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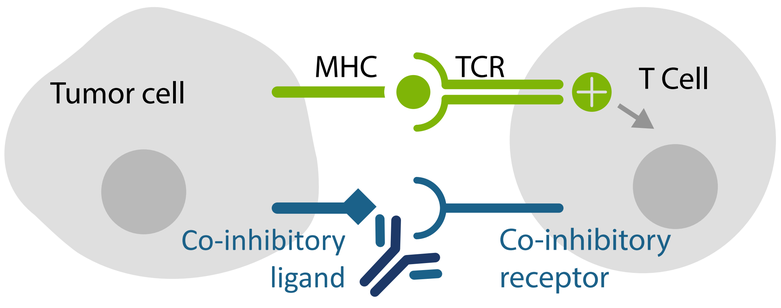
COMPUTATIONAL DISCOVERY OF NOVEL IMMUNE CHECKPOINTS

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1 Computational Discovery of Novel Immune Checkpoints

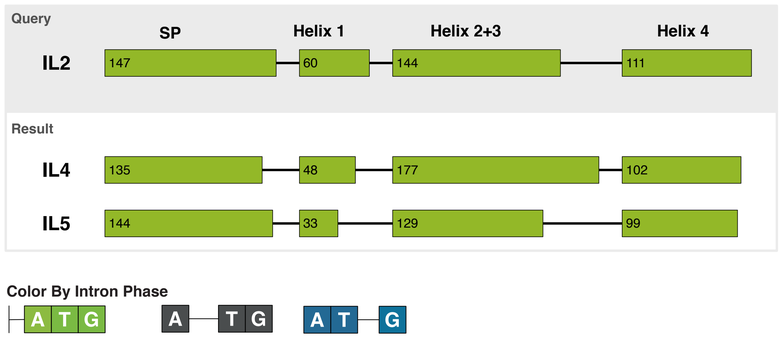
Introduction

The immune system constantly identifies and destroys malignant cells. Some tumors evade the immune system by expressing co-inhibitory ligands that inhibit T cells. Blocking the co-inhibitory signal allows the T cells to attack the tumor.
Checkpoint blockade is a breakthrough approach to cancer therapy with impressive clinical benefits. However, the majority of cancer patients still do not respond and new targets, target combinations and drug modalities are needed.



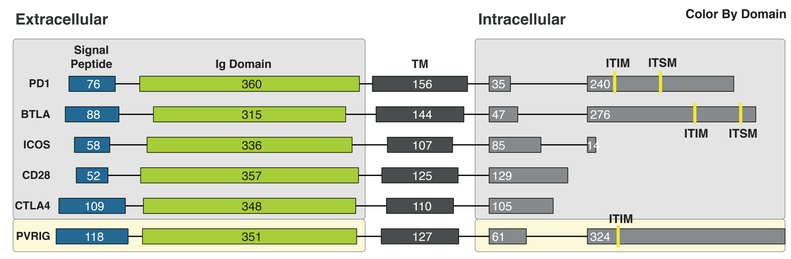
A. The Concept

Immune genes often have no sequence similarity to any other gene within the organism (have no paralogs). For instance, IL2 and PD-1, do not resemble any other human gene by sequence.
If immune related genes, such as cytokines, that have no paralogs by sequence similarity evolved from divergence, there must be a signature in the genome indicative of their related evolutionary origins. We found that gene structure was more conserved than seqeunce for those genes.

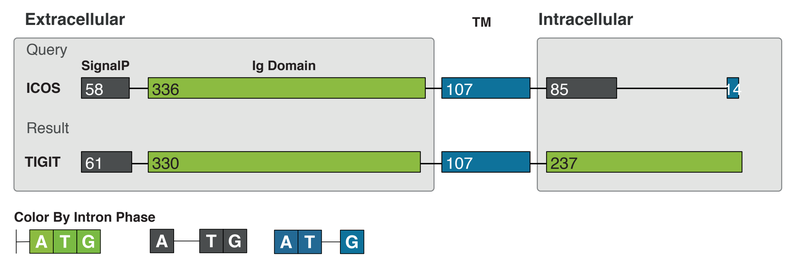


B. Discovery of Novel Immune Checkpoints

Known B7/CD28 proteins have the following typical gene structure:



