



Computational Identification, Functional Characterization and Antibody Blockade of a New Immune Checkpoint in the TIGIT Family of Interacting Molecules

JOHN HUNTER
SITC 2016 ANNUAL MEETING

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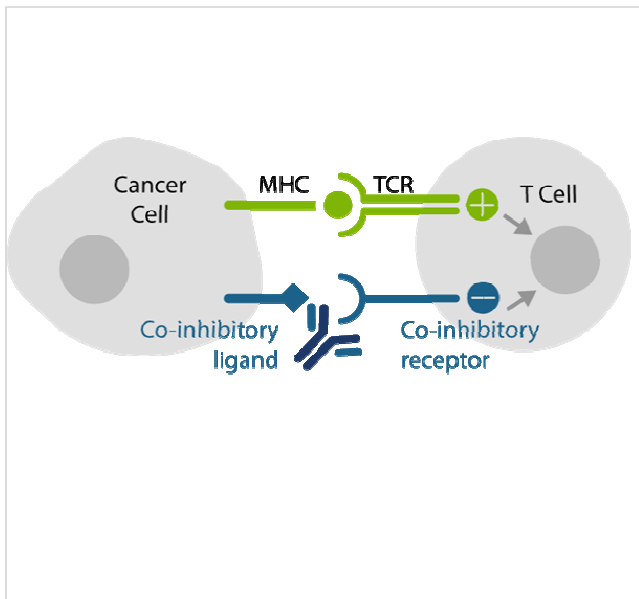
Presenter Disclosure Information

The following relationships exist related to this presentation:

Compugen – Employee with stock options

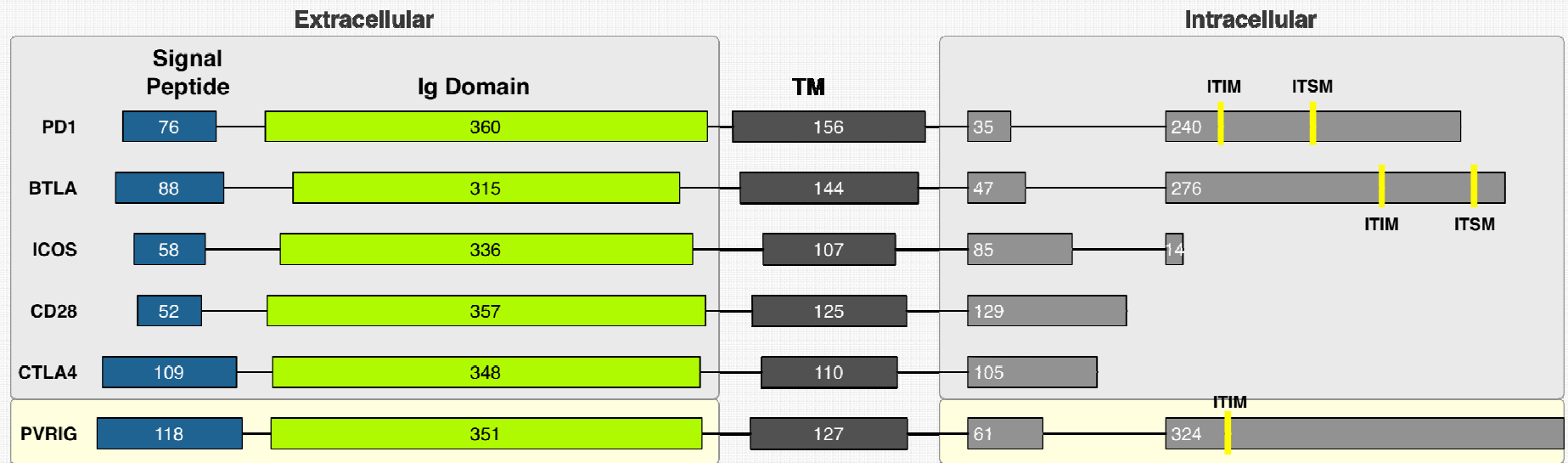
THE SEARCH FOR NEW IMMUNE CHECKPOINTS

Addressing Non-responsive Patient Populations



- Therapeutics targeting immune checkpoints have revolutionized cancer treatment
 - Durable responses in a subset of patients
 - Expansion of responsive populations with combination treatment
- Majority of patients don't derive lasting benefit
 - New treatment options needed

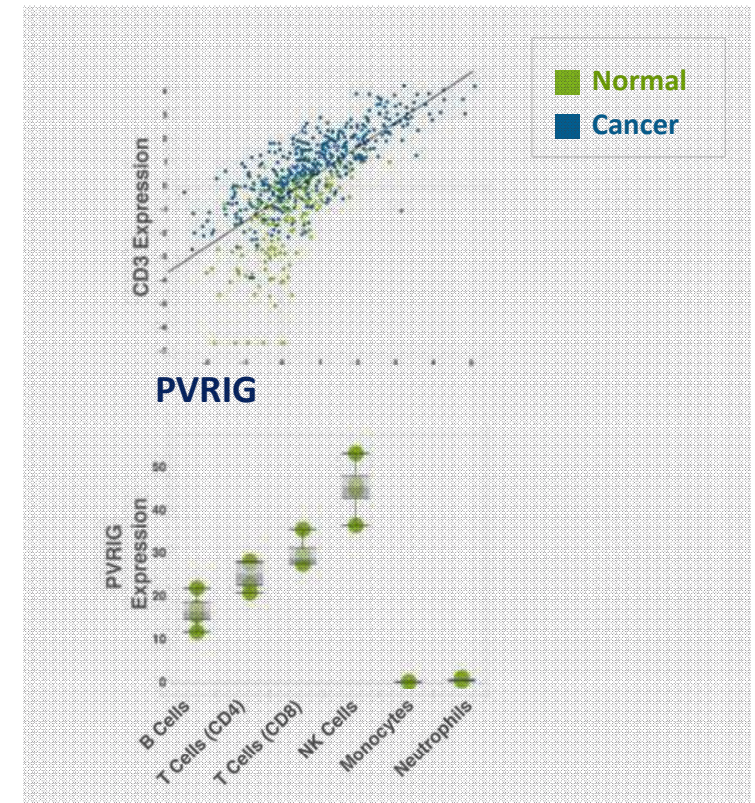
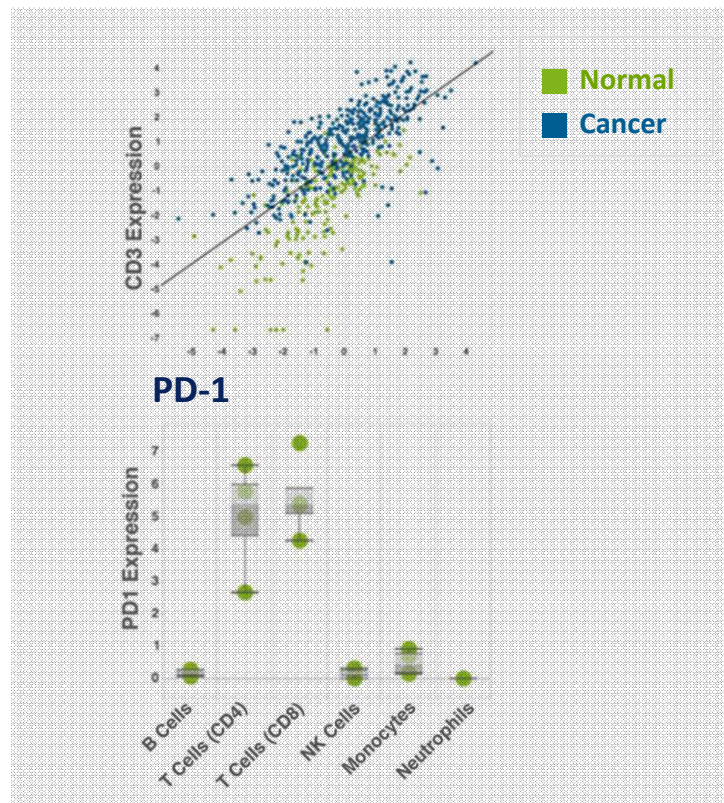
PVRIG (CGEN-15029) FUNCTIONAL GENE STRUCTURE MATCHES KNOWN IMMUNE CHECKPOINT RECEPTORS



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

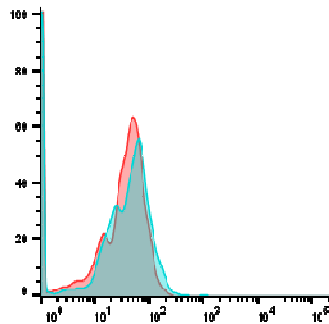
PVRIG EXHIBITS TUMOR EXPRESSION CHARACTERISTICS CONSISTENT WITH T-CELL RECEPTOR CHECKPOINTS

