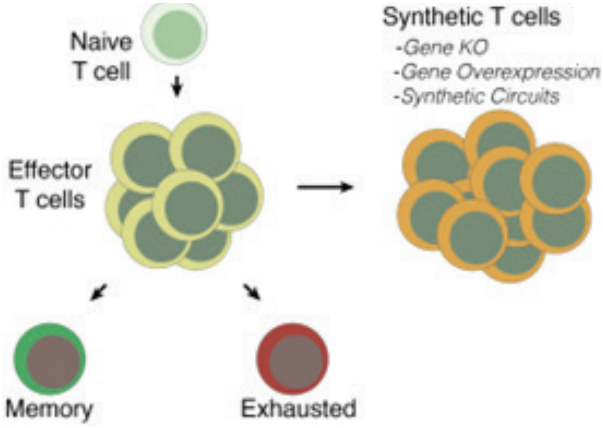

Figure 1: T cells naturally differentiate from naïve to effector T cells upon encountering cognate antigen and then form memory T cells when the antigen is eliminated. In chronic viral infections and tumors, T cells become exhausted due to chronic exposure to antigen and immunosuppression and do not form memory. Engineering strategies such as gene deletion, overexpression, or synthetic transcriptional response circuits can be used to engineer synthetic T cells that do not become exhausted.

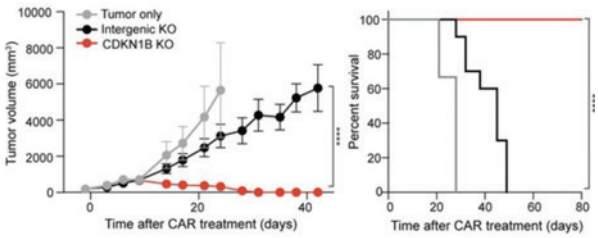

Figure 2: Tumor volume over time (left) and survival (right) for RPMI-8226 multiple myeloma tumors treated with intergenic control sgRNA CAR T cells (gray), CDKN1B KO CAR T cells (red), or no treatment (black). CDKN1B KO CAR T cells mediate complete control of tumor growth in 100% of mice.

Engineering Next Generation CAR T Cell Therapies for Solid Tumors

Robert Manguso, PhD
Associate Professor of Medicine, Mass General Cancer Center & Harvard Medical School; Co-Director Tumor Immunotherapy Discovery Engine, Broad Institute
rmanguso@mgh.harvard.edu

Cell-based immunotherapies have revolutionized the treatment of B cell and plasma cell-derived malignancies and are beginning to impact solid tumors, with TCR T cell therapy and TIL therapy recently approved in synovial sarcoma and melanoma. Despite this progress, the development of CAR T cell therapies for solid tumors has been slow and marked by several failed clinical trials for solid tumors such as pancreatic and ovarian cancer.

CAR T cell efficacy in solid tumors is limited by a process called T cells exhaustion, which is the progressive dysfunction of T cells in the harsh immunosuppressive tumor microenvironment. T cell exhaustion is an evolutionarily programmed state of dysfunction that exists to protect the host from T cell-mediated immunopathology during chronic infections. To maximize the therapeutic potential of CAR T cells, we must genetically engineer the T cells to prevent T cell exhaustion and dysfunction and create synthetic T cells that do not activate this maladaptive program (Fig 1).

We have built a high-throughput in vivo CRISPR screening platform to rapidly identify the modifications that most effectively enhance CAR T cell efficacy in tumors. Our in vivo screen in a BCMA+ model of multiple myeloma identified that deletion of the cell cycle checkpoint CDKN1B/p27 dramatically improves the persistence of CAR T cells in myeloma tumors and leads to durable control of multiple myeloma preclinical models (Fig 2). Thus, in vivo screens can be used to rapidly identify the most critical regulators of CAR T cell function in tumors and prioritize genetic modifications that should be tested in clinical trials.

We are extending the platform to solid tumor models, using gain-of-function approaches, and screening to identify tumor-intrinsic checkpoints that limit CAR T cell killing. Together these approaches will provide an unprecedented level of understanding of the complex molecular circuitry that governs T cell function in tumors and instructions for how to rewire it for therapeutic purposes.