COM902, a Novel Therapeutic Antibody Targeting TIGIT Augments T Cell Function and the Activity of PVRIG Pathway Blockade In Vitro and In Vivo

Kathryn Logronio[1], Samir Qurashi[1], Sarah Whelan[1], Kyle Hansen[1], Sandeep Kumar[1], Ling Leung[1], Hsin-Yuan Cheng[1], Zoya Alteber[2], Rupashree Sen[3], Michele Doucet[3], Mark White[1], Spencer Liang[1], Eran Ophir[2], Sudipto Ganguly[3], John Hunter[1], Drew Pardoll[3] and Maya Kotturi[1] [1]Compugen USA, Inc, South San Francisco CA, [2]Compugen Ltd, Holon Israel, [3]Bloomberg Kimmel Institute for Cancer Immunotherapy, John Hopkins University, Baltimore, MD

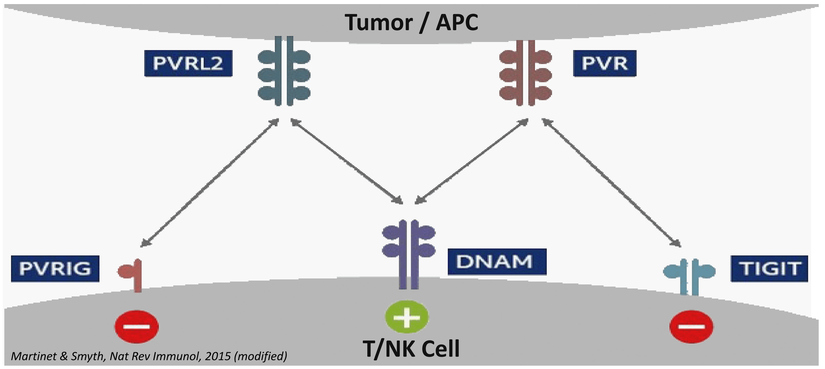
ABSTRACT

Background: TIGIT is a coinhibitory receptor that is highly expressed on tumor infiltrating lymphocytes (TILs), including effector and regulatory (Treg) CD4$^+$ T cells, effector CD8$^+$ T cells, and NK cells. Engagement of TIGIT with its cognate ligand PVR directly suppresses lymphocyte activation. TIGIT and PVR are broadly expressed in different types of solid tumors, suggesting that TIGIT-PVR signaling may be a dominant immune escape mechanism for cancer. Utilizing COM902, a therapeutic antibody targeting TIGIT, we demonstrate that co-blockade of TIGIT and a new checkpoint inhibitor, PVRIG, augments T cell responses in vitro and in vivo.

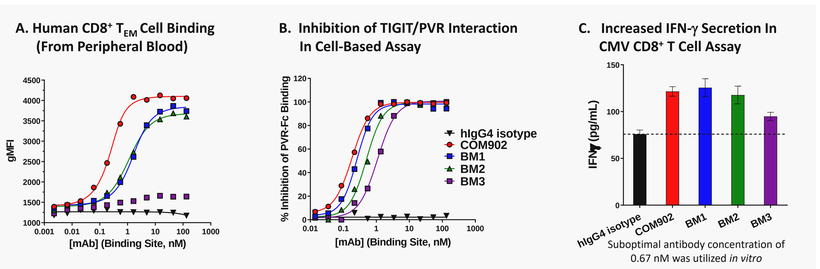
Results: COM902 is a mouse/cyno cross-reactive fully human antibody that binds TIGIT with high affinity and specificity and disrupts the binding of TIGIT to PVR. This antibody binds to TIGIT on human CD8$^+$ T cells with higher affinity than tested benchmark antibodies. In dissociated tumor samples, TIGIT expression was highest on TILs in endometrial, head and neck, kidney and lung tumors, and directly correlated with PVRIG expression. Except for breast tumors, PVR was moderately to highly expressed in all tumor types examined, while PVRL2 expression was highest in prostate, ovarian, liver and endometrial tumors. Combination of COM902 and COM701 resulted in enhanced CD3$^+$ TIL activity in vitro. Furthermore, the combination of chimeric COM902 and anti-PVRIG resulted in significant CT26 tumor growth inhibition and enhanced overall survival, which was comparable to the combination of chimeric COM902 and anti-PD-L1.

Conclusion: COM902 is a high affinity antagonistic TIGIT antibody, that is currently in preclinical development. Co-expression of TIGIT with PVRIG in TILs and their non-redundant inhibitory effects on T cell activation suggest a potential therapeutic advantage in clinical combinations targeting both pathways. Towards this end we are planning a trial that will eventually incorporate combinations of COM902 with the anti-PVRIG antibody, COM701.