Normal RNA
expression
restricted to
lymphocytes;
higher expression
in solid tumors

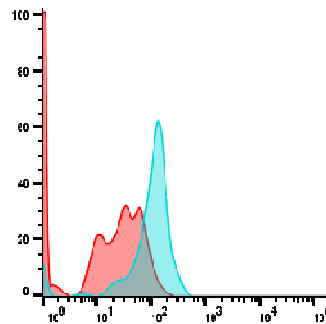


PVRIG EXPRESSION ON NAÏVE PBMC SUBSETS

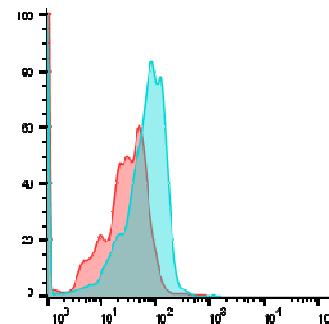
B cells



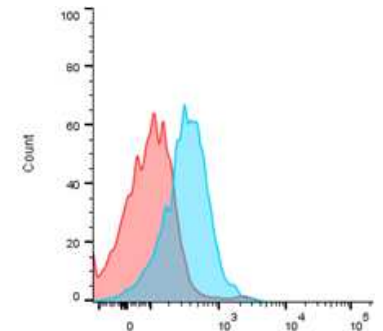
CD56 bright NK cells



CD56 dim NK cells

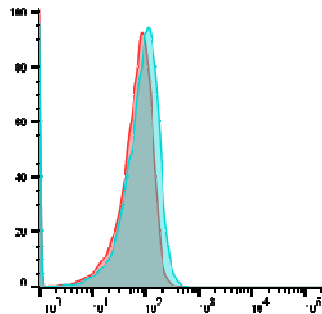


$\gamma\delta$ /NKT enriched

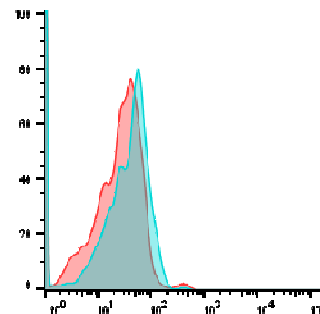


PVRIG

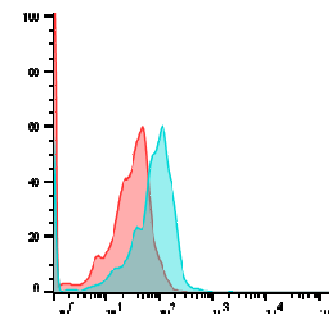
monocytes



CD4 T cells



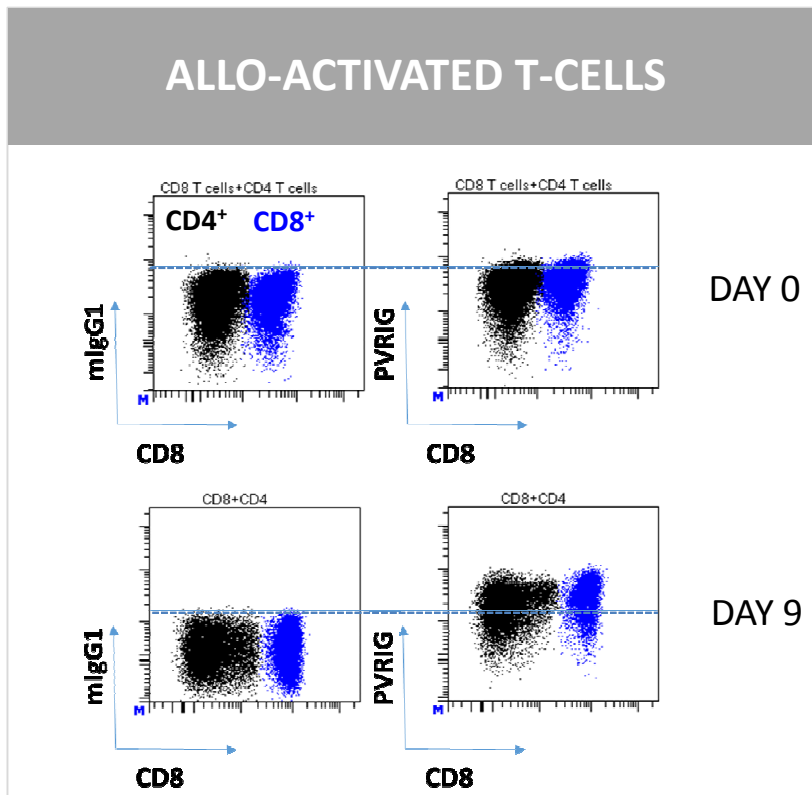
