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DISCOVERY AND DEVELOPMENT OF COM701, A THERAPEUTIC ANTIBODY TARGETING THE NOVEL IMMUNE CHECKPOINT PVRIG

Poster 581

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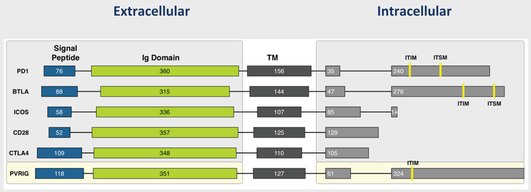
BACKGROUND, METHODS

BACKGROUND: While blockade of the CTLA4 and PD1 pathways has emerged as an effective treatment of cancer, the majority of patients do not derive long term benefit.
This provides a rationale for identifying and targeting additional checkpoints. Employing our unique computational algorithms, we identified PVRIG, a new member of the B7/CD28 family. We report here the expression pattern, functional characterization, and anti-tumor activity of blocking antibodies targeting PVRIG and the effect of PVRIG deficiency on tumor growth in mice.

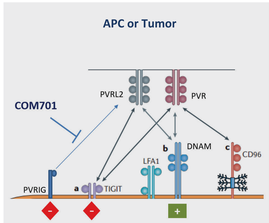
Materials and Methods: The binding of PVRIG, DNAM, TIGIT to PVR and PVLR2 was assessed by ELISA. Antibody discovery was performed using phage display and hybridoma platforms and antibodies against human PVRIG were screened by binding to PVRIG, disrupting PVRIG-PVRL2 interaction, and enhancing T-cell activity in vitro. Expression of PVRIG was evaluated in healthy donor PBMCs and from dissociated human tumors by flow cytometry. Immunohistochemistry for PVRL2 and PD-L1 was conducted on serial sections of melanoma, colon, lung, and ovarian cancer TMAs. Surrogate anti-mPVRIG antibodies that also disrupted mouse PVRL2-PVRIG interactions were assessed in syngeneic models for effects on tumor growth. PVRIG deficient mice were generated and characterized in tumor models.

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

PVRIG FAMILY IS A NOVEL CHECKPOINT AXIS

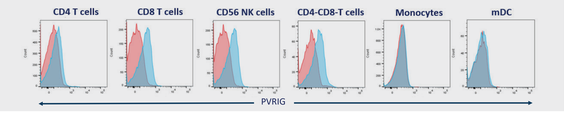


Expression of DNAM/TIGIT/PVRIG Family

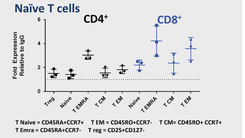
	DNAM	TIGIT	PVRIG	PVR	PVRL2
CD4 T cells	Yes	Yes (Tregs+)	Yes	Yes	No
CD8 T cells	Yes	Yes	Yes	Yes	No
NK cells	Yes	Yes	Yes	No	No
Mono/Macs	Yes	No	No	Yes	Yes
DCs	Yes	No	No	Yes	Yes
Tumor Epithelium	No	No	No	Induced on tumor	Induced on tumor

PVRIG EXPRESSION ON RESTING AND ACTIVATED HUMAN LEUKOCYTES

Expression of PVRIG detected on Resting Lymphocytes Red= isotype Blue= PVRIG

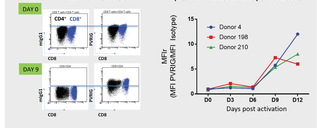


Higher PVRIG Expression on Memory vs Naïve T cells

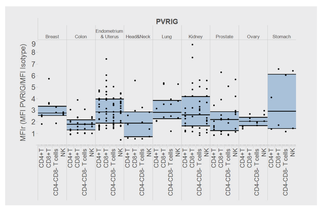


T Naive = CD45RA+CCR7+ T EM = CD45RO+CCR7- T CM= CD45RO+ CCR7+
T Emra = CD45RA+CCR7- T reg = CD25+CD127-

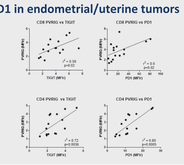
Induction of PVRIG on Activated T cells



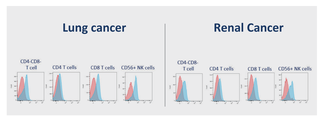
EXPRESSION OF PVRIG DETECTED IN MULTIPLE TUMOR TISSUES



Correlation of PVRIG with TIGIT and PD1 in endometrial/uterine tumors



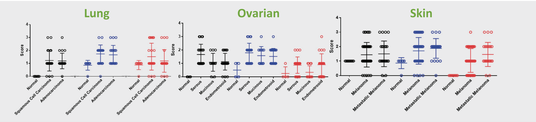
Lung cancer | **Renal Cancer**



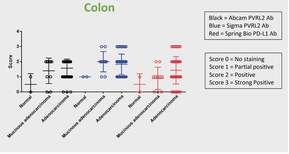
Human tumor samples were dissociated and stained with lineage markers for various immune subsets. For each sample, expression of PVRIG was evaluated on T cells and NK cells. Each dot represents an individual tumor sample.

