Development and Functional Characterization of COM902, a Novel Therapeutic Antibody Targeting the Immune Checkpoint TIGIT

Sandeep Kumar[1], Radhika Desai[1], Hsin-Yuan Cheng[1], Kyle Hansen[1], Andy Drake[1], Patrick Wall[1], Kathryn Logronio[1], Gady Cojocaru[2], John Hunter[1], Mark White[1], Spencer Liang[1], and Maya Kotturi[1]

[1]Compugen USA, Inc, South San Francisco CA, [2]Compugen Ltd, Holon Israel

compugen FROM CODE TO CURE

Poster#344

ABSTRACT

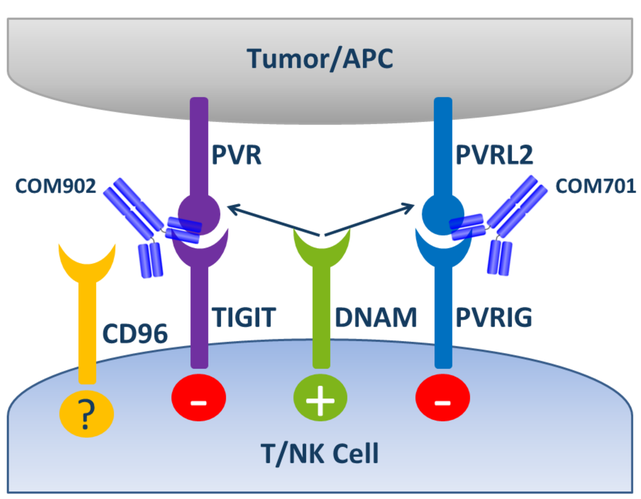
Background: TIGIT is a coinhibitory receptor that is highly expressed on lymphocytes, including effector and regulatory CD4⁺ T cells (Tregs), effector CD8⁺ T cells, and NK cells, that infiltrate different types of tumors. Engagement of TIGIT with its reported ligands, poliovirus receptor (PVR) and PVR-like proteins (PVRL2 and PVRL3) directly suppresses lymphocyte activation. The TIGIT-PVR signaling axis may be a dominant immune escape mechanism for cancer. We report here the biophysical and functional characterization of COM902, a therapeutic antibody targeting TIGIT.

Materials and Methods: Human phage display and mouse hybridoma antibody discovery campaigns were conducted to generate therapeutic anti-TIGIT antibodies. The resulting antibodies were evaluated for their ability to bind to recombinant and cell surface-expressed human TIGIT with high affinity. Cross-reactivity of the antibodies to cynomolgus macaque and mouse TIGIT was also examined. A subset of antibodies that bound with high affinity to human TIGIT, and cross-reactive to cynomolgus TIGIT was further characterized for their ability to block the interaction between TIGIT and PVR. Blocking antibodies were screened for their ability to enhance antigen-specific T cell activation *in vitro* either alone, or in combination with an anti-PD-1 antibody, or an anti-PVRIG antibody, COM701.

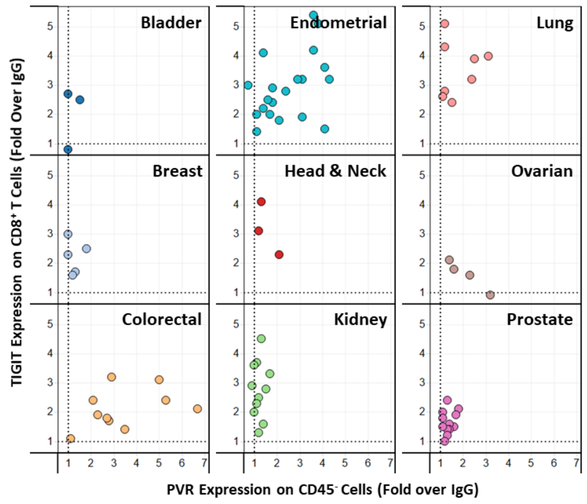
Results: We identified a lead antibody, COM902, that bound to human TIGIT with high triple digit femtomolar affinity. We demonstrated that TIGIT is co-expressed with PVR in several solid tumors. TIGIT expression was predominant on Tregs and effector CD8⁺ TILs, suggesting that these populations would likely be preferentially targeted by COM902. Furthermore, TIGIT expression correlated with PVRIG on CD4⁺ and CD8⁺ TILs. COM902 bound to TIGIT endogenously expressed on human CD8⁺ T cells with higher affinity than tested benchmark antibodies, and was also cross-reactive to both cynomolgus and mouse TIGIT. When tested for *in vitro* activity, COM902 augmented IFN-γ secretion and tumor cell killing by CMV-specific CD8⁺ T cells with superior or equivalent potency to the tested benchmark antibodies. Combination of COM902 with an anti-PD-1 antibody or COM701 resulted in enhanced CMV-specific CD8⁺ T cell activity. In contrast, a blocking anti-CD96 antibody had no effect on IFN-γ secretion.