CD8 T cells



PVRIG

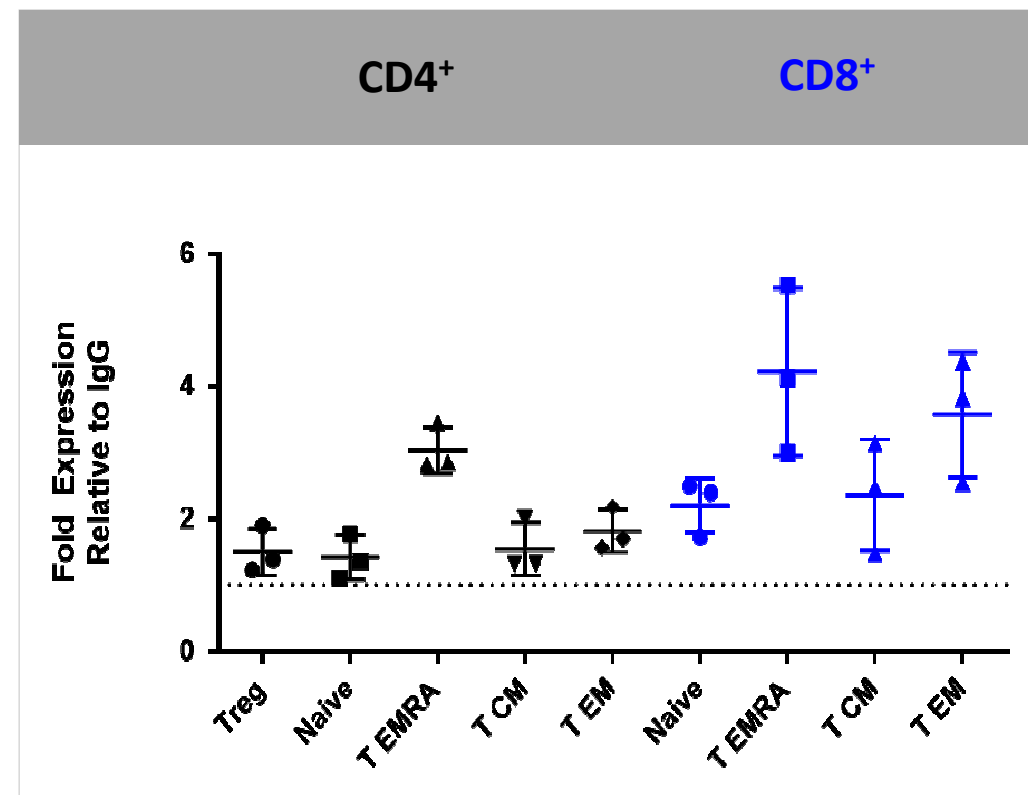
Red= isotype
Blue= PVRIG

PVRIG EXPRESSION IS INDUCED FOLLOWING T-CELL ACTIVATION AND ELEVATED ON T_{EMRA} AND T_{EM} CELLS



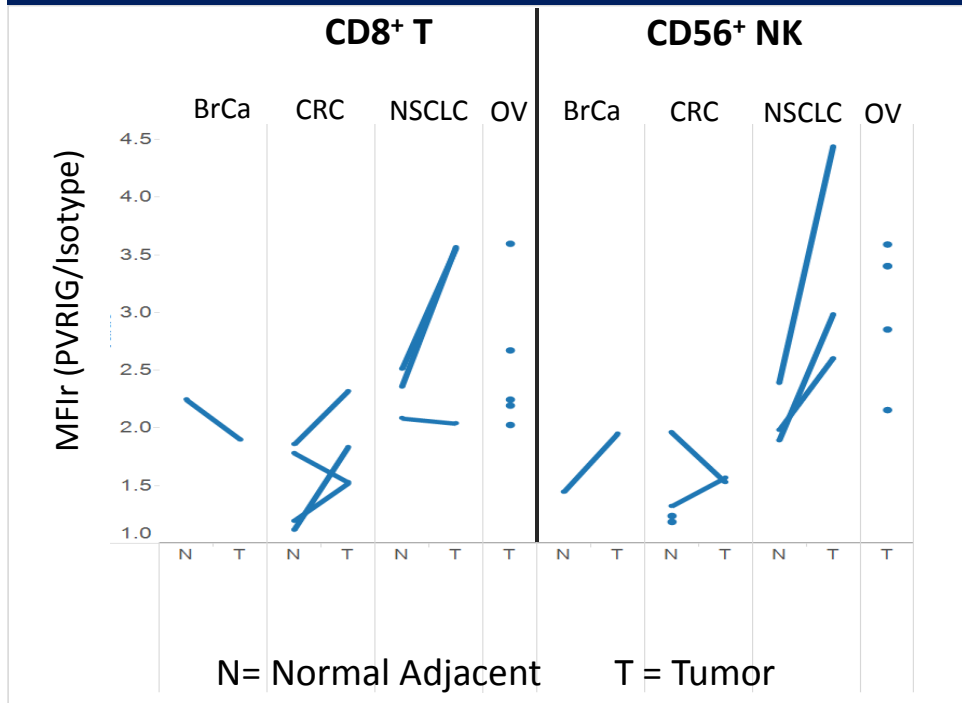
compugen

Ganguly and Pardoll, Johns Hopkins Univ.

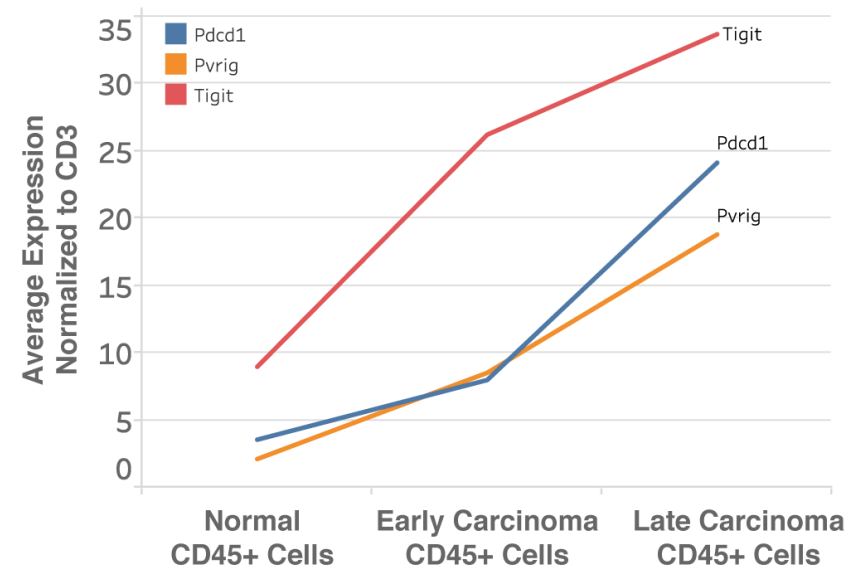


PVRIG EXPRESSION IS UPREGULATED IN HUMAN AND MOUSE TUMORS

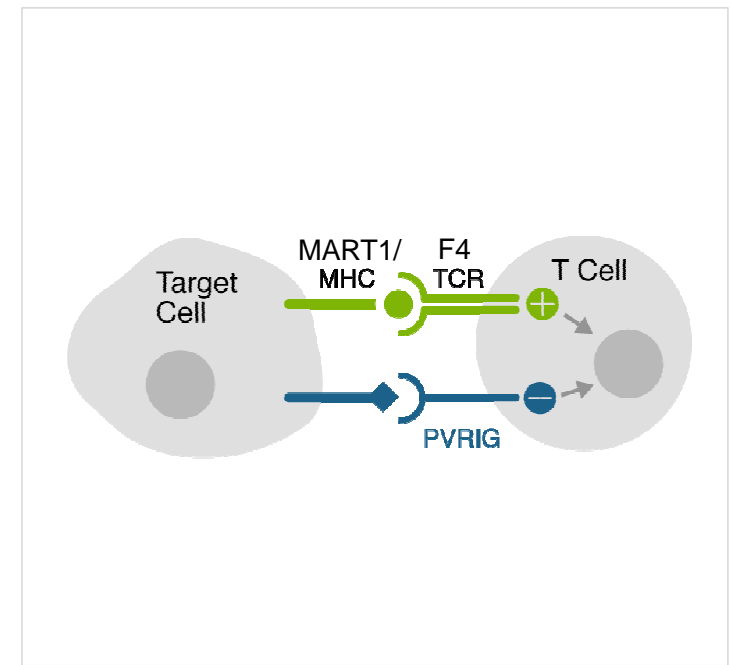
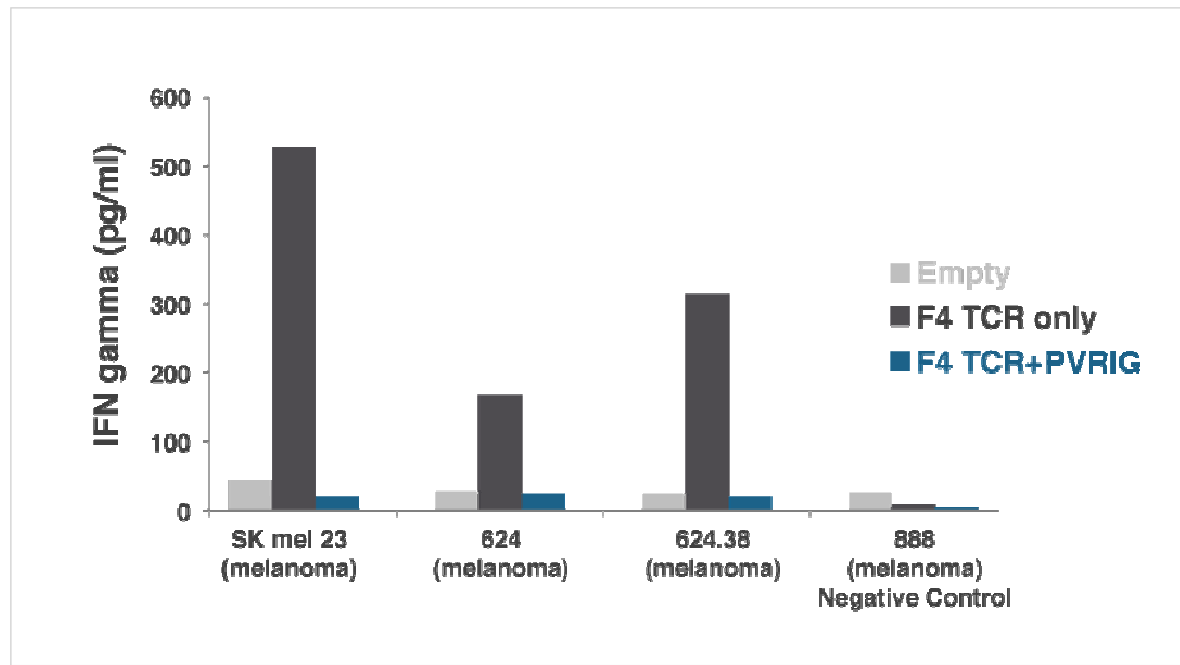
FACS DATA FROM HUMAN TUMORS



