ANTI-CANCER ACTIVITIES OF EU103 IN A PRECLINICAL MODEL OF OVARIAN CANCER

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Background V-set and immunoglobulin domain-containing 4 (VSIG4) is one of the B7 family-related proteins that includes PD-L1, VISTA, and CTLA4 ligand. VSIG4 overexpression is correlated with poor prognosis in patients with ovarian cancer, lung cancer, gastric cancer, high-grade glioma, and multiple myeloma. VSIG4 is also known to function as a receptor for complements and the negative regulation of T cell proliferation. Although VSIG4 is highly expressed in tissue-resident macrophages and tumor-associated macrophages (TAM), its role in the tumor microenvironment (TME) is not fully elucidated.

Methods In vivo model Generation
PBMC-humanized mouse model shows a relative enrichment of human T cells but generally not enough numbers of human monocyte/macrophage. Therefore, a strategy of adding M2 macrophages was used in the tumor site. Human PBMC were injected i.v. into the NSG mice to humanize.

Results We previously developed a therapeutic antibody, EU103, in a humanized form of a VSIG4-specific antibody. Most importantly, we demonstrated that EU103 directly acts on the tumor-associated macrophages (TAM) and mechanismically induces repolarization of TAM to tumor killing M1 macrophages and blocking VSIG4-mediated T cell suppression, eventually leading to CD8+ T cell proliferation and tumor suppression in a PBMC-humanized human lung cancer mouse model. Expanding our previous findings with the therapeutic potential of EU103 in a non-small cell lung carcinoma (NSCLC), here, we also proved its therapeutic effect in human ovarian cancer. Firstly, TAMs isolated from ovarian cancer patients express high levels of VSIG4 with immunosuppressive M2 macrophage phenotype. Secondly, EU103 treatment of the TAMs in in vitro studies induces M2-to-M1 conversion and activation of T cells in the ascites leading to ovarian tumor cell killing in a dose-dependent manner. Thirdly, in vivo therapeutic efficacy of EU103 in ovarian cancer, especially through M2-to-M1 conversion, is also verified in both CD34+ cell and peripheral blood mononuclear cell (PBMC) humanized mouse models. Finally, we validate the results above by treating ovarian cancer patient-driven ascites with EU103.

Conclusions Almost 300,000 women are diagnosed with ovarian cancer worldwide each year, and ovarian cancer ranks fifth in cancer deaths among women. In the United States alone, we expect approximately 20,000 new diagnoses and more than 12,000 deaths for this year. Given our findings in this study and clinical significance, we propose here the therapeutic potential of EU103, previously developed by our proprietary antibody discovery and engineering technology, in ovarian cancer.

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