Discovery and Development of COM701, a Therapeutic Antibody Targeting the Novel Immune Checkpoint PVRIG

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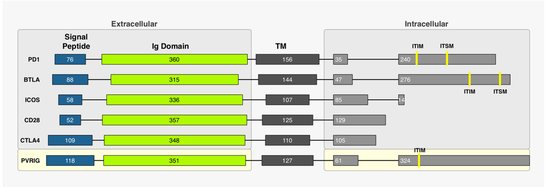
ABSTRACT

Background: While inhibitors of CTLA4 and PD-1 have emerged as effective cancer therapies, the majority of treated patients do not derive long term benefit. Employing our computational discovery platform, we discovered PVRIG as an immune suppressive molecule expressed on T and NK cells and identified COM701, an antibody (Ab) targeting human PVRIG that enhances T cell function and anti-tumor responses. **Methods:** Anti-human PVRIG Ab COM701 was identified as an antagonistic Ab that enhanced T cell function in multiple assays. Antagonistic anti-mouse PVRIG Abs and PVRIG deficient (PVRIG$^{-/-}$) mice were generated and characterized using syngeneic tumor models. **Results:** PVRIG was induced upon T cell activation, with long term activation leading to the highest expression. PVRL2 was identified as the ligand for PVRIG, placing PVRIG in the DNAM/TIGIT immunoreceptor axis. Compared to normal adjacent tissues, PVRIG and PVRL2 were both induced in the tumor microenvironment of several human cancers. To target PVRIG for therapeutic intervention, we identified COM701, a high affinity Ab that disrupts the interaction of PVRIG with PVRL2. COM701 enhanced CD8 T cell proliferation and IFN-γ production in vitro and had an additive or synergistic effect on T cell activation when further combined with an anti-PD-1 or anti-TIGIT Ab. Consistent with a checkpoint function for human PVRIG, mouse PVRIG$^{-/-}$ T cells showed increased function compared to wild type T cells. An antagonistic anti-mPVRIG surrogate Ab reduced growth of CT26 tumors when combined with an anti-PDL1 Ab in vivo and reduced growth of B16 tumors in TIGIT deficient mice. MC38 tumors also grew slower in PVRIG$^{-/-}$ mice compared to wild type mice and ex vivo analysis pointed to functional differences in T cell responses. **Conclusions:** We demonstrated that targeting PVRIG with COM701, a high affinity antagonistic Ab, increased human T cell function. We further showed that PVRIG was induced in the tumor microenvironment and that disruption of PVRIG/PVRL2 interaction resulted in reduced tumor growth in preclinical models. These data demonstrate that PVRIG is a promising target for the treatment of cancer and provide the rationale for COM701 as a potential cancer immunotherapy.

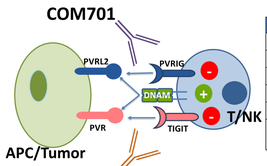
BACKGROUND

PVRIG FUNCTIONAL GENE STRUCTURE MATCHES KNOWN IMMUNE CHECKPOINT RECEPTORS



Use of 'Functional Homology' in absence of sequence similarity based on exon size, phase, and functional elements within exons

COM701 and COM902 TARGET 2 CHECKPOINTS IN THE DNAM/TIGIT/PVRIG FAMILY



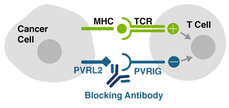
Expression of DNAM/TIGIT/PVRIG Family

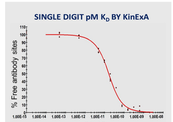
	DNAM	TIGIT	PVRIG	PVR	PVRL2
CD4 T cells	Yes	Yes (Tregs+)	Yes	Yes	No
CD8 T cells	Yes	Yes	Yes	Yes	No
NK cells	Yes	Yes	Yes	No	No
Monocytes	Yes	No	No	Yes	Yes
DCs	Yes	No	No	Yes	Yes
Tumor Epithelium	No	No	No	Induced on tumor	Induced on tumor

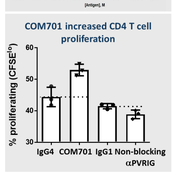
COM701: A HIGH AFFINITY PVRIG ANTAGONIST

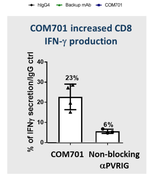
DEVELOPMENT OF COM701: A HIGH AFFINITY PVRIG ANTAGONIST

- **COM701 selected as therapeutic lead**
  - **High affinity (< 1nM Kd)**
  - **Blocks PVRIG – PVRL2 interaction**
  - **Enhances T cell function in cell based assays**