Median value is depicted by the center line and inter-quartile range is depicted in blue. A Spearmans correlation was performed between PVRIG and PD-1 or TIGIT

INDUCTION OF PVRL2 IN MELANOMA, LUNG, OVARIAN, COLON CANCER



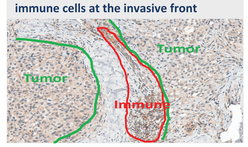
Colon



Black = Abcam PVRL2 Ab
Blue = Sigma PVRL2 Ab
Red = Spring Bio PD-L1 Ab

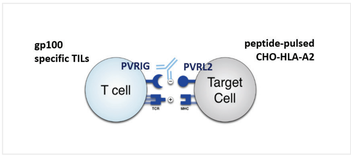
Score 0 = No staining
Score 1 = Partial positive
Score 2 = Positive
Score 3 = Strong Positive

Expression of PVRL2 on tumor cells and immune cells at the invasive front

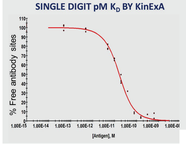


DEVELOPMENT OF COM701: A HIGH AFFINITY PVRIG ANTAGONIST

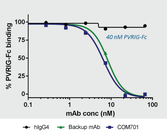
- Human phage display and standard hybridoma
- Antibodies screened for:
  - High affinity (KD < 1nM)
  - Ability to block PVRIG/PVRL2 binding
  - In vitro enhancement of T-cell activation
- COM701 selected as therapeutic lead
  - IND anticipated in 2017



SINGLE DIGIT pM K_D BY KinExA

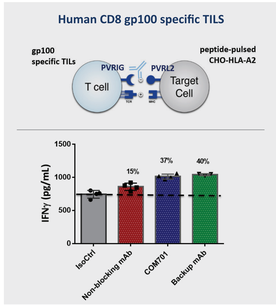


PVRIG-Fc binding to HEK cells

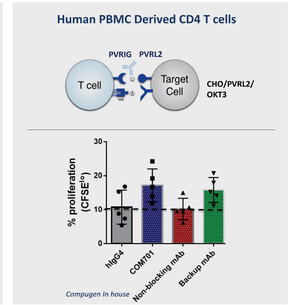


ANTI-PVRIG BLOCKING ANTIBODIES ENHANCE CD4 AND CD8 T CELL ACTIVATION

Human CD8 gp100 specific TILS



Human PBMC Derived CD4 T cells



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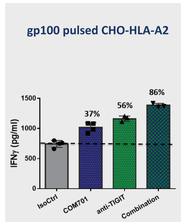
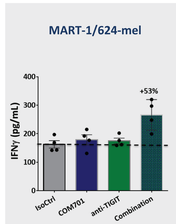
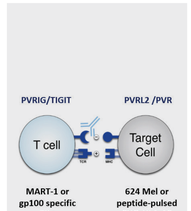
COMBINING PVRIG AND TIGIT BLOCKADE INCREASES TIL ACTIVATION

gp100 pulsed CHO-HLA-A2



MART-1/624-mel





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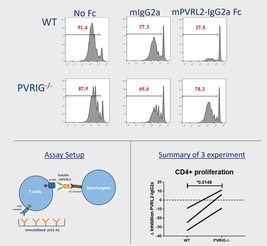
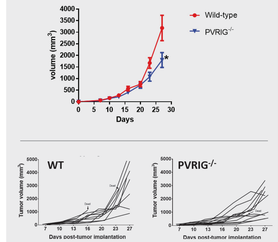
INCREASED T CELL ACTIVATION AND REDUCED TUMOR GROWTH OBSERVED WITH PVRIG$^{-/-}$ MICE

PVRIG$^{-/-}$ T cells have increased proliferation in vitro



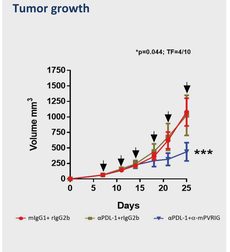
Reduced MC38 tumor growth in PVRIG$^{-/-}$ mice



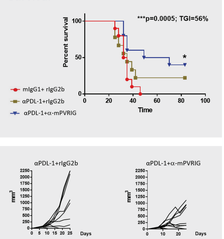
PVRIG BLOCKING ANTIBODIES REDUCE TUMOR GROWTH AND INCREASE SURVIVAL IN COMBINATION WITH PD1 PATHWAY BLOCKADE

CT26 syngeneic model

Tumor growth



Survival





CONCLUSIONS:

- PVRIG is a novel inhibitory T cell receptor that is expressed in the TME.
- COM701 is a high affinity antagonistic antibody that is currently in preclinical development.
- COM701 increased T cell activation of resting and effector human T cells
- PVRIG$^{-/-}$ mice display increased T cell function and reduced MC38 tumor growth
- A surrogate Ab to PVRIG reduced tumor growth in combination with PD-L1 antibody
- Antibody blockade of the PVRIG-PVRL2 interaction has the potential to be efficiently combined with PD1 or TIGIT blockade for enhancing anti-tumor immunity.