CCR8 has been identified as an important chemokine receptor expressed on intratumoral Treg cells and CCR8-expressing Treg (CCR8+Treg) has been demonstrated to be a major driver for immunosuppression in solid tumors. Clinical studies have shown that CCR8 is selectively up-regulated by tumor resident Tregs in several tumor types including clear cell renal carcinoma (ccRCC), breast2, and bladder cancers. In these tumor types, CCR8 exhibit strong expression on tumor resident Tregs while it is rarely observed on Tregs in peripheral blood mononuclear cells (PBMCs). High level of CCR8+ Tregs was associated with the immune tolerance and predicted poor survival in breast and bladder patients. These results suggest CCR8 as a promising therapeutic target; and anti-CCR8 mAbs could selectively inhibit a subpopulation of tumor resident Tregs in the tumor microenvironment (TME), to augment antitumor immunity.

Anti-CCR8 antibody HBM1022 specifically binds to cell lines that over-express human or cynomolgus CCR8, as well as TIL-Tregs in multiple cancer types with the high affinity. HBM1022 potently blocks signal transductions mediated by human CCL1-CCR8 and cynomolgus CCL1-CCR8. Furthermore, with enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) activity, HBM1022 exhibits potent in vitro killing activity on CCR8-expressing cells. HBM1022 shows tumor growth inhibition as monotherapy in preclinical syngeneic models. Moreover, HBM1022 shows enhanced antitumor activity with the combination of Keytruda® in preclinical xenograft model.

Our finding reveals HBM1022 as an innovative immunotherapy targeting intratumoral suppressive Treg cells to change suppressive tumor to hot tumor. HBM1022 presents its great potential as mono or combo anti-tumor therapies.

**Rationale and Immunization/Screening Strategy**

HBM1022 Recognizes N-terminal Domain of Human CCR8

HBM1022 Inhibits Tumor Growth as Monotherapy or Combotherapy

**Highlights**

- Harbour BioMed generated novel anti-CCR8 mAb (HBM1022):
  - Shows comparable cross-cyto activity
  - Depletes hCCR8+ intra-tumoral Treg cells potently
  - Blocks CCL1/CCR8 binding thereby inhibit CCL1-induced suppressive signaling pathway efficiently
  - Inhibits tumor growth robustly as monotherapy as well as combotherapy with Keytruda®

**With cross-cytonogolous Activity, HBM1022 Depletes CCR8+ Cells by ADCC and Inhibits CCL1/CCR8 Signaling Pathway**

- **Figure 3.** HBM1022 inhibits CCL1 induced calcium flux in CCR8+ cells
- **Figure 4.** HBM1022 specifically binds to overexpressed human and cynomolgus CCR8 as well as endogenous CCR8, inhibits potent Fc-mediated ADCC killing activity to CCR8+ cells and inhibits CCL1 induced calcium flux as well as cell migration. (A) HBM1022 binds to human CCR8 and cynomolgus CCR8 on CCR8 overexpressed CHO-K1 cells, (B) HBM1022 recognizes endogenous human CCR8 on ccRCC patient’s TIL-Tregs, (C) HBM1022 depletes CCR8 expressing cells in the in vitro Fc mediated ADCC killing assay. (D) HBM1022 inhibits intracellular calcium flux mediated by human CCL1/human CCR8 and cyno CCL1/human CCR8 in CCR8 overexpressed CHO-K1 cells. (E) HBM1022 blocks the migration of Bag7-CR8 cells induced by human CCL1.

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