516 CD47 X B7-H3 BISPECIFIC ANTIBODY OFFERS A NEW STRATEGY FOR TREATING B7-H3$^+$/CD47$^+$ TUMORS

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Background B7-H3, also known as CD276, is a member of the B7 family and highly expressed in multiple types of human cancers. B7-H3 overexpression has been frequently associated with poor prognosis. In addition, B7-H3 plays an immunoregulatory role in the T cell and NK activation, and thus has been highlighted as an attractive target for cancer therapy. CD47/SIRPa axis is an important checkpoint of innate immune system, CD47 interacts with its ligand signal regulatory protein-alpha (SIRPa) on myeloid cells, conveys a 'don't eat me' signal and blocks macrophage mediated phagocytosis.[1] Tumor cells, which express high level of CD47, exploit this mechanism to evade from immune surveillance. CD47 is considered a prominent target for cancer treatment. However, the wide expression of CD47 on normal cells could cause safety issues, such as anemia and thrombocytopenia. To address these challenges, we developed a novel CD47xB7-H3 bispecific antibody, which selectively targets tumors expressing both CD47 and B7-H3.[2]

Methods Anti-B7-H3 antibodies were generated from mouse hybridoma and rabbit B cell cloning. A panel of bispecific CD47xB7-H3 antibodies were generated and characterized by a series of in vitro assays including FACS binding, SIRPa blocking, antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cellular cytotoxicity (ADCC), red blood cells (RBC) binding and hemagglutination. In vivo efficacy of CD47xB7-H3 bispecific antibody was evaluated in xenograft tumor models that co-express B7-H3 and CD47.

Results Novel anti-B7-H3 antibodies were characterized for their binding affinity and epitope specificity. Anti-B7-H3 antibodies were paired with our proprietary anti-CD47 antibody to generate CD47xB7-H3 bispecific antibodies. VBI-009, the lead CD47xB7-H3 bispecific antibody, was identified by its best overall activities across various in vitro and in vivo functional assays. It exhibits potent SIRPa blocking, ADCP and ADCC activities on CD47$^+$/B7-H3$^+$ tumor cells. However, it has little or no activity on cells that do not express B7-H3. VBI-009 has no significant binding to red blood cells and doesn't cause hemagglutination. In vivo studies have shown that VBI-009 is effective against lung cancer models with complete tumor growth inhibition.

Conclusions Our findings suggest that the novel CD47xB7-H3 bispecific antibody selectively binds to CD47$^+$/B7-H3$^+$ tumor cells and has minimum RBC binding compared to the bivalent CD47 monoclonal antibodies. The bispecific antibody shows potent CD47/SIRPa blocking activity on B7-H3 overexpressing tumor cells. It also demonstrates strong functional activities in vitro and efficacy in vivo on B7-H3 and CD47 positive tumor cells. CD47xB7-H3 bispecific antibody offers a novel approach for treating CD47$^+$/B7-H3$^+$ tumors.

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