COMBINATION THERAPY WITH ANTI-VSIG4 AND ANTI-PD-L1 SUPPRESS GROWTH OF TUMOR VIA CONDITIONING OF TUMOR MICROENVIRONMENT

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Background V-set and immunoglobulin domain-containing 4 (VSIG4) is a B7 family-related protein which includes PDL1, VISTA and CTLA4 ligand. The known functions of VSIG4 are a receptor for complement to inhibit complement activity and negative regulation of proliferating T cell. Although VSIG4 is highly expressed in tissue-resident macrophage and tumor-associated macrophage (TAM), the mechanism of the signal transduction in tumor microenvironment (TME) is not fully elucidated.

Methods
Conversion assay CD14+ monocytes from PBMC were differentiated to M0 macrophages by rhM-CSF, and subsequently to M2 macrophages with rhIL-4/rhIL-13. The conversion of M2 macrophages to M1 was carried out by incubating the macrophages with LPS/rhIFN-gamma or EU103.

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. To establish a lung cancer orthotopic model, A549-luci lung cancer cells were injected i.v. with differentiated M2 macrophages into the naïve NSG mice, followed by PBMC infusion. The degree of humanization was determined by measuring the ratio of human CD45+ cells in the mouse PBMC. Tumor size was measured using IVIS twice a week.

Results Here we investigate the pivotal roles of anti-VSIG4 therapeutic antibody, EU103 in TAM. EU103 engagement altered a broad range of type II macrophage (M2) transcriptome which was related to immune-tolerance and increased the proliferation of cytotoxic CD8+ T cells. EU103 induced phosphorylation of JNK and p38MAPK and in consequence, decreased the expression of M2 marker CD14, CSF-1R and CD163 while type I macrophage (M1) marker CD86 and CD40 were increased. In the PBMC-based humanized mouse, human orthotopic lung cancer model, stimulation of VSIG4 suppressed tumor growth and promoted infiltration of IFN-gamma-producing CD8+ T cells into tumor tissue. Furthermore, treatment of EU103 showed synergistic anti-cancer activity with an anti-PD-L1 therapy.

Conclusions Our finding suggests that EU103 directly act on TAM and induce repolarization of TAM to tumor suppressive M1 macrophages, leading to a CD8+ T cell proliferation and tumor suppression. Since the main cause of Immune Checkpoint Inhibitor (ICI) resistance is an immune-suppressive TME, EU103 could be an option for ICI-resistant patients, and synergistic anti-tumor effect could be expected with a combination with ICIs. Overall, targeting the VSIG4 would be an advantageous approach in cancer therapeutics.