CAR-T cells are now being used to treat both hematologic and solid malignancies. In addition, other immune cells including natural killer (NK) cells are being modified with CARs to target specific cancers. Although CAR-T cells have significantly improved survival for pediatric patients with relapsed leukemias and lymphomas, still 60% of patients who receive CAR-T cells relapse for various reasons – some of which are related to poor persistence of the CAR-T cells in the patient.

The goal of my research project is to enhance the persistence and anti-tumor efficacy of CAR-T and NK cells by blocking a self-destruction pathway in these cells. Both T and NK cells express the FAS receptor, which triggers a cell death cascade called apoptosis in these cells upon exposure to FAS ligand. By genetically modifying the FAS receptor, we have successfully been able to block this self-suicide pathway in T and NK cells. We have demonstrated so far that by making the FAS receptor dysfunctional in CAR-T and NK cells we can successfully block apoptosis in these cells, which ultimately enhances their survival in test tubes (in vitro) and in mice (in vivo). We have found that not only do these FAS deficient CAR-T and NK cells live longer, they also have greater tumor killing capacity in vitro and in vivo against leukemia and lymphoma cells.

Given our promising results, moving forward, we also plan to apply our gene therapy strategy to enhance the persistence and anti-tumor efficacy of CAR-T and NK cells targeting solid tumors as well, where maintaining adequate persistence of CAR modified immune cells has been challenging.

We hope that our research will ultimately establish a novel, broadly applicable gene therapy strategy to enhance the persistence and antitumor efficacy of cellular immunotherapies for childhood cancers.