

# **DBMR Prize for Innovative Research Idea 2024**

## **CAR T cells secreting synthetic proteins engaging solid tumors**

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Chimeric antigen receptor (CAR) T cells have changed the treatment landscape of hematological malignancies. Still, antigen escape, reduced immune cell fitness, heterogeneous target antigen expression, and resistance through tumor and tumor microenvironment (TME) remain persistent barriers for CAR T cells in the quest against solid tumors. Recently, we generated a CAR T cell aiming at mesothelin able to secrete a T cell engaging molecule (TEAM) targeting not only pancreatic adenocarcinoma (PDAC) but also its TME. We could show the superiority of this CAR T cell construct in multiple ex-vivo and in-vivo model systems.

Considering the various modification options of such a CAR T cell construct, we will use synthetic single-domain proteins such as 'Designed Ankyrin Repeat Proteins' (DARPs) being integrated to be secreted by a CAR T cell. DARPs are not only small in size and stable, they have recently been approved for clinical use.

Taking advantage of the experience from earlier work in the lab of Dr. Maus (MGH, Harvard, MIT), I will generate CAR T cells targeting different types of solid tumors secreting synthetic proteins recruiting cells of the adaptive and innate immune system to increase the therapeutic use and efficacy of CAR T cells in solid tumors.