# COMPUTATIONAL DISCOVERY OF NOVEL IMMUNE CHECKPOINTS

Yair Benita, Amit Novik, Gady Cojocaru, Itamar Borukhov, Assaf Wool, Yossef Kliger, Tomer Zekharya, Zurit Levine, Sergey Nemzer, Eran Ophir, Meir Azulay,
Maya Kotturi, Sudipto Ganguly*, Drew M Pardol*, Ofer Levy, Amir Toporik

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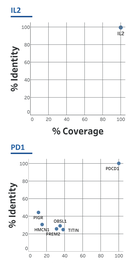
## 1 Computational Discovery of Novel Immune Checkpoints

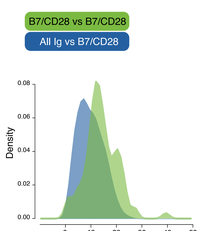
### A. The Concept

Immune genes often have no sequence similarity to any other gene within the organism (have no paralogs).
IL2 and PD-1, for instance, do not resemble any other human gene by sequence.

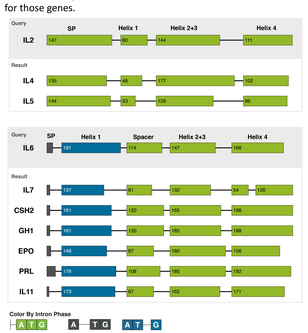



Sequence similarity is a limited approach for detection of novel immune genes.

Known B7/CD28 proteins have low sequence similarity to one another. A similar squence similarity can be observed with any Ig protein

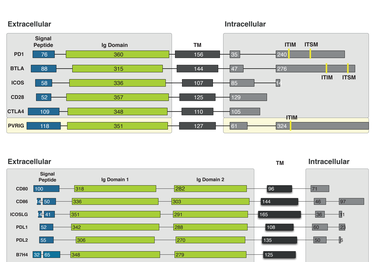



Assumptions: if cytokines, for instance, evolved from divergence there must be a signature in the genome indicative of similarity. We found that gene structure was more conserved than sequence for those genes.

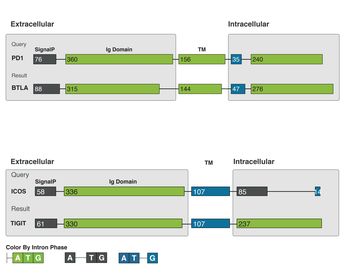



### Discovery of Novel Immune Checkpoints

The extracellular domains of known B7/CD28 proteins have the following typical gene structure: gene




Based on this gene structure, a BLAST-like algorithm identified BTLA as closest to PD-1 and TIGIT as closest to ICOS. This algorithm identified TIGIT in 2009 (Proc Natl Acad Sci U S A. 2009 Oct 20; 106(42)7858–17863)

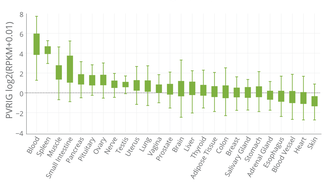



* Johns Hopkins University School of Medicine, Baltimore, MD, USA

## 2 Computational Characterization of Immune Checkpoint for Cancer Immunotherapy

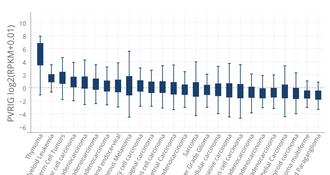
### Normal Tissues
Highly enriched in immune tissues compared to solid tissues

**In Normal Tissues PVRIG Is Highly Expressed in Blood & Spleen**



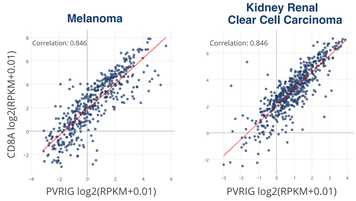

### Tumor Expression
Expressed in cancer

**In Cancer PVRIG Is Expressed in Multiple Solid Tumors**



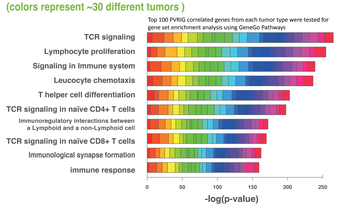

### Tumor Correlation
PVRIG Is Correlated with immune infiltrating T cells

**PVRIG Correlation with CD8**



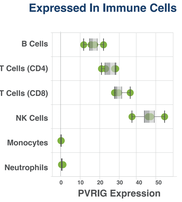

### Tumor Correlation
Most Correlated PVRIG Genes in Cancer Are T Cell Genes

**PVRIG expression signature in cancer is associated with lymphocytes**
(colors represent ~30 different tumors )

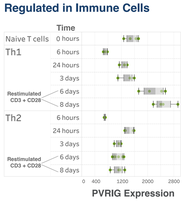



### Immune Cells
PVRIG Is Expressed and regulated in immune subsets

**Expressed In Immune Cells**

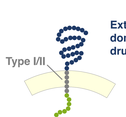



**Regulated in Immune Cells**




### Druggable
PVRIG Has Favorable Drug Features

**Single pass membrane protein**
**Favorable toxicity profile**
**Has mouse ortholog with similar expression profile**

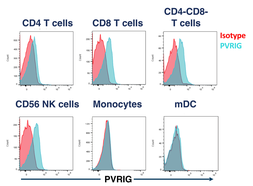



## 3 Validation of Novel Immune Checkpoint for Cancer Immunotherapy

**TARGET EXPRESSION**

RNA | Protein

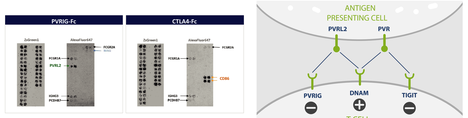
In Immune Cells From Tumors




PVPIG protein is expressed in immune cells

**COUNTERPART IDENTIFICATION**

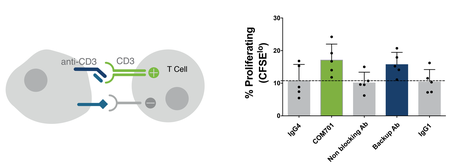
Cell Binding Assays | Screening Technologies




Identifying PVRL2 as the PVIRG counterpart, suggests PVRIG in the TIGIT Pathway

**FUNCTIONAL**

In-Vitro Functional Inhibition Assays




Antagonist PVRIG Antibodies Increase CD4+ T cell Proliferation

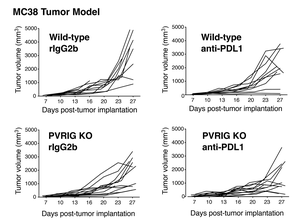
**TUMOR MODELS**

WT | KO

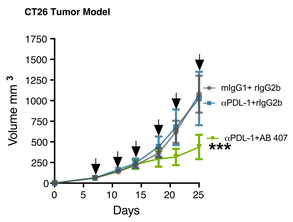
Inhibits T Cells in-vivo

Anti-tumor immunity in KO/mAb Blockade

PVRIG Knockout Mice Treated with anti-PDL1 Show Tumor Growth Inhibition Compared To Wild Type




PVRIG Blocking Antibody Reduces Tumor Growth in Combination with Anti-PDL1




*For more on PVRIG, please see our additional poster 581 / 15:*
*Discovery and development of COM701, a therapeutic antibody targeting the novel immune checkpoint PVRIG*