BACKGROUND

COM902 AND COM701 TARGET TWO DIFFERENT COINHIBITORY RECEPTORS IN THE NECTIN & NECTIN-LIKE FAMILY

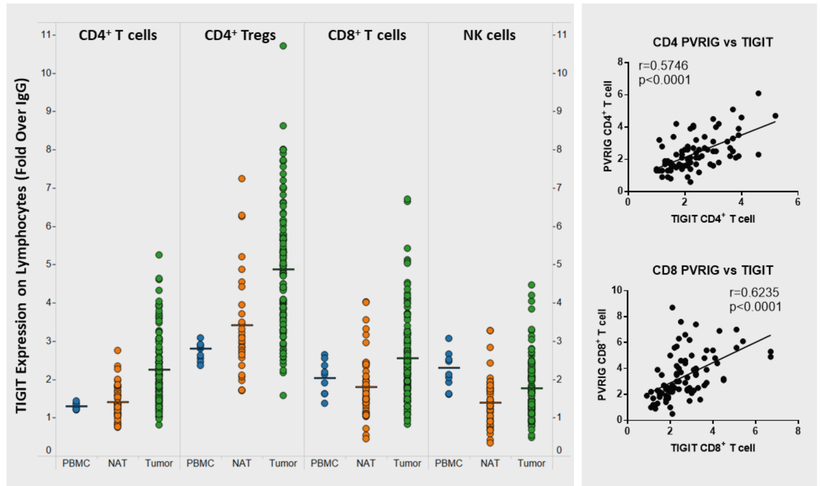


TIGIT AND PVR ARE CO-EXPRESSED IN THE TME



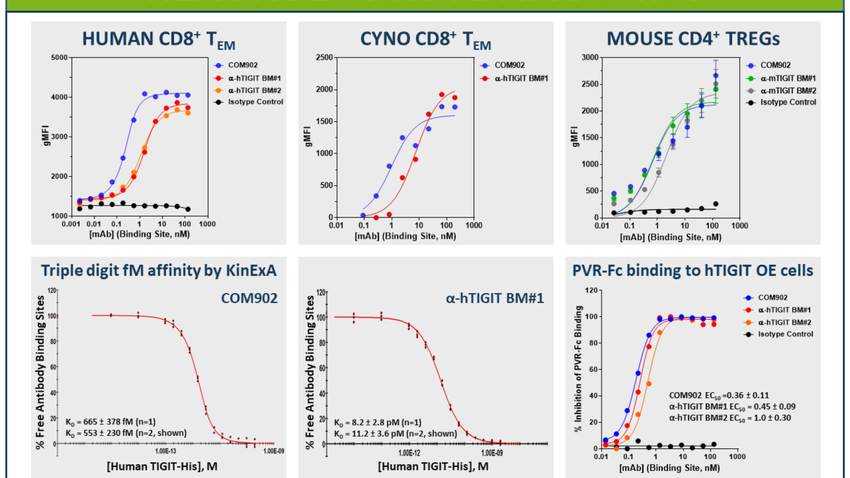
Tumor samples (n=129) were dissociated and stained with anti-TIGIT & anti-PVR antibodies. Plotted gMFI of anti-TIGIT or anti-PVR antibody over isotype IgG. Highest co-expression of TIGIT and PVR observed in colorectal, endometrial, & lung tumors.