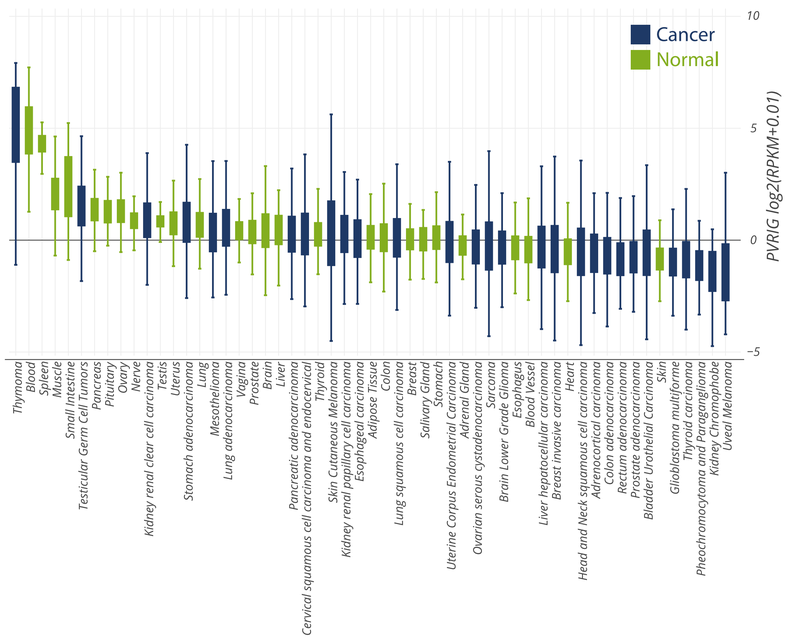
Based on this gene structure, a BLAST-like algorihm identified BTLA as closest to PD-1 and TIGIT as closest to ICOS. The TIGIT finding was published in 2009 (Proc Natl Acad USA. 2009 Oct 20; 106(42) 7858-7863).



2 Computational Characterization of Immune Checkpoint for Cancer Immunotherapy

Normal and Cancer Tissues

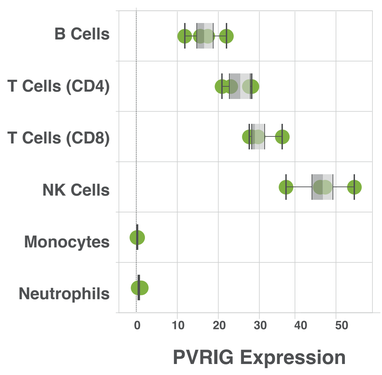
Highly enriched in normal immune tissues vs normal solid tissues and expressed in multiple solid tumor types



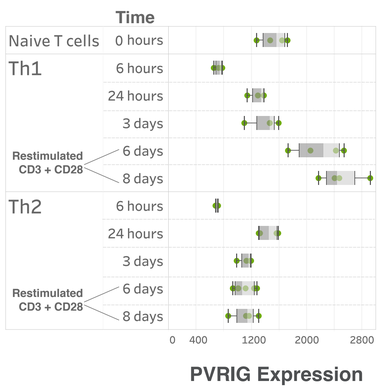
Immune Cells

PVRIG Is expressed and regulated in immune subsets

Expressed In Immune Cells



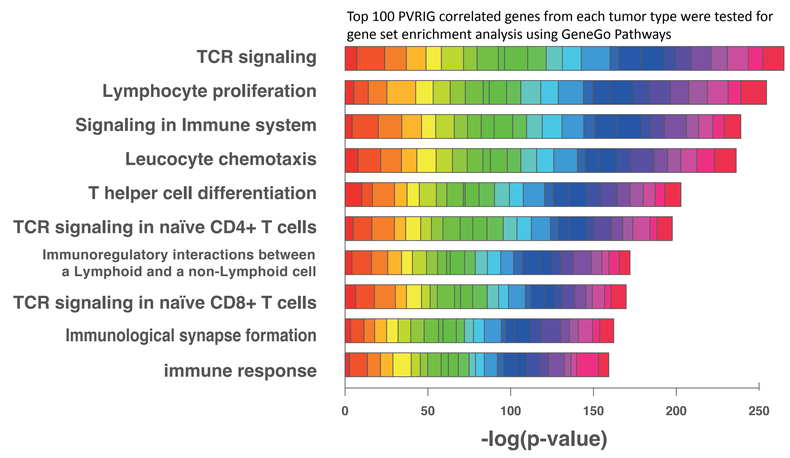
Regulated in Immune Cells



Tumor Correlation

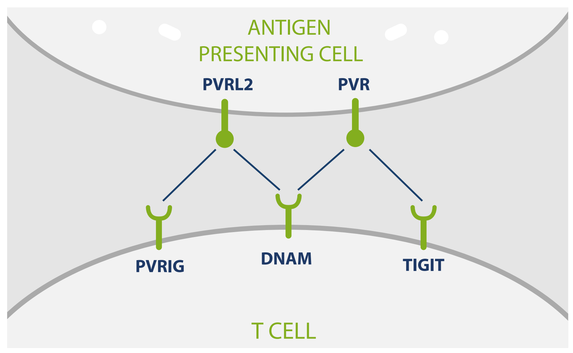
Most correlated PVRIG genes in cancer are T cell genes

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

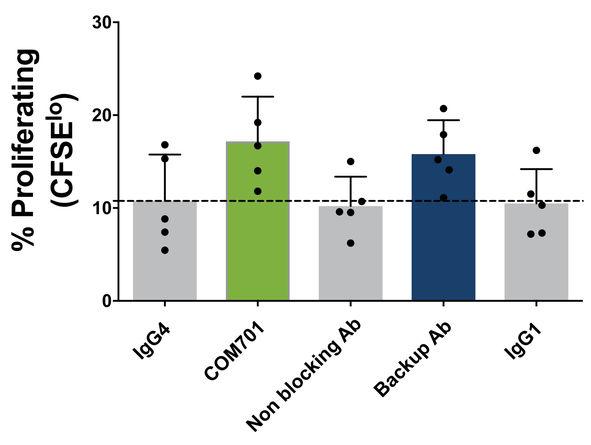


3 Validation of a Novel Immune Checkpoint for Cancer Immunotherapy

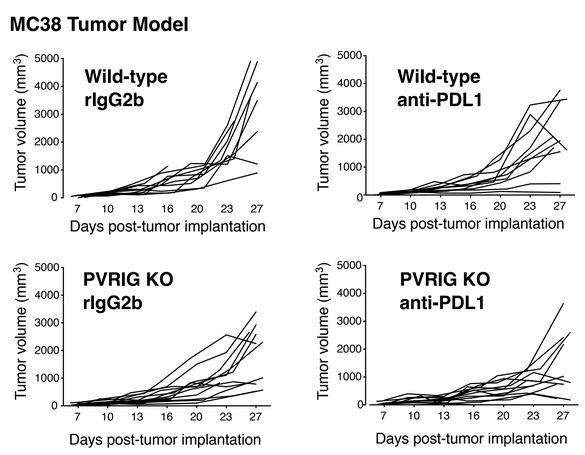
Identifying PVRL2 as the PVRIG Counterpart Suggests PVRIG is in the TIGIT Pathway



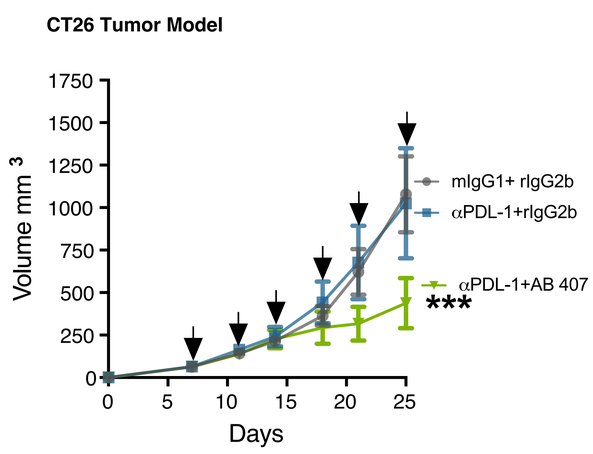
Antagonist PVRIG Antibodies Increase CD4+ T cell Proliferation *in-vitro*



PVRIG Knockout Mice Treated with anti-PDL1 Show Tumor Growth Inhibitition Compared to Wild Type



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



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