CD47 x EPCAM BISPECIFIC ANTIBODY REPRESENTS A NOVEL APPROACH FOR TREATING EPCAM OVEREXPRESSING SOLID TUMORS

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Background CD47 conveys a "don’t eat me" signal through the interaction with its ligand signal regulatory protein-alpha (SIRPα) on myeloid cells and blocks macrophage mediated phagocytosis. Tumor cells, which express high level of CD47, exploit this mechanism to evade from immune surveillance. CD47/SIRPα axis is an important checkpoint of innate immune system and CD47 is considered a prominent target for cancer treatment. However, the wide expression of CD47 on normal cells could cause antigen sink and lead to safety issues, such as anemia and thrombocytopenia. EpCAM is highly expressed in many epithelial cancers, particularly in colorectal, gastric, endometrial and lung cancers. Here we describe a novel CD47 x EpCAM bispecific antibody, which specifically targets CD47+/EpCAM+ tumors in preclinical studies.

Methods The CD47 x EpCAM bispecific antibody was generated using novel anti-CD47 antibody and anti-EpCAM antibody. A series of in vitro assays including FACS binding, FACS-based SIRPα blocking, ADCP, RBC binding and hemagglutination were performed to characterize the CD47 x EpCAM bispecific antibody. In vivo efficacies of this bispecific antibody were evaluated in xenograft tumor models with high EpCAM and CD47 expression.

Results Compared to monoclonal CD47 antibody, the CD47 x EpCAM bispecific antibody selectively binds to tumor cells overexpressing EpCAM. The bispecific antibody exhibited potent SIRPα blocking and antibody-dependent cellular phagocytosis (ADCP) activity on CD47+/EpCAM+ tumor cells, but not on cells lacking EpCAM expression. Compared to its parental CD47 monoclonal antibody, the EC50 of SIRPα blocking activity were improved 30–80 folds with the treatment of the CD47 x EpCAM bispecific antibody in tumor cell lines with high EpCAM expression. No significant RBC binding and RBC phagocytosis were observed upon treatment with the CD47 x EpCAM bispecific antibody. The bispecific antibody did not cause any appreciable hemagglutination with up to 1μM antibody treatment. Most importantly, the bispecific antibody demonstrated potent anti-tumor activities in in vivo solid tumor cell line-derived xenograft (CDX) models that overexpress both CD47 and EpCAM.

Conclusions Our findings suggest that the novel CD47 x EpCAM bispecific antibody selectively binds to CD47 and blocks CD47/SIRPα binding on EpCAM overexpressing tumor cells. The bispecific antibody has minimum RBC binding compared to the bivalent CD47 monoclonal antibodies. The bispecific antibody shows potent in vivo efficacy and specificity toward EpCAM positive tumor cells and represents a novel approach for treating EpCAM+ tumors.

REFERENCES

Ethics Approval The protocol and any amendment(s) or procedures involving the care and use of animals in these animal studies were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of WuXi AppTec prior to conduct. During the studies, the care and use of animals were conducted in accordance with the regulations of the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC)