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

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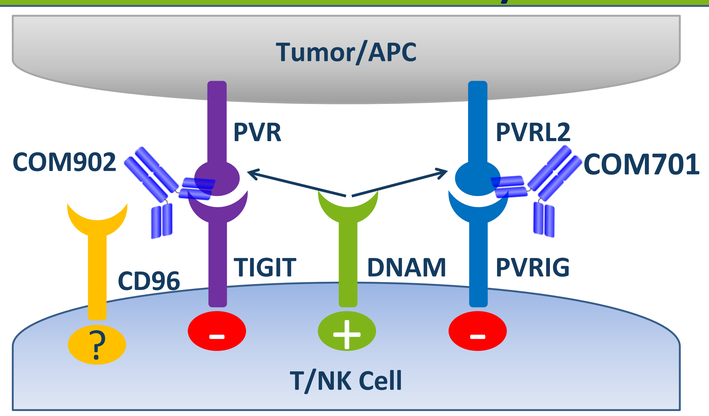
Abstract

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/PVR 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



Expression Profiling of PVRIG/TIGIT Axis In Tumors

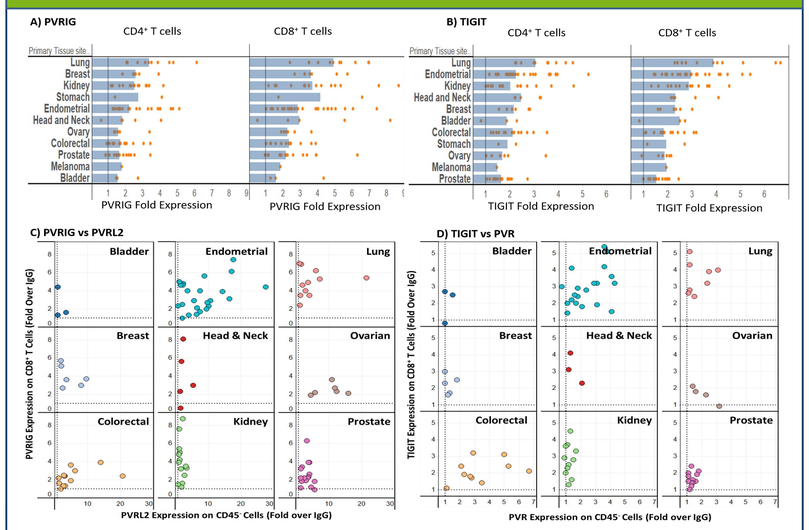


Figure 1. Lung and endometrial cancers are high for both PVRIG-PVRL2 and TIGIT-PVR pathway. (A, B) PVRIG and TIGIT expression were analyzed on CD4$^+$ and CD8$^+$ T cells from dissociated human tumors by FACS. Fold expression was calculated by dividing the MFI of PVRIG or TIGIT by the MFI of the IgG control. Grey line = No expression detected. Each orange dot is a distinct tumor sample and median of samples shown by the blue bar. C, D) Expression of PVRIG on CD8$^+$ T cells vs PVRL2 on CD45$^-$ cells or TIGIT on CD8$^+$ T cells vs PVR on CD45$^-$ cells is plotted from dissociated human tumors. Each dot represents an individual tumor sample.

PVRIG$^+$TIGIT$^+$PD1$^+$ cells Are The Highest % And Most Exhausted Of CD8$^+$ TILs

