Fully human anti-CAIX antibodies for RCC immunotherapy

Globally, there are roughly 270,000 new cases and 116,000 deaths attributed to kidney cancer occur each year. More than 90% of kidney neoplasms are classified as renal cell carcinoma (RCC), which accounts for 3% of all adult malignancies. RCC is resistant to both radiotherapy and chemotherapy, but could be treated by immunotherapy. Among the most promising immune therapy agents to treat cancer are human monoclonal antibody (mAb) drugs, which are becoming the standard of care in the treatment of a growing number of cancers. Tumor associated antigens are the focus of both diagnostic and therapeutic strategies against many forms of cancer, and in RCC carbonic anhydrase IX (CAIX) is the most well characterized. In this study, we examined the therapeutic effect of anti-CAIX mAbs and the possible mechanisms mediated by anti-CAIX mAbs in vitro and in vivo.

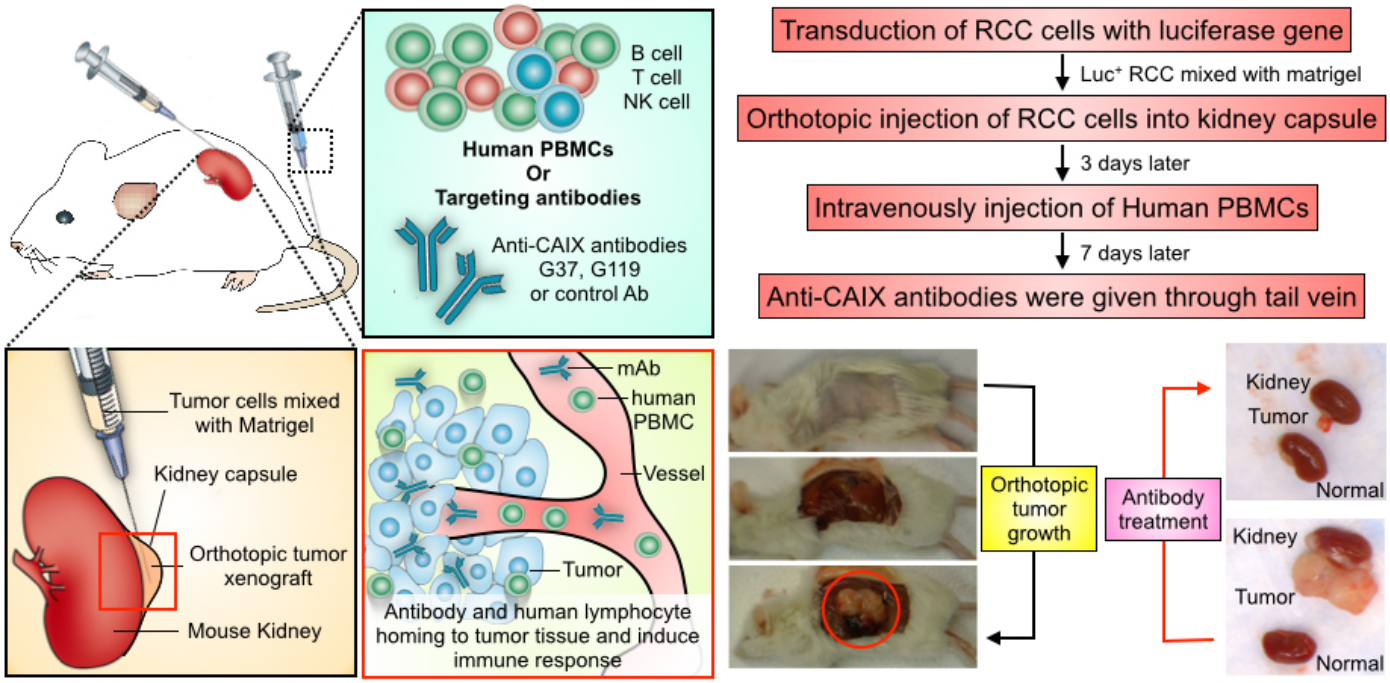

Fig.1. Design of the orthotopic RCC model and humanization with PBMC. Outline and diagram of establishment and treatment in the orthotopic model is shown. The orthotopic implantation and engraftment of a human RCC line is transduced with luciferase and transplanted into the subrenal capsule of mouse kidney. Subsequent to tumor engraftment, human blood cells and then anti-CAIX or control mAb treatment is administered to mice intravenously, with repeated dosing of treatment and measurement of tumor growth by BLI every 3-4 days.

In our study, we have identified several fully human anti-CAIX mAbs and demonstrated the capacity of anti-CAIX mAbs that inhibit CA enzymatic activity. These anti-CAIX mAbs have been

further tested in vitro and resulted in immune-mediated killing of RCC, including nature killer (NK) cell-mediated antibody-dependent cellular cytotoxicity, complement dependent cytotoxicity, and macrophage-mediated cellular phagocytosis. However, characterization of the anti-tumor properties of human anti-CAIX mAbs in current in vivo mouse models has significant limitations since the role of human effector cells in tumor cell killing in vivo is not directly evaluated. To understand the potential of our anti-CAIX mAbs in clinic, we established an organ-orientated tumor transplanted animal model and developed human immune system reconstituted mice for preclinical efficacy/safety testing (Figure 1). This animal model can mimic clinically relevant tumor growth and could be used to test the potent therapeutic effect of anti-cancer drugs. Utilizing this animal model, the anti-CAIX mAbs were found to beneficially inhibit tumor growth. To further understand the mechanism triggered by anti-CAIX mAbs, we investigated the tumor killing activity of human lymphocytes. Natural killer cells were found in the tumor tissues in the anti-CAIX mAbs-treated mice in the early treatment. During the treatment, human T cells were increased and activated in the tumor tissues in the anti-CAIX mAbs-treated mice. The treated mouse blood showed anti-tumor activity in the presence of anti-CAIX mAbs.

Recent clinical trials highlight the pressing need for the development of novel therapeutics targeting CAIX on RCC and other cancers. Our findings demonstrate that several of our high affinity, fully human anti-CAIX mAbs mediate potent anti-tumor activities and have therapeutic potential in the unmet medical need of targeted killing of CAIX positive RCC. Our development of the orthotopic tumor xenografted humanized mouse provides an improved model to confirm the capacity of these mAbs to mediate tumor growth inhibition in vivo. This study supports further clinical development of these anti-CAIX mAbs as CAIX-targeting therapeutics in RCC. In addition, the recently defined role of CAIX in the incidence and progression of breast cancer offers another potential means by which the dual-targeting capacity of these anti-CAIX mAbs may be leveraged.

Publication

Human anti-CAIX antibodies mediate immune cell inhibition of renal cell carcinoma in vitro and in a humanized mouse model in vivo.
Chang DK, Moniz RJ,4, Xu Z, Sun J, Signoretti S, Zhu Q, Marasco WA.
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