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**YH38560, A NOVEL BISPECIFIC FUSION PROTEIN TARGETING 5T4 AND CD47 IN A TUMOR-SELECTIVE MANNER FOR THE TREATMENT OF SOLID CANCERS**

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**Background** 5T4 (also known as trophoblast glycoprotein; TPBG) is highly expressed across a wide range of solid cancer indications, including NSCLC (non-small cell lung cancer), head and neck, colorectal, gastric, renal, pancreatic, bladder, breast, ovarian and cervical cancers, with limited expression in normal tissues, making it an attractive target as a tumor-specific antigen. CD47 (Cluster of Differentiation 47), a ubiquitously expressed innate immune checkpoint receptor, is also overexpressed in most solid and hematological cancers. CD47 interacts with signal-regulatory protein alpha (SIRP $\alpha$ ) on myeloid cells, and this leads to the inhibition of tumor cell phagocytosis and anti-tumor immune responses. However, the development of novel treatment agents targeting CD47 is hampered by its ubiquitous expression, which often leads to rapid drug elimination and hemotoxicity including anemia or thrombocytopenia. Herein, YH38560 is a bispecific fusion protein targeting 5T4 and CD47 designed to overcome the on-target hematological toxicities and limited efficacies of monospecific CD47 blockers.

**Methods** *In vitro* binding potencies of YH3860 to human cancer cell lines and RBC (red blood cells) were analyzed by flow cytometry. The tumor selectivity of YH38560 was determined in co-culture system with human cancer cells and RBC *in vitro*. The Fc $\gamma$ R-mediated activities of YH38560 were quantified with ADCC (antibody-dependent cellular cytotoxicity) and ADCP (antibody-dependent cellular phagocytosis) reporter bioassays. The tumor cell killing activities of YH38560 were measured in the co-culture system with NK (natural killer) cells or macrophages. *In vivo* anti-tumor effects of YH38560 were evaluated in human 5T4/CD47 expressing MC38 tumor model using hSIRP $\alpha$  knock-in (KI) mice as monotherapy and in combination with anti-PD-1 or PD-L1 antibody (Ab).

**Results** YH38560 exhibited stronger binding potency to human cancer cells than RBC and this is consistent with the preferential binding of YH38560 to cancer cells when co-cultured with RBC. YH38560 facilitated potent phagocytosis against tumor cells via CD47/SIRP $\alpha$  blockade and Fc $\gamma$ RIIa-dependent ADCP. YH38560 demonstrated superior NK-mediated cytotoxicity to tumor cells through Fc $\gamma$ RIIIa-dependent ADCC. Correspondingly, YH38560 alone showed significant tumor growth inhibition superior to monospecific CD47 blockers and it exerted synergistic and durable anti-tumor effects when combined with either anti-PD-1 or PD-L1 Ab in MC38 syngeneic mouse model.

**Conclusions** These findings suggest that YH38560 holds promising potential to improve patient outcomes over CD47-targeted therapies currently under development.

<http://dx.doi.org/10.1136/jitc-2022-SITC2022.0467>