mRNA DATA FROM PYMT-MMTV TUMORS

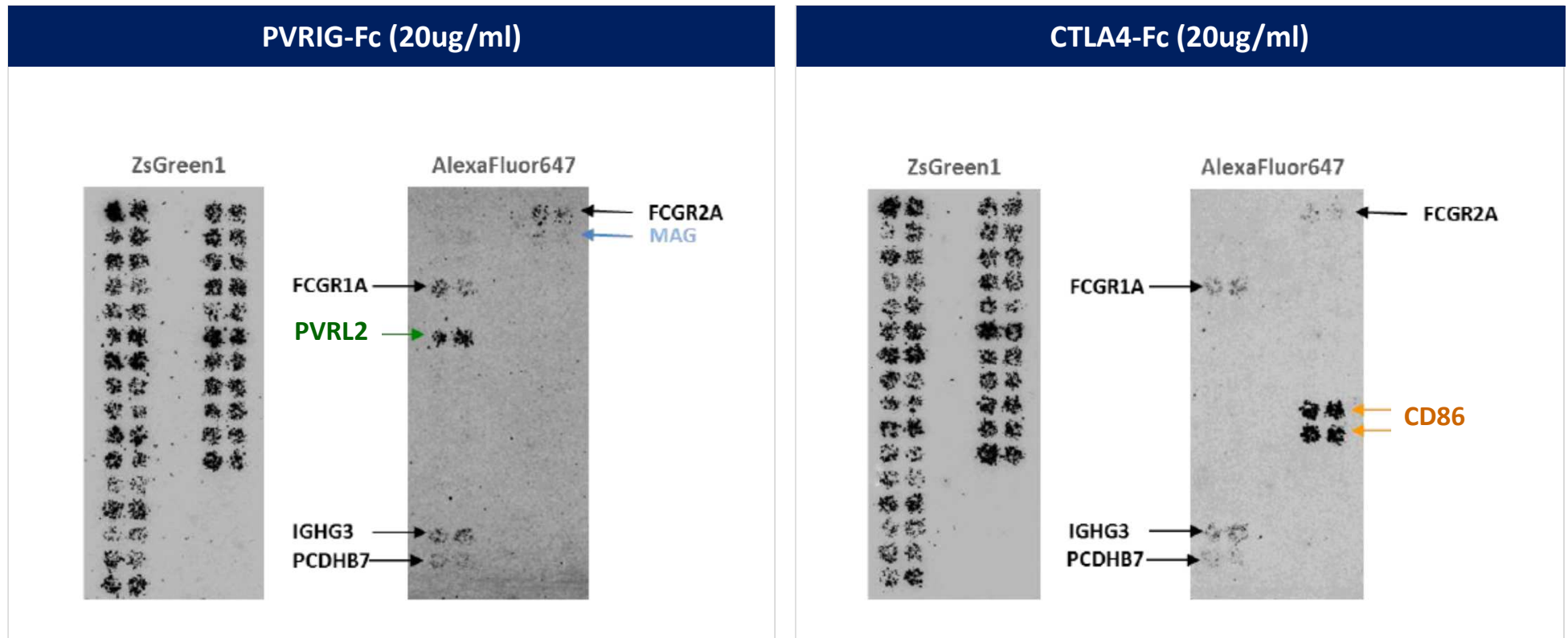


INHIBITION OF T-CELL ACTIVATION BY PVRIG OVEREXPRESSION



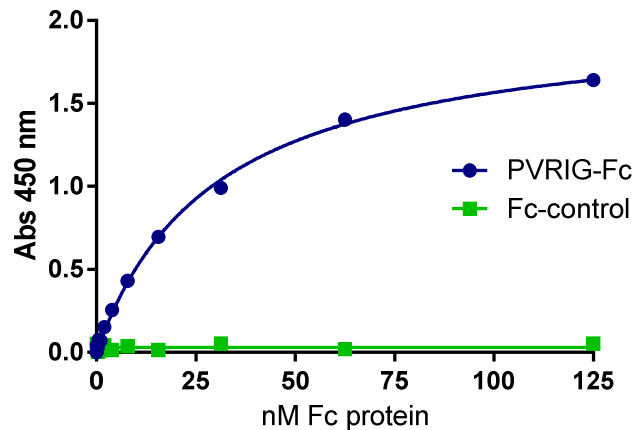
IDENTIFICATION OF PVRL2 AS THE LIGAND FOR PVRIG

RETROGENIX CELL MICROARRAY

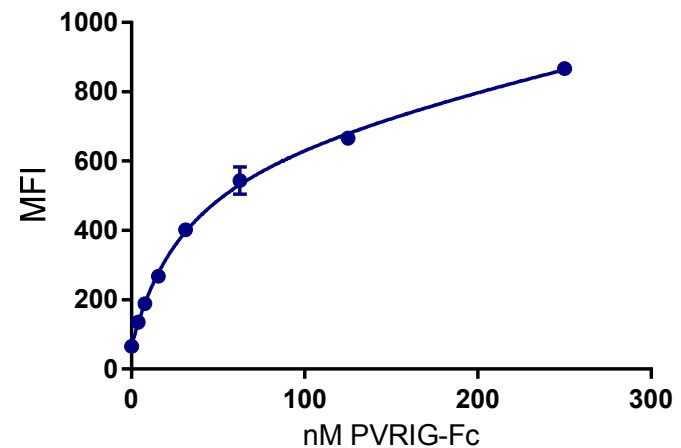


CONFIRMATION OF PVRIG (CD112R) BINDING TO PVRL2 (CD112)

PVRIG-Fc binding to PVRL2 (ELISA)

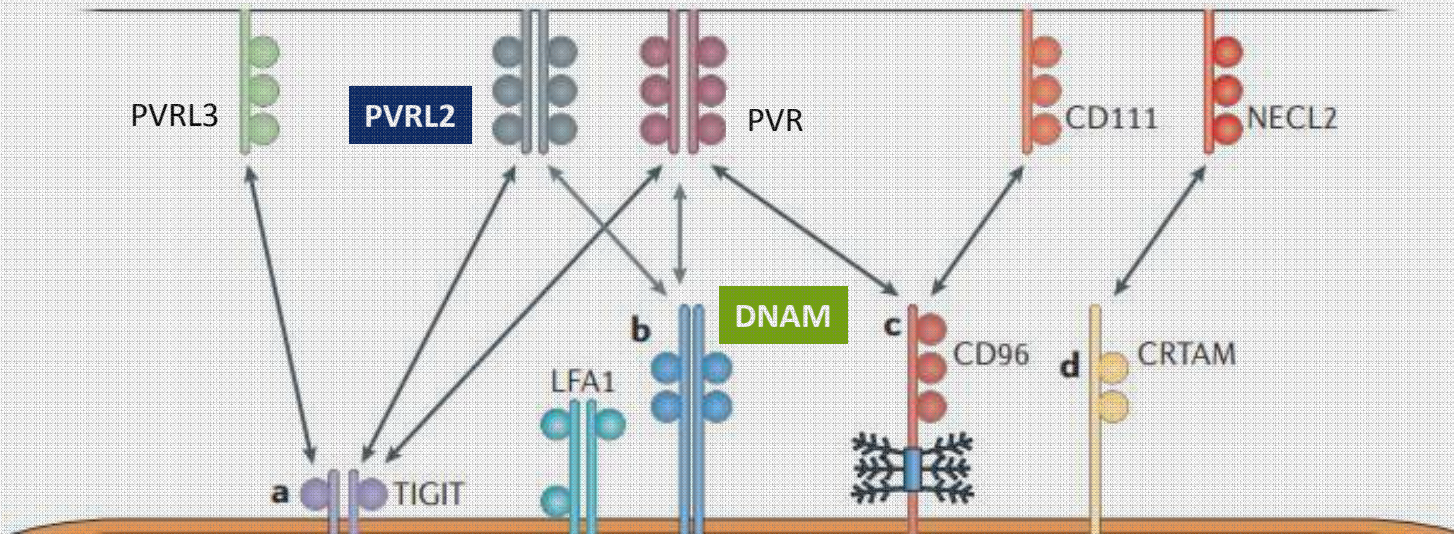


PVRIG-Fc binding to PVRL2 expressing HEK293 cells

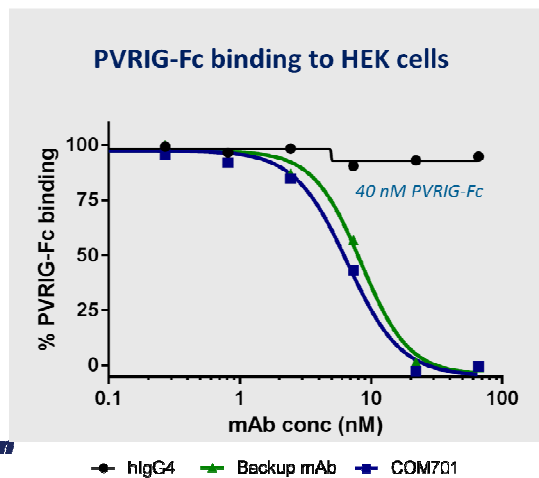
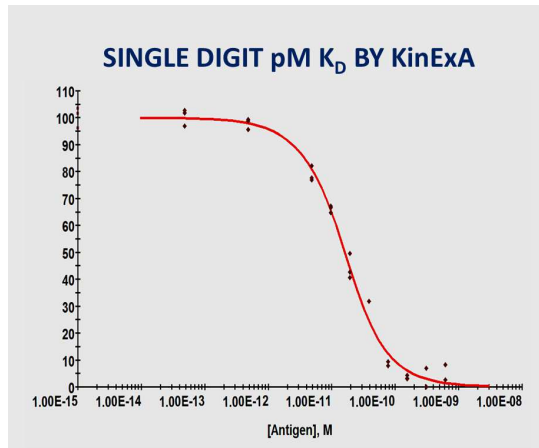


