equally robust T cell proliferation in both the inguinal and mediastinal lymph nodes (LNs). However, RNA sequencing of adoptively transferred 2C T cells isolated 3-days after transfer from draining LNs identified that T cells activated in the mediastinal LN had reduced levels of IL-2 signaling and blunted effector functions early during priming. Flow cytometry confirmed that T cells primed in the mediastinal LNs did not express CD25, GZMB, or IFN-g, while T cells in inguinal LNs upregulated all three of these effector molecules. Delivery of IL-2 and IL-12 during priming was sufficient to restore effector molecule expression on 2C T cells in mediastinal LNs. Analysis of published patient data identified that a subset of lung cancer patients showed a sizable population of CD8+ TIL with low IL-2 signaling and low expression of effector molecules, including common targets of CBT.

Conclusions Immunotherapy resistance in T cell-inflamed tumors is due to defective CD8+ T cell effector differentiation. IL-2-based therapies could enhance differentiation of functional CD8+ effector T cells and could turn immunotherapy resistant tumors to immunotherapy sensitive tumors. This is the first mechanistic study providing evidence for a distinct type of T cell dysfunction resistant to current CBT.

Ethics Approval This study was approved by MIT's Committee on Animal Care, protocol number 0220-006-23.

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184 TWO TYPES OF ANTI-TIGIT ANTIBODIES WITH DISTINCT BINDING EPITOPE AND FUNCTIONAL ACTIVITIES

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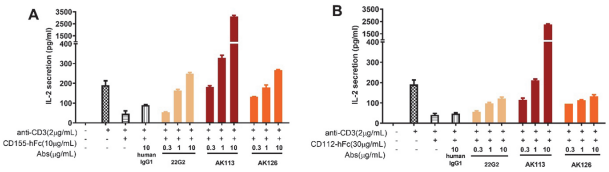
Background TIGIT is an inhibitory receptor mainly expressed on natural killer (NK) cells, CD8+ T cells, CD4+ T cells and Treg cells. TIGIT competes with CD226 for binding with CD155. In cancers, CD155 has been reported to up-regulate on tumor cells, and TIGIT was found to increase on TILs.[1] Activation of TIGIT/CD155 pathway would mediate immunosuppression in tumor; while blockade of TIGIT promotes antitumor immune response.

Methods AK126 and AK113 are two humanized anti-human TIGIT monoclonal antibodies developed by Akesobio. Binding activity of AK126 and AK113 to human TIGIT, and competitive binding activity with CD155 and CD112, were performed by using ELISA, Fortebio, and FACS assays. Cross-reactivity with cynomolgus monkey TIGIT and epitope binning were also tested by ELISA assay. In-vitro assay to investigate the activity to promote IL-2 secretion was performed in mixed-culture of Jurkat-TIGIT cells and THP-1 cells.

Results AK126 and AK113 could specifically bind to human TIGIT with comparative affinity and effectively blocked the binding of human CD155 and CD112 to human TIGIT. X-ray crystal structure of TIGIT and PVR revealed the C'-C'' loop and FG loop regions of TIGIT are the main PVR interaction regions.[2] The only amino acid residue differences in these regions between human and monkey TIGIT are 70C and 73D. AK126 binds to both human and monkey TIGIT, AK113 binds only to monkey TIGIT. This suggests that these residues are required for AK113 binding to human TIGIT, but not required for AK126. Interestingly, results from cell-based assays indicated that AK126 and AK113 showed significantly different activity to induce IL-2 secretion in mixed-culture of Jurkat-TIGIT cells and THP-1 cells (figure 1A and B), in which AK126 had a comparable capacity of activity to 22G2, a leading TIGIT mAb developed by another company, to induce IL-2 secretion, while, AK113 showed a significantly higher capacity than 22G2 and AK126.



Abstract 184 Figure 1
Anti-TIGIT Antibodies Rescues IL-2 Production in Vitro T-Cell Activity Assay in a dose dependent manner. Jurkat-TIGIT cells (Jurkat cells engineered to over-express human TIGIT) were co-cultured with THP-1 cells, and stimulated with plate-bound anti-CD3 mAb in the presence of TIGIT ligand CD155 (A) or CD112 (B) with anti-TIGIT antibodies. After incubated for 48h at 37° C and 5.0% CO2, IL-2 levels were assessed in culture supernatants by ELISA. Data shown as mean with SEM for n = 2.

Conclusions We discovered two distinct types of TIGIT antibodies with differences in both epitope binding and functional activity. The mechanism of action and clinical significance of these antibodies require further investigation.

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185 CAMRELIZUMAB MONOTHERAPY OR COMBINATION THERAPY IN PATIENTS WITH RECURRENT OR METASTATIC CERVICAL AND ENDOMETRIAL CARCINOMA:A RETROSPECTIVE STUDY

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Background Patients with recurrent or metastatic cervical and endometrial carcinoma have poor prognosis and few treatment options. Blocking the interaction between PD-1 and its ligands is a promising treatment strategy. Camrelizumab is a humanised anti-programmed death-1 (anti PD-1) antibody. This study aimed to assess the anti-tumour activity and safety of camrelizumab in patients with recurrent or metastatic cervical and endometrial carcinoma.

Methods We performed a retrospective analysis for recurrent or metastatic cervical and endometrial carcinoma patients. Eligible patients were aged 28–73 years with an Eastern Cooperative Oncology Group performance status of 0 or 2. Patients received camrelizumab alone(200 mg iv d1 q2w)or in combination with chemoradiotherapy/chemotherapy. The primary endpoint was objective response (ORR). The secondary endpoints included disease control rate (DCR), median progression-free survival (mPFS) and safety.

Results A total of 21 patients were enrolled between September 20, 2019, and July 8, 2020. 18 patients were evaluated for efficacy and 21 patients were available for safety analysis.