Analysis of the TIGIT/PVRIG Axis In Human Cancers To Support Indication Selection And Biomarkers For COM701 And COM902

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**Abstract**

**Background:** PVRIG and TIGIT were identified by Compugen’s Predictive Discovery Platform as immune inhibitory receptors and have been reported to inhibit anti-tumor activity. We are pursuing clinical development of antagonistic antibodies to PVRIG (COM701) and to TIGIT (COM902). Here, we analyzed primary human cancer tissues and immune cells to characterize expression in the TIGIT/PVRIG axis to support indication selection and combination strategies for COM701 and COM902.

**Methods:** COM701 and COM902 were identified based on the ability to block the interaction of PVRIG or TIGIT with their cognate ligands (PVRL2 or PVR respectively) and for the ability to enhance primary, freshly isolated CD3+ tumor infiltrating lymphocytes (TILs) and antigen-specific CD8+ T cell activation in a co-culture with tumor cell lines.

**Results:** PVRIG/PVRL2 and TIGIT/PVRIG expression were highest in endometrial, lung, kidney, ovarian, and head and neck cancers compared to normal adjacent tissue. On dissociated human tumors, PVRIG expression was detected on T and NK TILs whereas PVRL2 expression was detected on CD45+ cells and myeloid cells. A co-expression analysis of PVRIG, TIGIT, and PD1 demonstrated that PVRIG was co-expressed with both TIGIT and PD1 and that PVRIG/TIGIT/PD1+ cells comprised a major proportion of exhausted Eomes+T-bet CD8+ TILs. In comparison to PD-L1, PVRL2 expression was more prevalent across several cancer types and expression of PVRL2 was detected in PD-L1 negative samples. Combination of COM701 with COM902 enhanced viral and tumor specific T cell function in vitro. Several immune receptors were induced in response of PVRIG blockade by COM701 on CD8+ T cells.

**COM902 & COM701 Target Two Different Co-inhibitory Receptors In The Nectin & Nectin-Like Family**

**PVRL2 Expression Is Induced In Cancer**

**Expression Profiling of PVRIG/TIGIT Axis In Tumors**

**PVRL2 Expression Is Induced In Cancer**

**Figure 1.** PVRL2 expression is induced in cancer. A) PVRL2 expression is induced in PD-L1+ tumors. B) Similar PVRL2 expression in PD-L1 and PD-L2 tumors. C) Endometrial Cancer.

**Figure 3.** PVRL2 is induced in cancer & expressed in PD-L1+ tumors. A) PVRL2 expression was assessed by IHC on lung, ovarian/endometrial, breast, colon, kidney, and skin tumors. Bars depict mean ± SEM. B) Expression of PD-L1 & PVRL2 was assessed by IHC on serial sections. Tumors were grouped based on tissue type & expression of PVRL2 on PD-L1+/- is shown. PD-L1+ staining was defined as membranous staining on at least 1 area of a tumor. Bars depict mean ± SEM for each group. C) Representative expression of a PVRL2/PVRL1 endometrial carcinoma tumor and a PVRL2/PD-L1 lung cancer.

**Figure 2.** PVRL/TIGIT/PD1+ CD8 TILs are highly prevalent and have an exhausted profile. A) CD8+ TILs from human tumors were stained for PD-L1, PVRIG, and TIGIT. The percentage of CD8+ TILs that express combinations of PD-L1, PVRIG, or TIGIT on CD8+ TILs was determined by Boolean gating. B) Representative PD-L1, PVRIG, and TIGIT expression on CD45+ and CD8+ TILs from a lung tumor are shown. C) TILs from human cancers were stained for cell surface PD-L1, PVRIG, and TIGIT on CD8+ TILs, permeabilized, and stained for Eomes and T-bet. The percentage of Eomes+/T-bet+ CD8+ TILs were shown. A paired Student’s t-test was performed and a p-value shown. D) Representative TIL FACs plots showing Eomes and T-bet expression on PD-L1, PVRIG, or TIGIT positive/negative expressing CD8+ TILs from an ovarian and bladder tumor are shown. E) The percentage of Eomes+/T-bet+ CD8+ TILs expressing PD-L1, PVRIG, and TIGIT expression was determined from human cancers.

**Blockade of PVRIG/PVRL2 Induces PD-1 and TIGIT Expression**

**Figure 6.** Blockade of PVRL2/PVRL2 induces PD-1 & TIGIT expression. COM905-specific CD8+ T cells from 2 donors were co-cultured with Panc05.04, COM905, and the indicated antibodies at 10 μg/ml for 18 hrs. Cells were stained and the percentage of PD-L1+, PD-1+, and LAG3+ CD8+ T cells following each treatment is shown.

**Conclusions**

- Immunohistochemistry and flow cytometry were performed to assess PVRIG/PVRL2 and TIGIT/PVRIG expression in multiple tumor types. High expression of these pathways were detected in lung, endometrial, head and neck, ovarian, and kidney cancers.
- Co-expression analysis of PVRIG, TIGIT, and PD1 demonstrated that PVRIG was co-expressed with both TIGIT and PD1- and that PD1/PVRIG/TIGIT+ cells were highly prevalent in tumors.
- PVRIG expression correlated with Eomes+T-bet transcription factor expression, a phenotype known to be associated with T cell exhaustion. Triple positive PVRIG/TIGIT/PD1+ cells were also high in percentage of Eomes+T-bet T cells.
- Combination of COM701 with anti-PD1 antibody or COM902 enhanced CD8+ T cell cytokine production, with the triple combination of COM701, COM902, and anti-PD1 antibody yielding the greatest increase in functional activity.
- PD-1 and TIGIT expression were induced in response to PVRIG blockade by COM701 on CD8+ T cells, suggesting potential biomarkers of response for COM701.
- COM701 and COM902 enhanced the activation of freshly purified human CD3+ tumor infiltrating lymphocytes with similar or greater potency than Pembrolizumab.
- An IND for COM701 is planned for 2018.