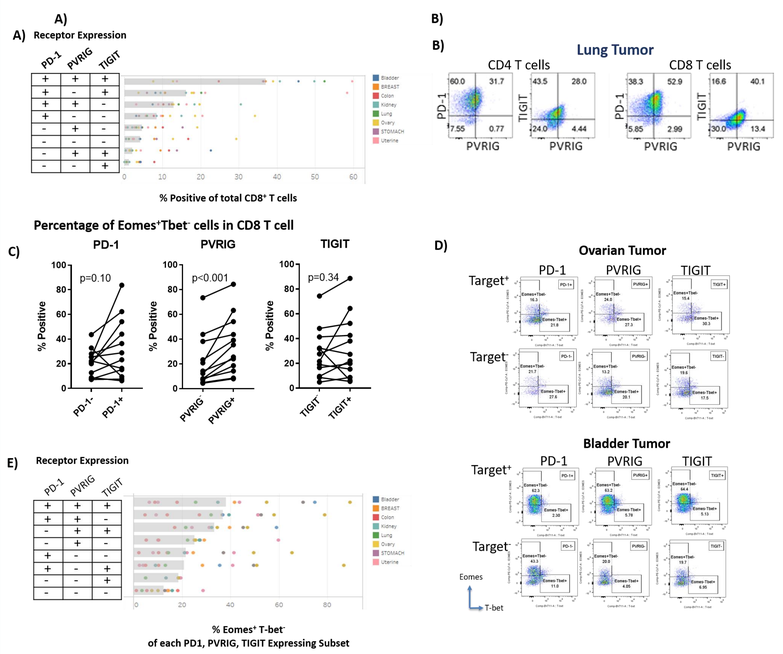


Figure 2. PVRIG$^+$TIGIT$^+$PD1$^+$ CD8$^+$ TILs are highly prevalent and have an exhausted profile. A) CD8$^+$ TILs from human cancers were stained for PD-1, PVRIG, and TIGIT. The percentage of CD8$^+$ TILs that express combinations of PD-1, PVRIG, or TIGIT on CD8$^+$ T cells was determined by Boolean gating. B) Representative PD-1, PVRIG, and TIGIT expression on CD4$^+$ and CD8$^+$ T cells from a lung tumor are shown. C) TILS from human cancers were stained for cell surface PD1, PVRIG, and TIGIT on CD8$^+$ T cells, permeabilized, and stained for Eomes and T-bet. The percentage of Eomes$^+$T-bet$^-$ CD8$^+$ T cells are shown. A paired Student's t-test was performed and p values shown. D) Representative TIL FACS plots showing Eomes and T-bet expression on PD-1, PVRIG, or TIGIT positive/negative expressing CD8$^+$ T cells from an ovarian and bladder tumor are shown. E) The percentage of Eomes$^+$T-bet$^-$ CD8$^+$ T cells expressing PD-1, PVRIG, and TIGIT expression was determined from human cancers.

PVRL2 Expression Is Induced In Cancer

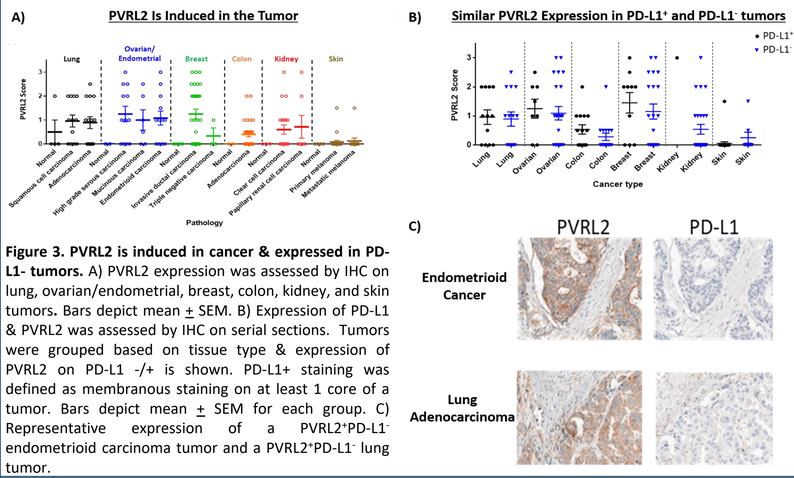


Figure 3. PVRL2 is induced in cancer & expressed in PD-L1- tumors. A) PVRL2 expression was assessed by IHC on lung, ovarian/endometrial, breast, colon, kidney, and skin tumors. Bars depict mean ± SEM. B) Expression of PD-L1 & PVRL2 was assessed by IHC on serial sections. Tumors were grouped based on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

COM701 and/or COM902 Have Similar Or Greater Potency Than Anti-PD-1 On Freshly Isolated Human TILS

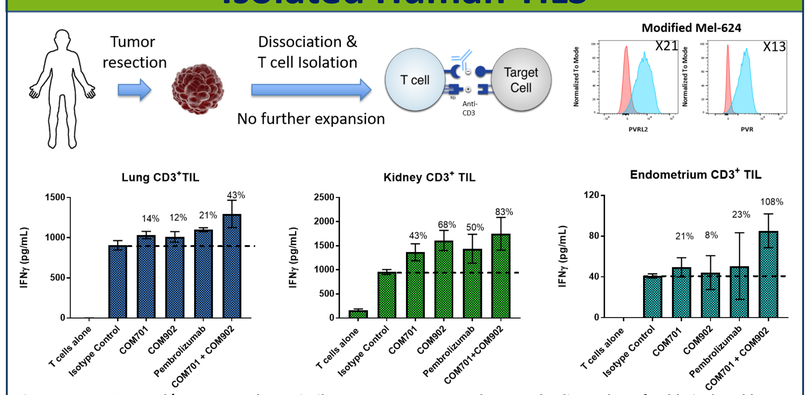


Figure 4: COM701 and/or COM902 have similar or greater potency than Pembrolizumab on freshly isolated human TILs. Human tumors obtained within 24 hours of surgical resection were dissociated and CD3$^+$ TILs were purified. Isolated CD3$^+$ TILs were co-cultured with a modified MEL624 tumor cell line, expressing surface bound anti-CD3, and the indicated antibodies at 10 μg/ml. IFN-γ secretion in the conditioned media was measured at 72 hours. The percentage change in IFN-γ for each treatment over the hIgG isotype control is shown.

