Background Agonistic drugs can enhance the immune system’s ability to fight cancer by overcoming immune suppression. They target immune pathways, such as OX40, CD40, GITR, and 4-1BB, which are present on various immune cells. These targets can be effective against different types of cancer, as they rely on specific biomarkers or molecular signatures rather than specific tumor types. Agonistic drugs can have broad applications as monotherapies, in combination therapies and personalized therapies tailored to individual patients based on their unique tumor and immune profiles, increasing the chances of treatment success. At Oxford BioTherapeutics, using the proprietary OGAP database, novel agonist targets on tumor infiltrating lymphocytes (TILs) have been identified that can lead to as an effective treatment option for cancer patients.

Methods and Results From proteomic analysis, OBT698R was discovered as surface protein on T cells with a co-stimulatory function. OBT698 is expressed on lymphocytes, however, higher expression is observed in TILs and activated or exhausted T cells. OX003R expression is observed by immunohistochemistry in infiltrating lymphocytes in a variety of solid tumor types offering an alternative therapeutic option for patients who may not be suitable candidates for anti-PD1 therapy. A fully humanized mAb was developed and characterized for specific binding by FACS and Retrogenix assay. To validate the target for cancer therapy, the lead therapeutic antibody was tested for undesirable cytokine storm effect in PBMCs and did not induce the release of dangerous cytokines in this setting. The lead antibody is an IgG/kappa with LALA mutation in FC region, which reduces the Fc receptor binding as observed by Bicore assay. Importantly, it exhibited safety by not inducing antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) activity in tumor cells expressing the target. The lead antibody OBT698 antibody shows a strong agonistic effect in a dose-dependent manner on CD8+ T cells promoting proliferation measured by CFSE dye dilution, IFN? cytokine secretion, Granzyme B release and Perforin accumulation indicating a strong cytolytic ability. Ex vivo assays conducted with lead antibody with fresh tumor showed increased IFN? release and cytotoxicity measured in ex vivo assays in various solid tumors.

Conclusions In conclusion, OBT698R is a promising immuno-oncology target with CMC ready lead therapeutic antibody. In vitro and ex vivo studies demonstrate its effectiveness and safety, showcasing its potential as an effective treatment option for cancer patients in solid tumors.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1334