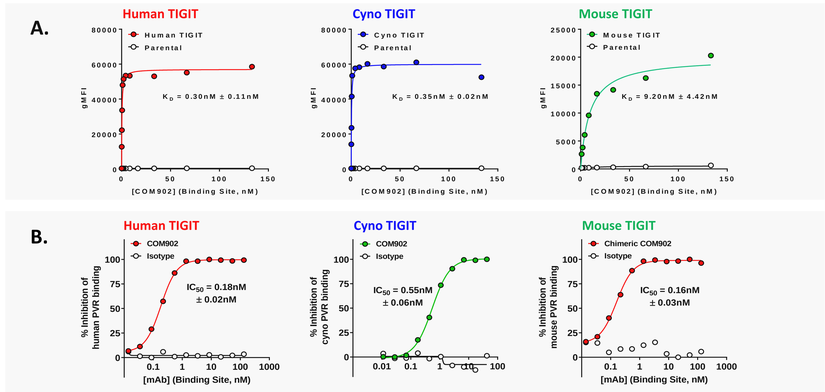
TIGIT AND PVRIG ARE PARALLEL, NON-REDUNDANT IMMUNE CHECKPOINTS IN THE PVR/NECTIN FAMILY



COM902 HAVE SUPERIOR BINDING CAPACITY & SIMILAR OR GREATER FUNCTION COMPARED TO CLINICAL ANTI-TIGIT BMs

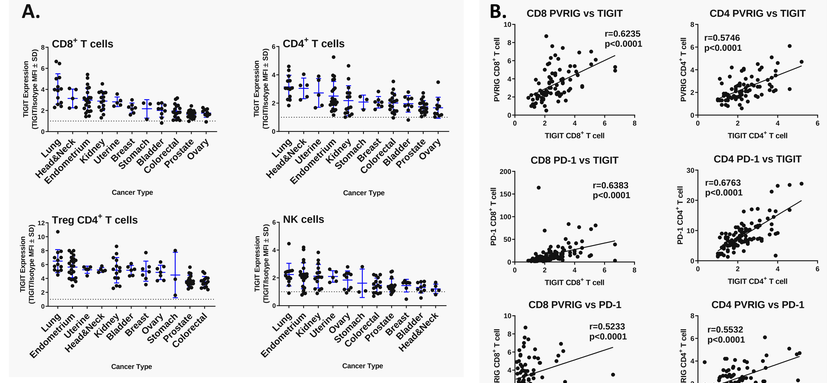


COM902: A HIGH AFFINITY, MOUSE/CYNO CROSS-REACTIVE TIGIT ANTAGONIST



A. COM902 binds with high affinity to human TIGIT and cross reacts with cynomolgus monkey and mouse TIGIT. **B.** COM902 blocks the interaction between TIGIT and PVR in a dose-dependent manner.

TIGIT IS EXPRESSED ON LYMPHOCYTES IN THE TME IN CORRELATION TO PVRIG AND PD1



A. TIGIT expression on CD8+, non-Treg CD4+, Treg CD4+ T cells, and NK cells is shown for indication.
B. Correlation analysis of TIGIT, PVRIG, and PD1 expression on CD8+ and CD4+ T cells from dissociated tumors.

PVR AND PVRL2 ARE EXPRESSED IN MULTIPLE TUMOR TISSUES

A.

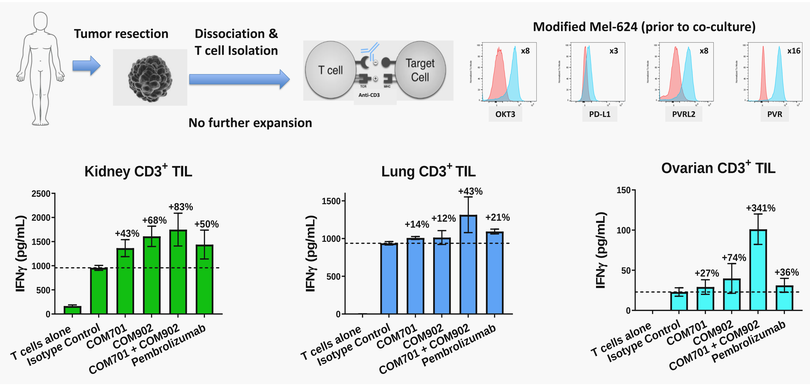
Tissue Type	Total Samples	% PVR Low (score 1)	% PVR Moderate (score 2)	% PVR High (score 3)
Colon	20	0	5	95
Prostate	21	0	14	86
Liver	10	0	10	90
Skin	8	13	25	63
Stomach	9	33	11	56
Brain	10	30	10	60
Head and Neck	24	33	21	46
Bladder	11	18	27	55
Endometrial	14	0	50	50
Lung	19	37	26	37
Pancreatic	11	27	36	36
Thyroid	10	60	20	20
Ovarian	10	20	50	30
Kidney	25	32	40	28
Breast	19	84	11	5

B.