Specific binding of PVRL2 to receptor PVRIG was confirmed by SPR, ELISA and FACS

PVRL2 IS A LIGAND IN THE DNAM-1/TIGIT IMMUNE CHECKPOINT AXIS

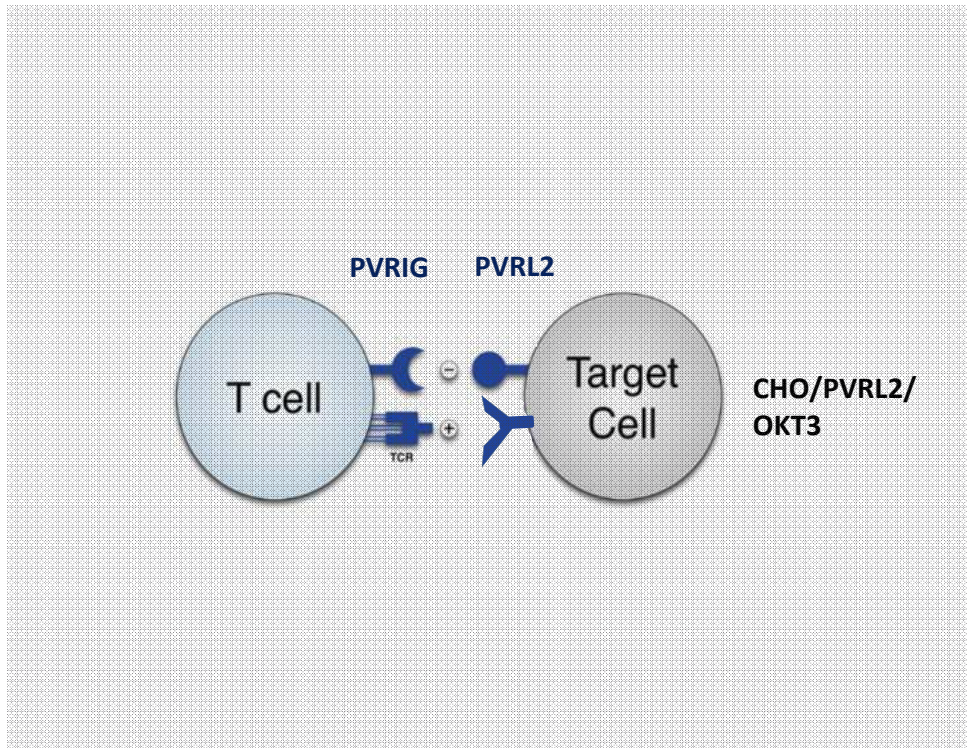
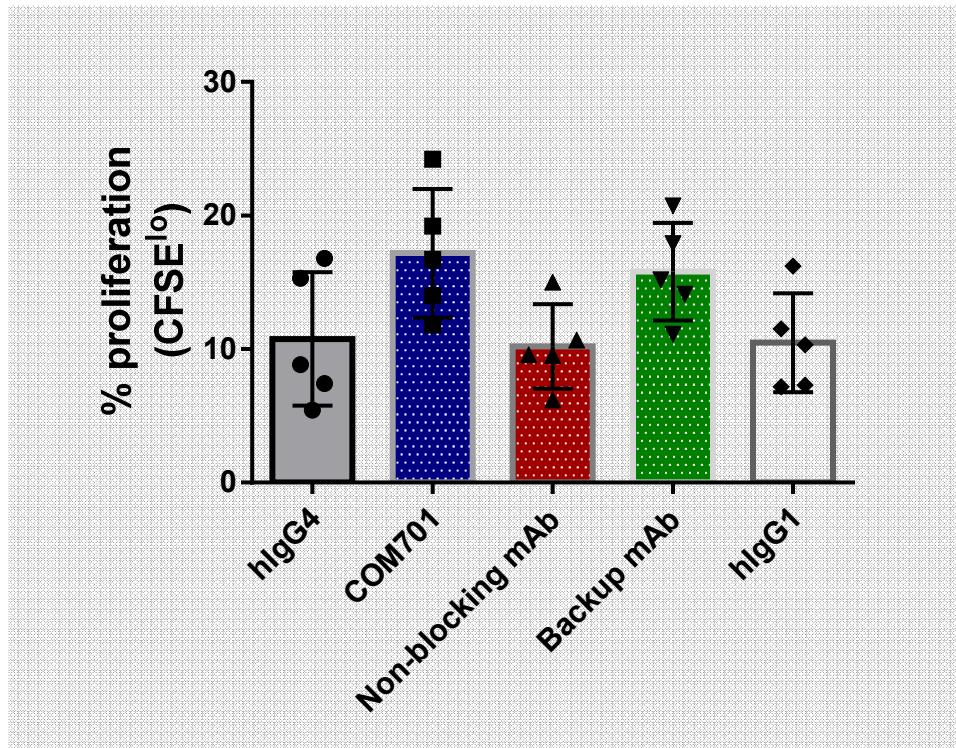


DEVELOPMENT OF COM701: A HIGH AFFINITY PVRIG ANTAGONIST

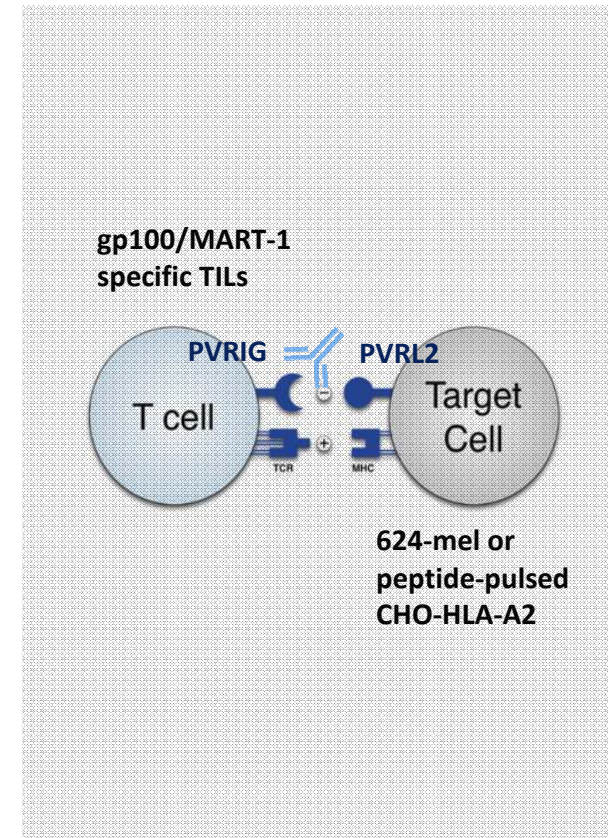
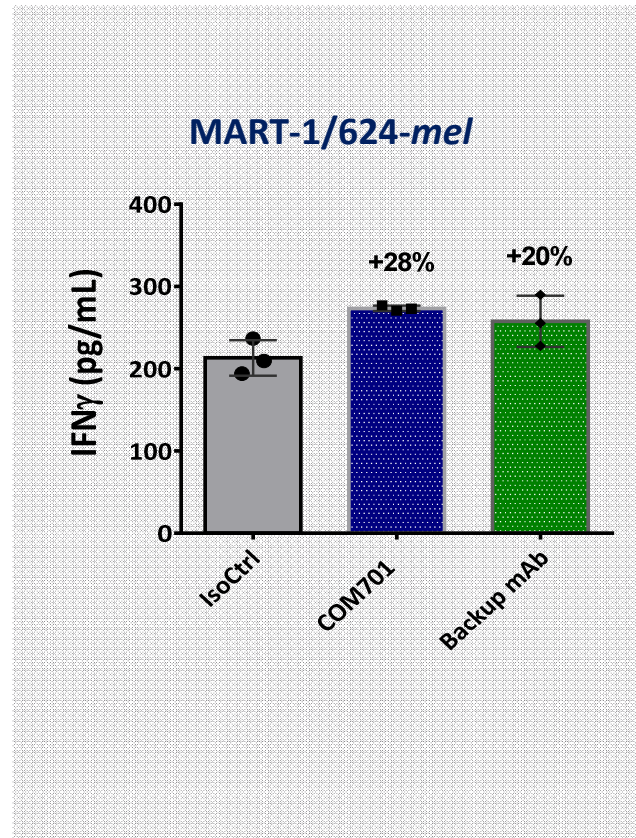
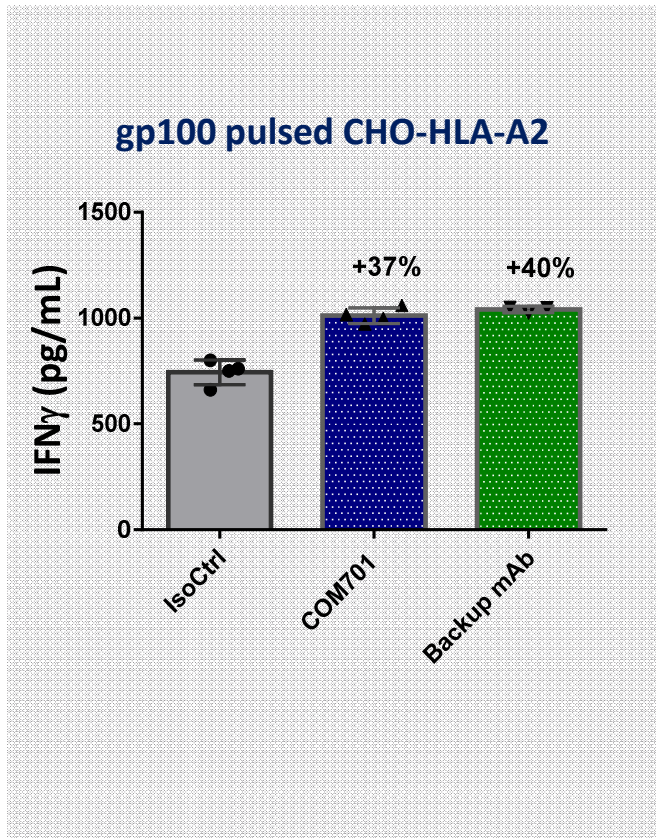


