GUCY2C-DIRECTED CAR-T CELL THERAPY FOR UPPER GI CANCERS
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Background More than 70% of esophageal and gastric (‘upper GI’) cancer cases in the US are fatal, resulting in >26,000 deaths annually, highlighting a vital need to improve therapeutic options for these patients. One investigational approach is chimeric antigen receptor (CAR)-T cell therapy, which has been remarkably effective for some hematologic cancers. However, success for upper GI cancer patients is limited by the absence of established upper GI cancer-specific surface targets and the immunosuppressive tumor microenvironment (TME). Therefore, identifying candidate CAR-T cell products and TME mechanisms underlying therapeutic resistance in this disease is paramount. Guanylyl cyclase C (GUCY2C) is a transmembrane receptor primarily expressed in the normal intestinal epithelium and retained in colorectal cancer (CRC). Importantly, it is ectopically expressed by esophageal and gastric adenocarcinomas, despite its absence in normal upper GI tissue. Previous preclinical data has established GUCY2C-directed CAR-T cells as safe and effective therapy for CRC, clearing CRC metastases without damage to healthy tissues. Here, we hypothesize that GUCY2C-directed CAR-T cells are effective therapy for upper GI cancer, which may overcome immunosuppressive mechanisms within these tumors.

Methods To assess cell killing in vitro, mCherry-expressing ESO26 (esophageal) and GSU (gastric) cell lines were plated in 96-well plates and treated with GUCY2C-directed CAR-T cells. Images were taken over 72 hours and cell killing was quantified by loss of mCherry signal. To assess antitumor efficacy in vivo, luciferase-expressing ESO26 and GSU cell lines, and patient-derived xenografts (PDXs) were injected into MHC-I/II knockout (KO) NSG mice. Once tumors were established, GUCY2C-directed CAR-T cells were administered and tumor burden and survival were monitored. Finally, to assess CAR-T cell efficacy in an immunocompetent TME, ESO26 or GSU cells and human peripheral blood mononuclear cells (PBMCs) were injected into MHC-I/II KO NSG mice to develop upper GI TMEs that emulate tumors in patients.

Results GUCY2C-directed CAR-T cells elicit effector function to target and control upper GI tumors both in vitro and in vivo. Moreover, adoptively transferred PBMCs successfully engrafted systemically and trafficked into upper GI tumors in immunocompromised mice, partially mimicking patient tumors.

Conclusions Preclinical studies suggest that GUCY2C-directed CAR-T cell therapy controls upper GI tumor burden and improves survival. While this therapy is effective in this immunocompromised mouse model, ongoing and future studies will further define the TME milieu following PBMC engraftment and its impact on GUCY2C-directed CAR-T cell therapy for upper GI cancers.

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