Anti-PVRIG, Anti-TIGIT, And Anti-PD-1 Synergistically Increases T Cell Function

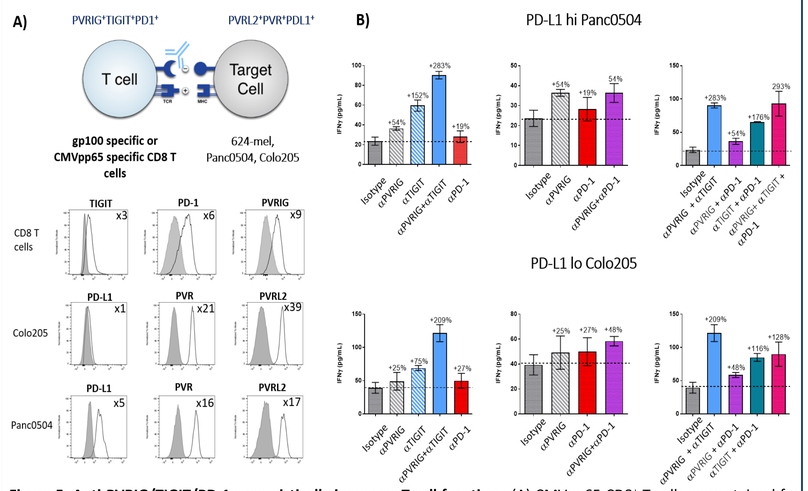


Figure 5: Anti-PVRIG/TIGIT/PD-1 synergistically increases T cell function. (A) CMVpp65 CD8$^+$ T cells were stained for TIGIT, PD-1, and PVRIG expression, and tumor cell lines (Panc.05.4, Colo205) were stained for PD-L1, PVR, and PVRL2. Representative FACs histograms are shown. B) CMVpp65 specific T cells were co-cultured with Panc.05.04 and Colo205 cells, CMVpp65 peptide and the indicated antibodies at 10 μg/ml. IFN-γ concentration in the conditioned media was determined at 18hrs. Percentages above bar graphs is % increase in IFN-γ secretion relative to isotype IgG.

Blockade of PVRIG/PVRL2 Induces PD-1 And TIGIT Expression

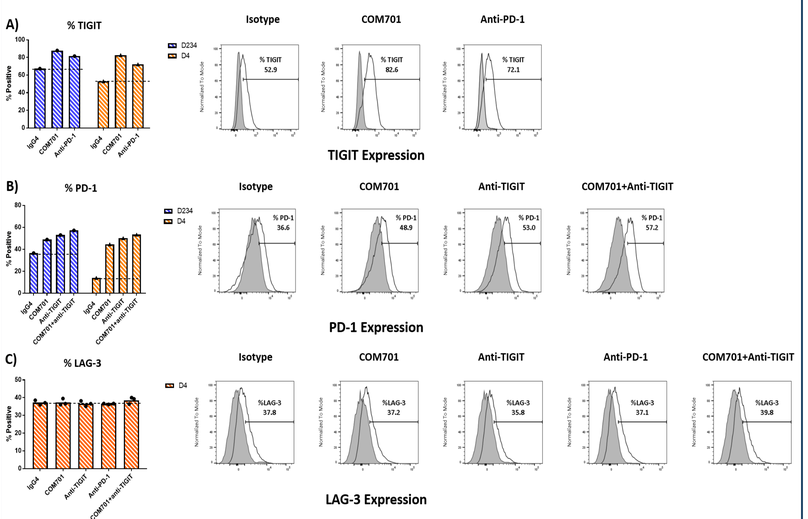


Figure 6: Blockade of PVRIG-PVRL2 induces PD-1 & TIGIT expression. CMVpp65-specific CD8$^+$ T cells from 2 donors were co-cultured with Panc.05.04, CMVpp65 peptide, and the indicated antibodies at 10 μg/ml for 18 hrs. Cells were stained and the percentage of TIGIT$^+$, PD-1$^+$, and LAG3$^+$ CD8$^+$ T cells following each treatment is shown.

Conclusions

- Immunohistochemistry and flow cytometry were performed to assess PVRIG/PVRL2 and TIGIT/PVR 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 PD-1 and that PVRIG$^+$TIGIT$^+$PD1$^+$ 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$^+$PD-1$^+$ cells were also high in percentage of Eomes$^+$T-bet$^-$ T cells.
- Combination of COM701 with anti-PD-1 antibody or COM902 enhanced CD8$^+$ T cell cytokine production, with the triple combination of COM701, COM902, and anti-PD-1 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