- Human phage display and standard hybridoma
- Antibodies screened for:
 - High affinity ($K_D < 1\text{nM}$)
 - Ability to block PVRIG/PVRL2 binding
 - In vitro enhancement of T-cell activation
- COM701 selected as therapeutic lead
 - IND anticipated in 2017

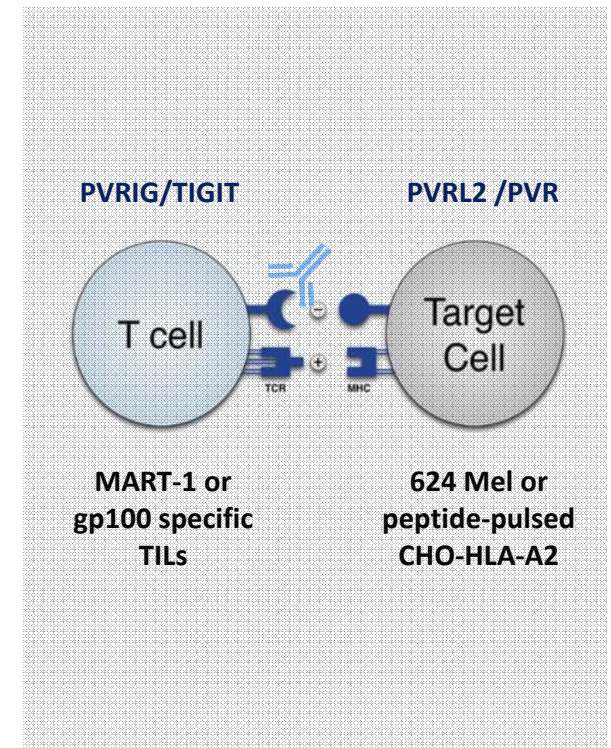
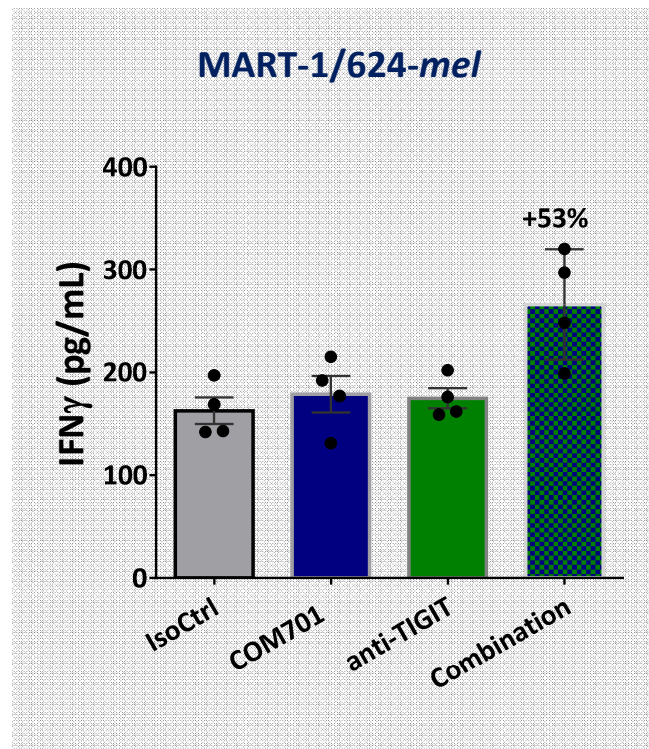
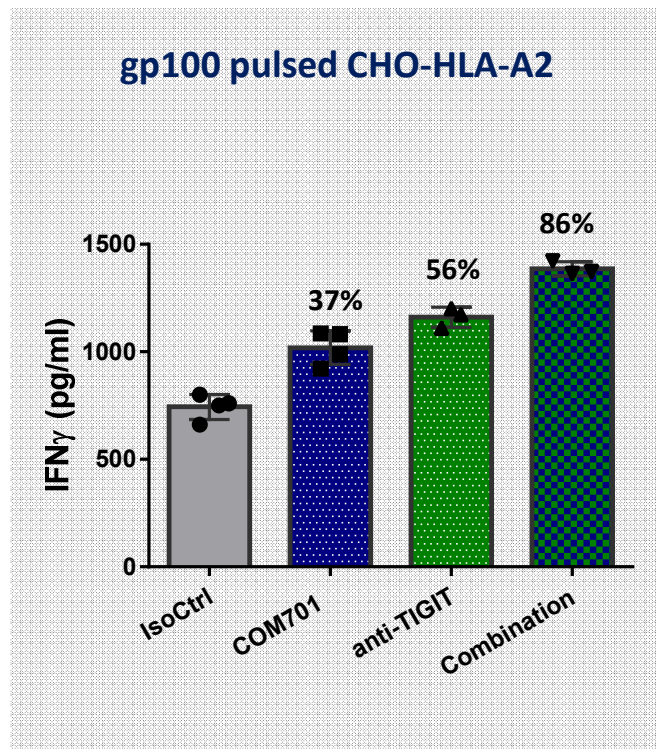
ANTAGONIST PVRIG ANTIBODIES INCREASE CD4⁺ T-CELL PROLIFERATION



