Using the immune system as a cancer treatment has the potential to induce long-term, durable remissions, and perhaps even cures for some patients. The T cells of the immune system are able to specifically kill the target cells they recognize. T cells are also able to persist in the body for many years, and form immune ‘memory,’ which enables the possibility of long-term protection. The Maus laboratory is interested in using genetic engineering techniques to re-direct T cells to find and kill tumor cells, while sparing healthy tissues. We aim to develop new ways to design molecular receptors to target T cells to liquid and solid tumors; use T cells as delivery vehicles for other drugs, and use drugs to help T cells work against tumors; and understand how T cells can work as “living drugs” to treat patients with cancer.

1. Contain molecular improvements in receptor design to enhance specificity, potency, and safety.

Most chimeric antigen receptors used to re-direct T cells to a new target are based on enforcing expression of either murine single-chain antibody fragments, natural ligands, or natural T cell receptors. However, novel types of antigen receptors are in development and could be exploited to re-direct T cells such that they can distinguish between antigen expressed on the tumor and the same antigen expressed in healthy tissues. In liquid tumors, it will also be important to improve the safety of CAR T cells, while in solid tumors, the focus is on increasing their potency.

2. Are administered in combination with other drugs delivered either (a) systemically or (b) as payloads attached to T cells to sensitize tumors to T cell mediated killing and/or potentiate T cell function.

Some recently developed targeted therapies have effects on T cells or...
tumor cells that potentiates the tumor-killing effects. Alternatively, T cells can be chemically or genetically loaded with drugs to potentiate T cell function, such as cytokines or antibodies to checkpoint inhibitors. In this case, re-directed T cells could be used as a delivery mechanism to target an otherwise toxic drug specifically to the tumor.

3. Have additional modifications that make CAR T cells (a) resistant to inhibitory mechanisms, (b) imageable, or (c) more feasible to manufacture and administer.

Control of T cell function is a complex process orchestrated by a variety of molecules, some of which deliver inhibitory signals. Tumors often express ligands to inhibit T cell function. Using a single vector, genetically modified T cells can be re-directed not only to recognize a new antigen on tumor cells, but also to be resistant to the inhibitory tumor micro-environment.

4. We aim to understand the basic biology and mechanisms that drive engineered T cell function.

The MGH Cellular Immunotherapy Program directed by Dr. Maus aims to generate a pipeline of genetically engineered CAR T cells to use as “living drugs” in patients with cancer. The program is composed of a “research and discovery” arm, “a regulatory/translational” arm to be able to test genetically-modified T cells in human subjects, and a “clinical/correlative” sciences arm of immune profiling to examine the engraftment, persistence, and bioactivity of T cell products infused into patients. The Immune Monitoring Laboratory is directed by Dr. Kathleen Gallagher.