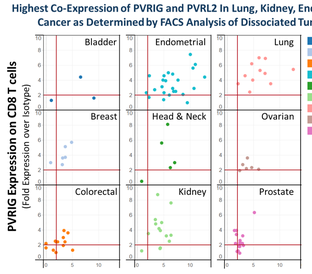


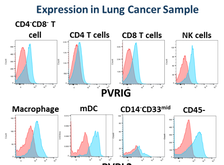


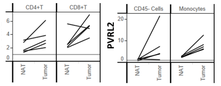




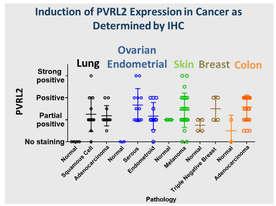
PVRIG AND PVRL2 ARE INDUCED IN MULTIPLE CANCERS

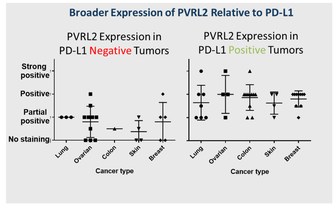






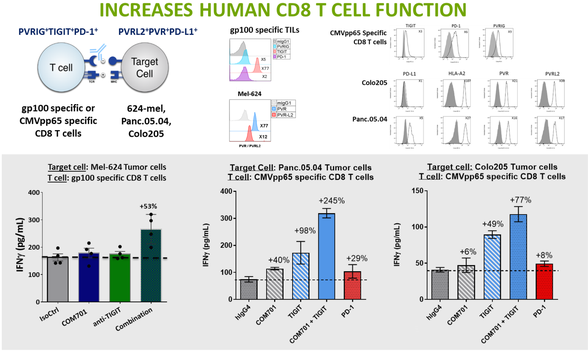
Matched NAT (Normal adjacent tissue) vs Tumor



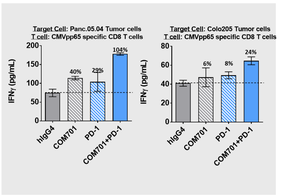


SYNERGISTIC ACTIVITY OBSERVED of COM701 in COMBINATION with PD-1 and TIGIT INHIBITORS

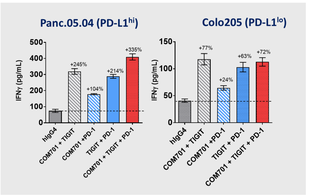
COMBINING PVRIG AND TIGIT BLOCKADE SYNERGISTICALLY INCREASES HUMAN CD8 T CELL FUNCTION



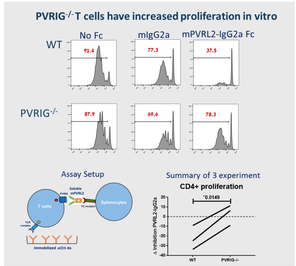
PVRIG AND PD-1 BLOCKADE SYNERGISTICALLY INCREASES CD8 T CELL FUNCTION

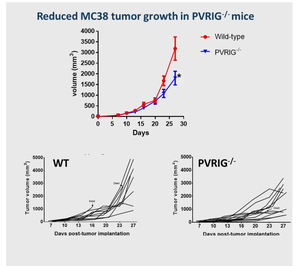


TRIPLE COMBO LEADS TO GREATEST INCREASE IN T CELL FUNCTION

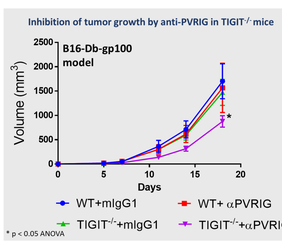


INCREASED T CELL ACTIVATION AND REDUCED TUMOR GROWTH OBSERVED WITH PVRIG$^{-/-}$ MICE

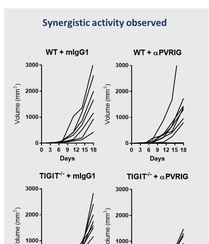




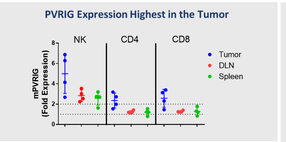
PVRIG ANTIBODY BLOCKADE REDUCED TUMOR GROWTH IN TIGIT$^{-/-}$ MICE

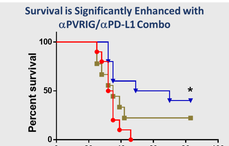


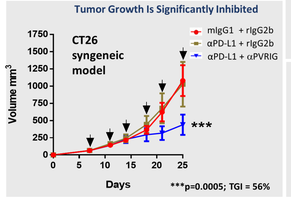
TGI compared to WT + mIgG1	Day 11	Day 14	Day 18
WT+ aPVRIG	17%	13%	8%
TIGIT$^{-/-}$ + mIgG1	17%	17%	13%
TIGIT$^{-/-}$ + aPVRIG	63%	53%	49%

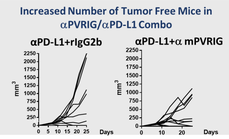


PVRIG BLOCKING ANTIBODIES REDUCE TUMOR GROWTH AND INCREASE SURVIVAL IN COMBINATION WITH PD-1 PATHWAY BLOCKADE









CONCLUSIONS

- PVRIG/PVRL2 is a novel inhibitory T cell checkpoint induced in the TME
- COM701 is a high affinity antagonistic antibody that blocks PVRIG/PVRL2 interaction
- PVRIG antagonism synergized with anti-PD-1 or anti-TIGIT/TIGIT ablation to synergistically increase T cell function and reduce tumor growth
- COM701 has the potential to improve anti-tumor responses