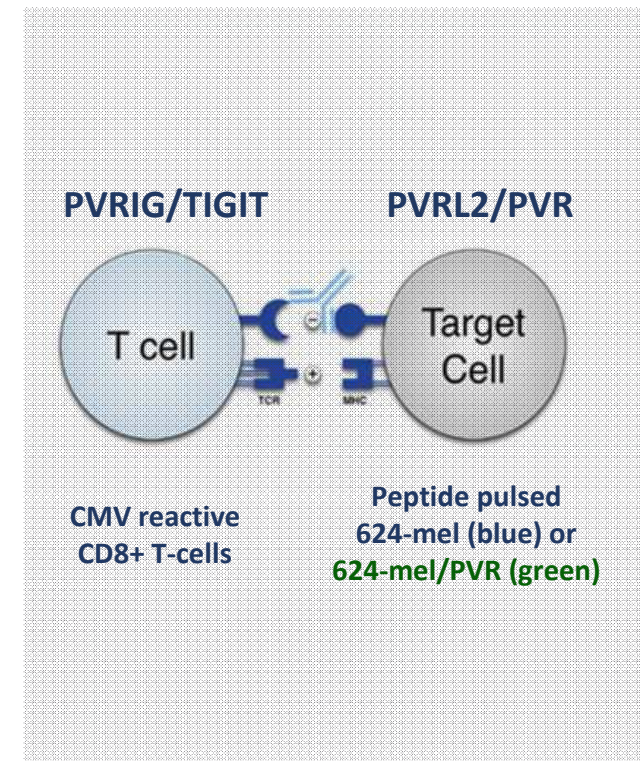
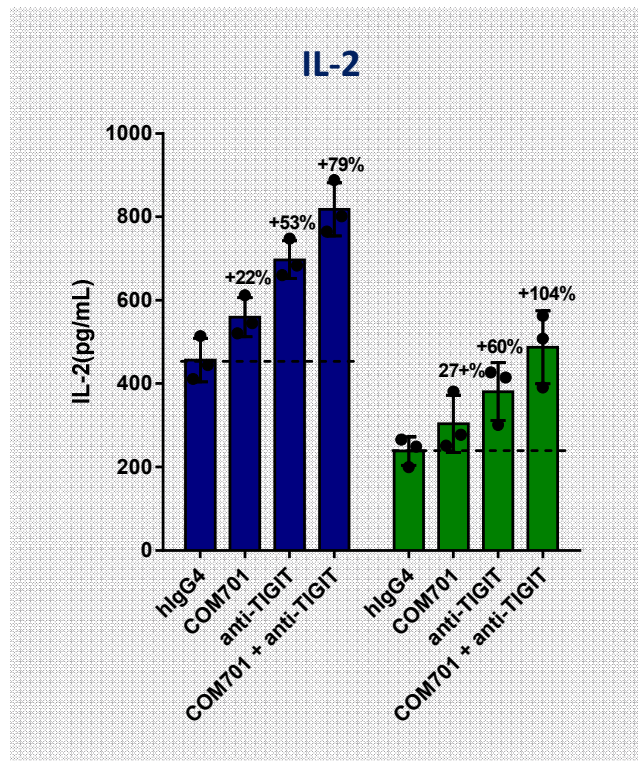
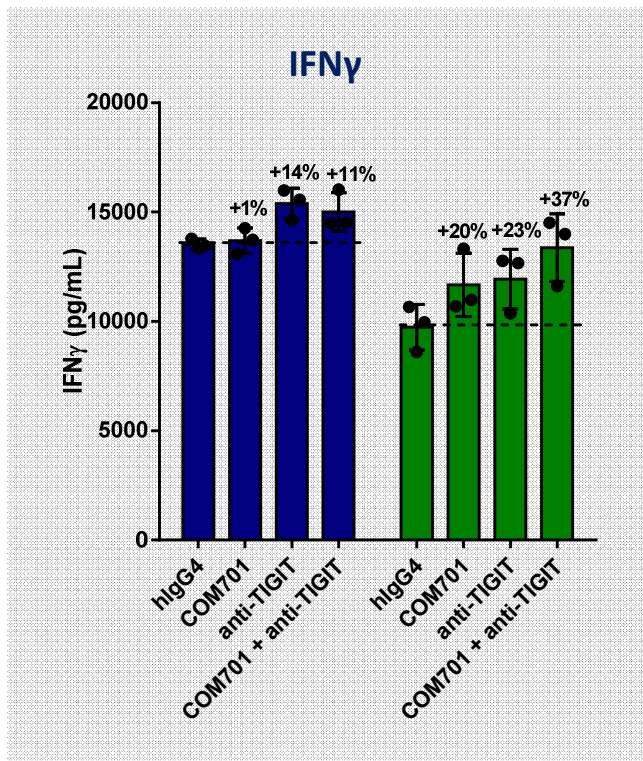
ANTI-PVRIG BLOCKING ANTIBODIES **ENHANCE TIL ACTIVATION**



COMBINING PVRIG AND TIGIT BLOCKADE **INCREASES TIL** **ACTIVATION**



COMBINING PVRIG AND TIGIT BLOCKADE RESULTS IN ENHANCED ACTIVATION OF CMV REACTIVE CD8⁺ CELLS

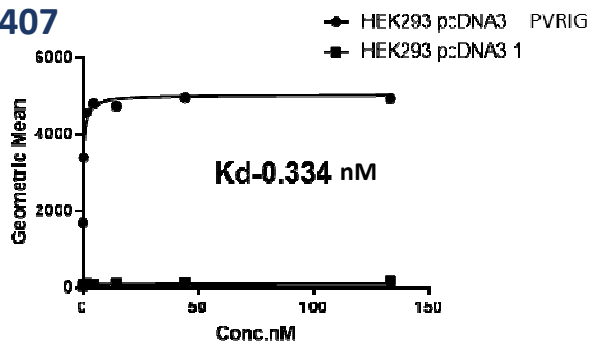


GENERATION OF HIGH AFFINITY ANTI-mPVRIG ANTIBODIES FOR IN VIVO TESTING

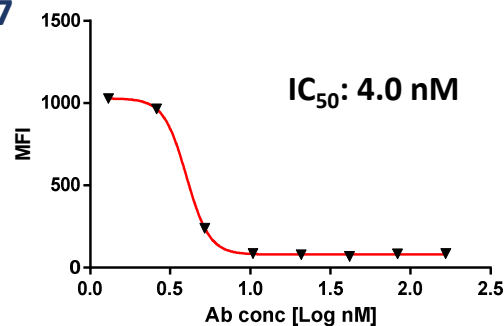
Rat anti-mPVRIG
antibodies generated
through DNA
immunization

High affinity
mPVRIG/mPVRL2
blockers selected for
in vivo testing

AB-407



AB-407



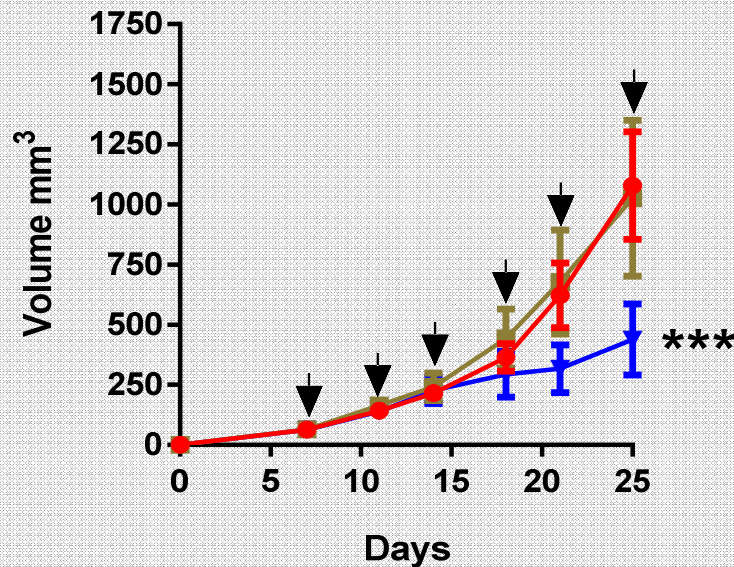
Blockade of mPVRIG-Fc binding to B16-F10 cells