TIGIT EXPRESSION IS ELEVATED IN CANCER & CORRELATES WITH PVRIG



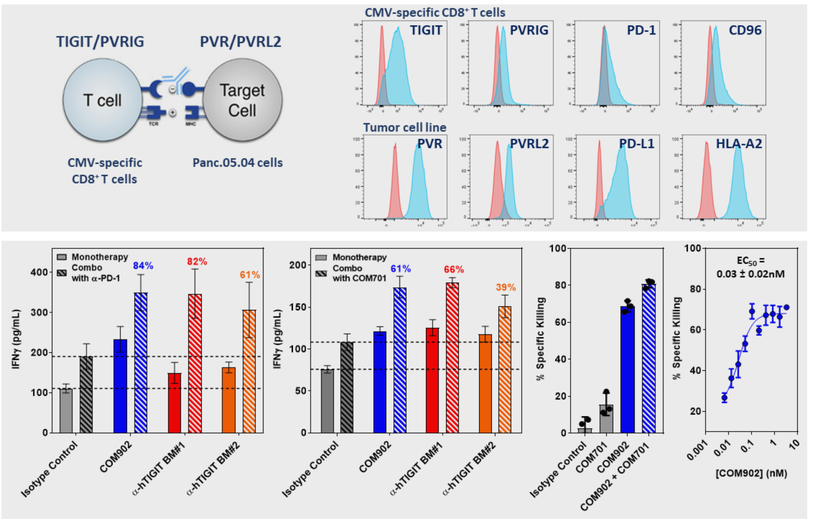
Tumor & normal adjacent tissue (NAT) samples were dissociated and stained with anti-TIGIT and anti-PVRIG antibodies. TIGIT expression in different lymphocyte subsets was examined in 145 tumor samples. PBMCs are not donor matched. Plotted gMFI of anti-TIGIT antibody over isotype IgG. Highest average TIGIT expression was detected in endometrial, kidney & lung tumors.

COM902: A HIGH AFFINITY, CROSS-REACTIVE TIGIT ANTAGONIST



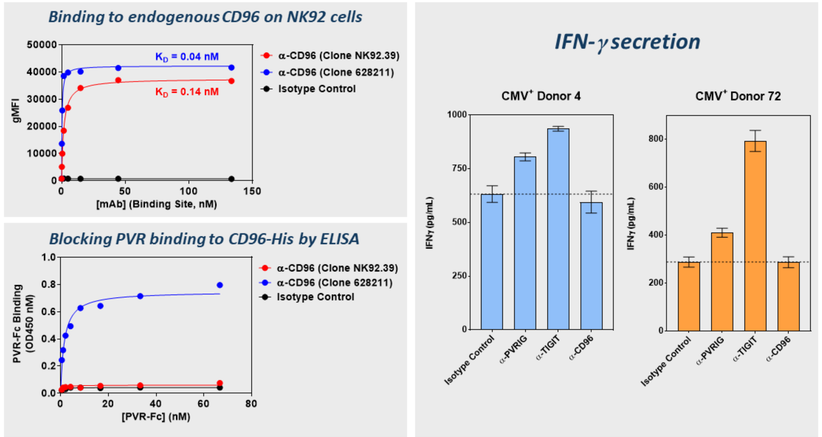
Representative healthy human and cynomolgus macaque PBMC donors, gated on effector memory CD95⁺CD28⁻CD8⁺ T cells (Tem) with n ≥ 2 experiments are shown. For TIGIT expression on cyno CD8⁺ Tem, gMFI of anti-TIGIT antibodies was normalized by subtracting the isotype control. No binding to human monocytes detected. Mouse Tregs derived from *ex vivo* Renca tumors (n=3). BM refers to benchmark antibody.

COM902 AUGMENTS IFN-γ RELEASE AND TUMOR CELL KILLING



Representative CMV-reactive CD8⁺ T cell donors with n≥2 experiments is shown. Percentages above bar graphs is % increase in IFN-γ secretion over isotype IgG. Anti-PD-1 antibody is pembrolizumab.

TIGIT AND NOT CD96 IS THE CHECKPOINT RECEPTOR THAT BINDS PVR



Anti-human CD96 antibodies, Clones NK92.39 and 628211, bind to endogenous CD96 on NK92 cells, but only Clone NK92.39 blocks human PVR binding to CD96. Representative CMV-reactive CD8⁺ T cell donors with anti-CD96 antibody, Clone NK92.39, with n≥2 experiments is shown. Anti-PVRIG antibody is COM701, and anti-TIGIT antibody is anti-hTIGIT BM#1.

Conclusion: We describe the development of a very high affinity antagonistic TIGIT antibody, COM902, that is currently in preclinical development with an anticipated IND filing in 2019. We postulate that the femtomolar affinity of COM902 could result in lower and less frequent dosing in patients. COM902 can enhance human T cell activation either alone or in combination with other checkpoint antibodies. Co-blockade of TIGIT and a new checkpoint inhibitor, PVRIG, augments T cell responses, while CD96 expressed on CD8⁺ T cells does not have checkpoint activity. These data suggest that TIGIT and PVRIG are the dominant coinhibitory receptors within the nectin family. Thus, our data demonstrates the utility of targeting TIGIT, PD-1, and PVRIG for the treatment of cancer.

Contact:
Maya Kotturi
Immuno-Oncology | Compugen USA, Inc.
Email: mayak@cgen.com
250 East Grand Ave Suite 65, South San Francisco, CA 94080, USA