**Introduction**

- **Background:** While antibody blockade of the CTLA4 and PD1 pathways has emerged as an effective treatment modality for cancer, the majority of patients do not derive long term benefit, suggesting a need for targeting of additional immune checkpoints. Employing our unique computational algorithms to define new members of the B7/CD28 family we identified PVRIG, which is expressed by multiple subsets of T and NK cells. We report here its expression pattern, functional characterization, and anti-tumor activity of blocking antibodies targeting this molecule.

- **Materials and Methods:** Using Compugen’s Predictive Discovery platform we identified PVRIG as a potential novel immune checkpoint, after which a retroviral cell screening library was used to identify new members of the B7/CD28 family. We determined binding to PVRL2, confirmed PVRIG/PVRL2 interaction, and generated a panel of high affinity human antibodies with the ability to block interaction of PVRIG with PVRL2. Antibody approaches. Antibodies against the human protein were screened for their ability to enhance T-cell activation in vitro, while antibodies targeting the mouse orthologue were assessed in vivo for effects on tumor growth inhibition in syngeneic models.

**PVRIG FUNCTIONAL GENE STRUCTURE MATCHES KNOWN IMMUNE CHECKPOINT RECEPTORS**

- **PVRIG Expression on Naive PBMC Subsets:**
  - **B cells**
  - **CD56 bright NK cells**
  - **CD56 dim NK cells**
  - **CD8 T cells**
  - **γδ T-cells**

- **PVRIG Expression Induced Following T-Cell Activation and Elevated on TEmb and TEm Cells:**
  - **CMV Activated CD8 Cells**
  - **CD4**
  - **CD8**

**PVRIG Blocking Antibodies Enhance TIL Activation**

- **Anti-PVRIG Blocking Antibodies Enhance TIL Activation**

**Summary**

- **Results:** A PVRIG-Fc fusion protein was found to bind PVRL2, with binding specificity confirmed both by ELISA and flow cytometry analysis. PVRIG demonstrated unique expression kinetics upon T-cell activation, with detection of the target on memory T-cells, as well as on NK cells and γδ T cells. A panel of high affinity human antibodies with the ability to block interaction of PVRIG with PVRL2 were generated, which when tested in vitro were shown to enhance activation of both primary CD4+ and tumor-derived CD8+ T-cells through a PVRL2-dependent mechanism. The lead antibody, COM-701, is currently in preclinical development. The development of a high affinity antagonistic antibody, COM-701, that is currently in preclinical testing with additional immune checkpoint inhibitors, as well as in PVRIG knockout mice, is ongoing. Data demonstrates the utility of targeting PVRIG in addition to other B7 family checkpoints for the treatment of cancer.