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

CT26
syngeneic
model

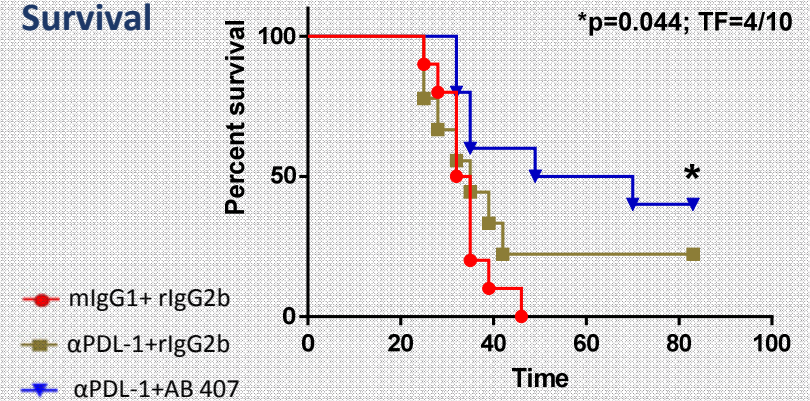
Tumor growth

***p=0.0005; TGI=56%

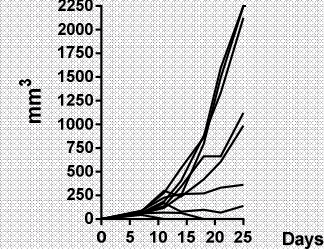


Survival

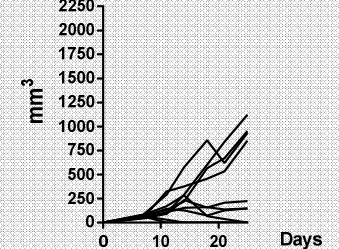
*p=0.044; TF=4/10



αPDL-1+rlgG2b



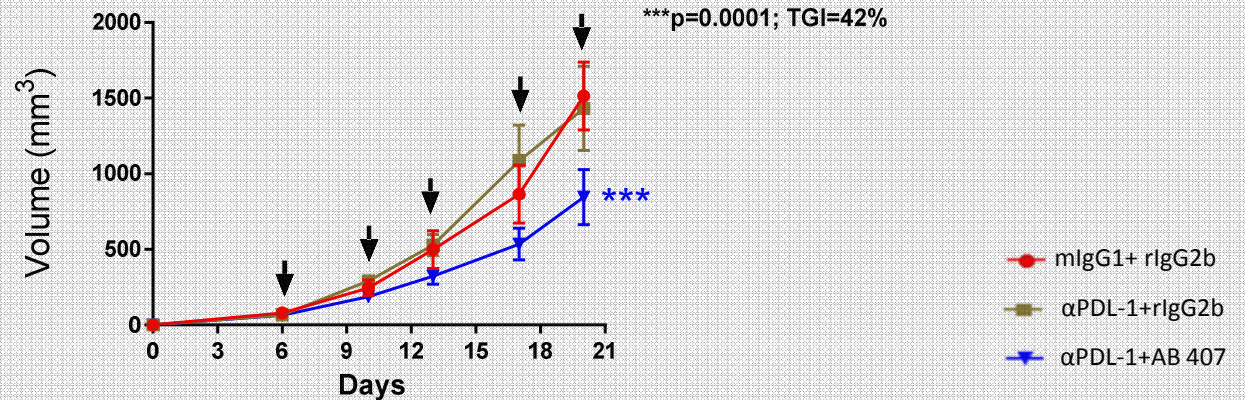
αPDL-1+Ab 407



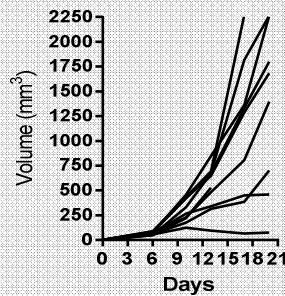
PVRIG BLOCKING ANTIBODIES REDUCE TUMOR GROWTH IN COMBINATION WITH PD1 PATHWAY BLOCKADE

B16-gp100-
H2D^b
syngeneic
model

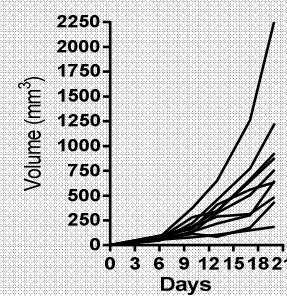
Tumor growth



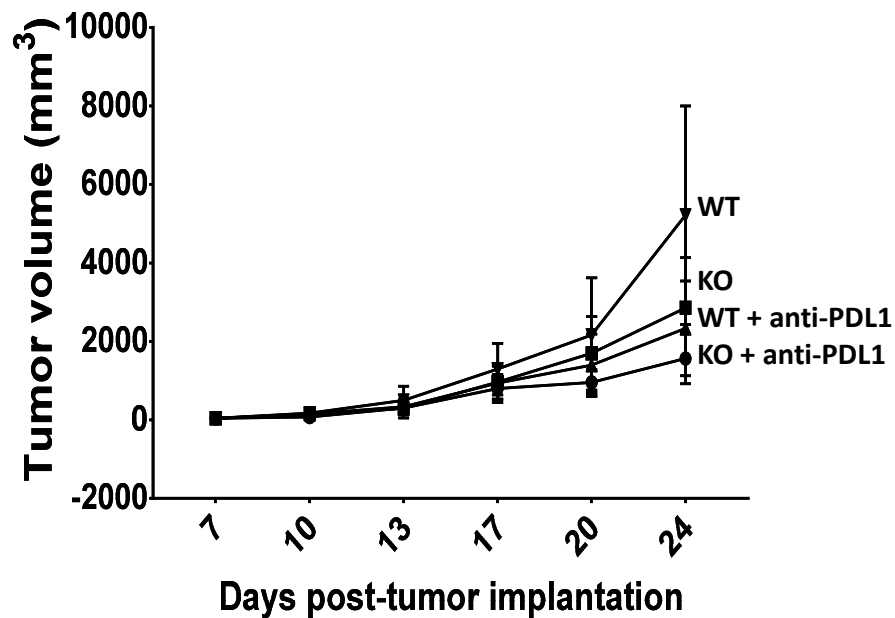
αPDL-1+rIgG2b



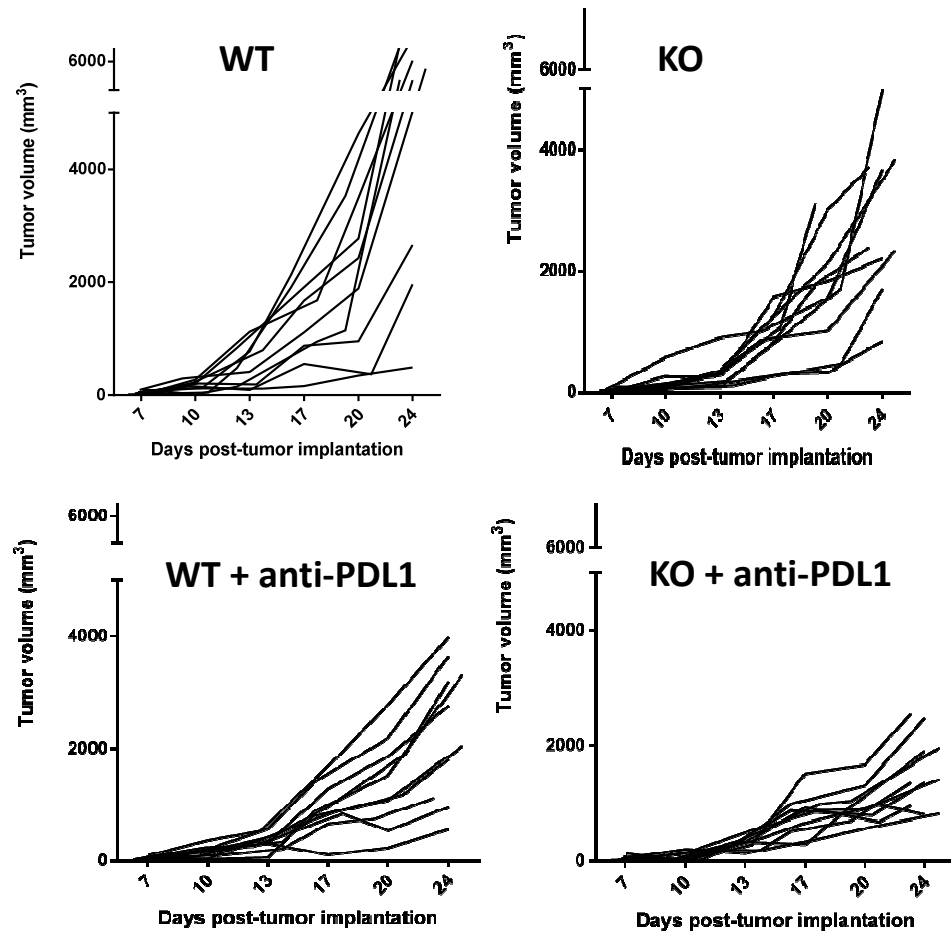
αPDL-1+Ab 407



MC38 TUMOR GROWTH IS REDUCED IN PVRIG KNOCKOUT MICE



Ganguly and Pardoll, Johns Hopkins Univ.



SUMMARY

- PVRIG was identified as a novel immune checkpoint on T cells that binds the DNAM-1 ligand PVRL2
- Antibody antagonism of PVRIG enhances T-cell activation in vitro, and in combination with PD-L1 inhibition results in decreased tumor growth in vivo
- Compugen has generated a high affinity PVRIG antagonistic antibody, COM701, that is currently in preclinical development
- The combined data demonstrates the utility of targeting PVRIG in addition to other B7 family checkpoints for the treatment of cancer

**PLEASE VISIT POSTER 450 FOR MORE
INFORMATION**

ACKNOWLEDGEMENTS

COMPUGEN	Johns Hopkins University
<ul style="list-style-type: none">• Ofer Levy• Chris Chan• Eran Ophir• Lance Stapleton• Ilan Vaknin• Ling Leung• Sandeep Kumar• Meir Azulay• Zoya Alteber• Kathryn Logronio	<ul style="list-style-type: none">• Sudipto Ganguly• Benjamin Murter• Xiaoyu Pan• Charles Drake• Drew Pardoll
<ul style="list-style-type: none">• Tal Fridman-Kfir• Sara Whelan• Yakir Vaknin• Maya Kotturi• Einav Safyon• Kyle Hansen• Ran Salomon• Shirley Greenwald• Hsin-Yuan Cheng• Lennard Dalit	Bar-Ilan University <ul style="list-style-type: none">• Cyrille Cohen
<ul style="list-style-type: none">• Liat Dassa• Amir Toporik• Gady Cojocaru• Ayelet Chajut• Arthur Machlenkin• Spencer Liang• Yossi Gozlan• Mark White• Zurit Levine	Tel Aviv University <ul style="list-style-type: none">• Neta Erez• Lilach Abramovitz