

ENHANCED ANTI-TUMOR ACTIVITY OF HBSAG SPECIFIC TCR-T (SCG101) IN HEPATITIS B VIRUS (HBV) RELATED HEPATOCELLULAR CARCINOMA (HCC) BY PREVENTING T CELL EXHAUSTION THROUGH PD-1/PD-L1 AXIS BLOCKADE

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Background Checkpoint inhibitors as standard of care for hepatocellular carcinoma have limited tumor response, highlighting the importance of the tumor-reactive T cell abundance for effective treatment and the potential synergy with adoptive T cell therapy. SCG101 is a first-in-class, autologous TCR-T encoding a high-avidity TCR directed towards HLA-A*02-restricted HBsAg, with preliminary clinical benefits demonstrated in HBV related HCC patients. Given the profound immune-suppressive microenvironment of HCC, combining TCR-T cell therapy with PD-1/PD-L1 inhibition may have a synergistic effect by TCR-T cells potentially infiltrating immunogenically cold tumors, and checkpoint inhibitors reversing TCR-T cell exhaustion. Herein, we report results from preclinical combination therapy of SCG101 and checkpoint inhibition.

Methods SCG101 CD4⁺/CD8⁺ T cells were isolated via magnetic bead enrichment. T cell functionality was performed using Real Time Cellular Analysis (RTCA) and Cytometric Bead Array (CBA). Expression of PD-1 was analyzed on SCG101 cells after co-culturing with HBsAg⁺ HepG2 cells. For in vitro tumor rechallenge assay, the cytokine secretion and target cell lysis were performed to evaluate the functional impact of combining SCG101 cells and PD-1/PD-L1 inhibitors. In vivo, anti-tumor activities were evaluated in HBsAg⁺ PD-L1⁺ HepG2 cell xenograft mice by i.v. infusing pre-exhausted PD-1⁺ SCG101 with and without PD-1 (Pembrolizumab) or PD-L1 (Atezolizumab) inhibitors.

Results Both CD8⁺ and CD4⁺ SCG101 T cells exert profound anti-tumor activities via target cell lysis and cytokine secretion, while CD8⁺ SCG101 T cells confer stronger effects. The expression level of PD-1 was significantly and specifically elevated in TCR transduced SCG101 cells co-cultured with either HBsAg⁺ HepG2 cells or HBsAg⁺ PDL1⁺ HepG2 cells, comparing to the HepG2 cell control. The elevation was observed preferably in SCG101 CD8⁺ T cells. In tumor rechallenge assay, serial antigen stimulation led to dramatic decrease of the cytokine secretion and cytotoxic activity due to PD-1 induced T cell exhaustion, which could be restored by Pembrolizumab (anti-PD-1) or Atezolizumab (anti-PD-L1). This finding was confirmed in HBsAg⁺ PD-L1⁺ HepG2 CDX model, where a more prolonged antitumor effect was achieved when pre-exhausted SCG101 were co-administered with anti-PD1 or anti-PD-L1 inhibitors.

Conclusions Continuous antigen exposure under tumor microenvironment results in activation-induced cell death of T cells with hallmark features of exhaustion including reduced proliferation capacity and cytotoxicity, and severe defects in cytokine production. The benefit of PD-1/PD-L1 axis blockade on adoptively transferred T cells was demonstrated in vitro and in vivo xenograft models. Combination studies with PD-1/PD-L1 inhibitors is planned to augment SCG101 functionality and persistence in HBV related HCC patients.

Ethics Approval Here to clarify that the animal study is outsourced to WuXi AppTec (Nantong) Co., Ltd., which was

fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC). Procedures used in this study were approved by the Institutional Animal Care and Use Committee (IACUC) at WuXi AppTec (Nantong) Co., Ltd. IACUC serial number: ON01-QD009-2020.

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