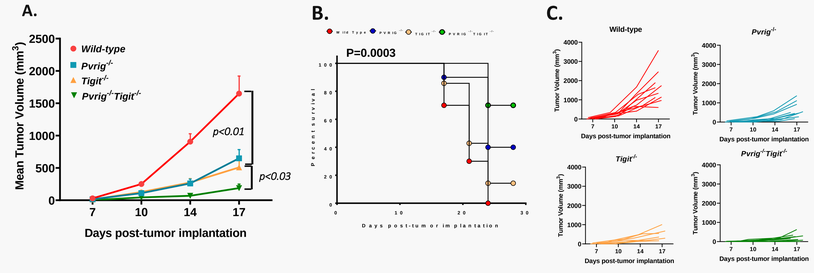
Tissue Type	Total Samples	% PVRL2 Low (score 1)	% PVRL2 Moderate (score 2)	% PVRL2 High (score 3)
Prostate	21	71	19	10
Ovarian	10	80	10	10
Liver	10	60	40	0
Endometrial	14	71	21	0
Bladder	11	73	18	0
Head and Neck	24	54	13	0
Skin	8	75	0	0
Stomach	25	72	0	0
Colon	20	50	0	0
Breast	21	67	0	0
Pancreatic	11	73	0	0
Lung	17	47	0	0
Thyroid	10	30	0	0
Kidney	25	0	0	0
Brain	10	0	0	0

The expression of PVR (**A.**) and PVRL2 (**B.**) in 16 different types of tumor tissues with n=10-20 patients per indication is shown. A polyclonal anti-PVRL2 antibody (HPA012759, Sigma-Aldrich) and a monoclonal anti-PVR antibody (Clone D8A5G, Cell Signaling Technology) were used.

COMBINATION OF COM902 AND COM701 DEMONSRATES COMPARABLE OR GREATER POTENCY THAN ANTI-PD1

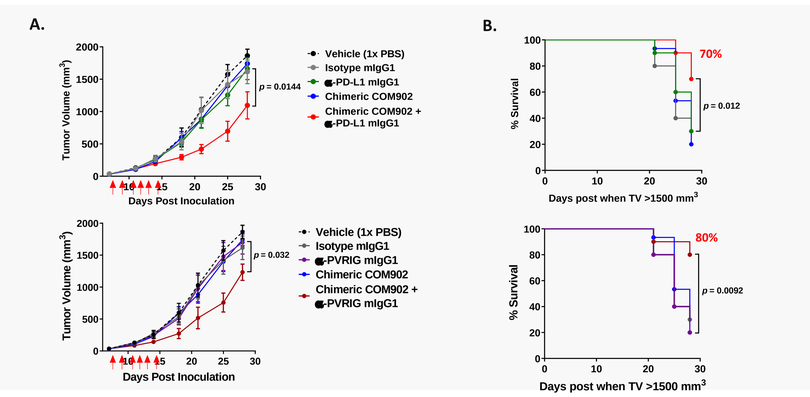


REDUCED TUMOR GROWTH IN PVRIG-/- AND TIGIT-/- MICE AND SYNERGISTIC TGI IN DOUBLE KO MICE IN B16-F10 MELANOMA CANCER MODEL



A. B16-F10 tumor volume in PVRIG-/-, TIGIT-/- or PVRIG-/-TIGIT-/- double KO mice are represented as the mean volume ± SEM. **B.** Kaplan-Meier survival curves. **C.** Individual tumors measurements for each mouse

COM902 INHIBITS TUMOR GROWTH & INCREASES SURVIVAL IN COMBINATION WITH ANTI-PVRIG OR ANTI-PDL1 IN CT26 COLON CANCER MODEL



A. Tumor volume for the chimeric COM902 (10 mg/kg) & anti-PD-L1 (3 mg/kg) combination, or the chimeric COM902 & anti-PVRIG (10 mg/kg) combination are represented as the mean volume ± SEM. **B.** Kaplan-Meier survival curves for the monotherapy treatments and combinations (n=10).