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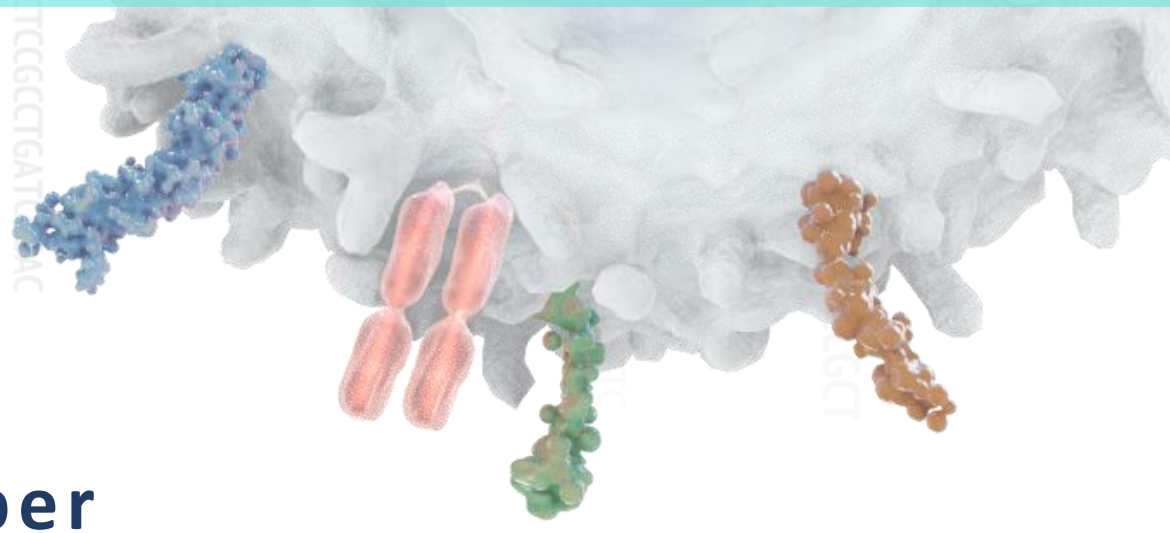


# THE TIGIT PATHWAY

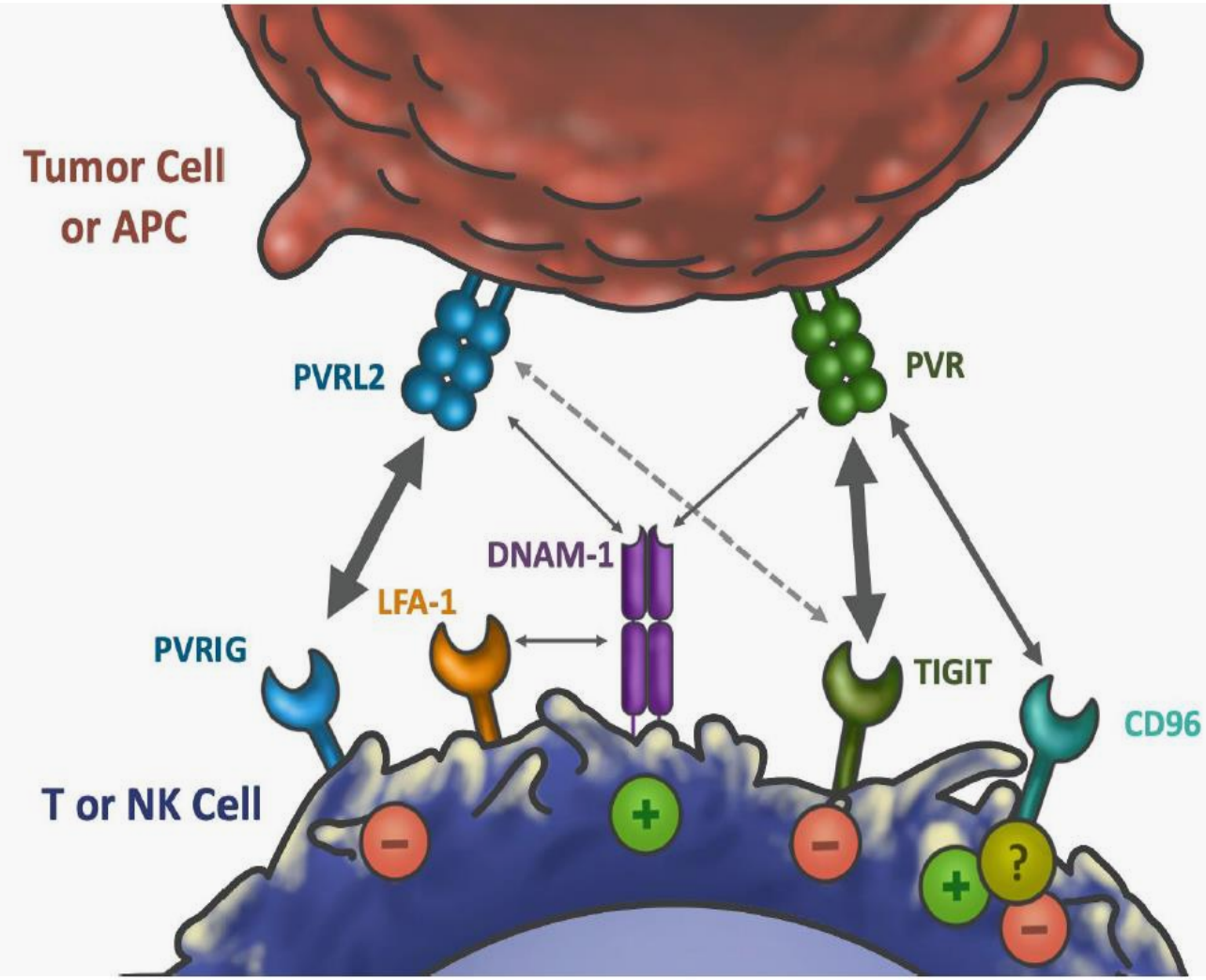
# PVRIG, a Novel Pathway Member

Targets for Cancer Immunotherapy: A Deep Dive

Eran Ophir, VP Research & Drug Discovery

June 2021

# The DNAM-1 Axis




- DNAM-1 axis plays an essential role in tumor immunology
- PVRIG binds PVRL2 as a functional ligand (TIGIT has a low affinity for PVRL2)

⬇

- DNAM-1 axis – two parallel dominant complementary inhibitory pathways (PVRIG & TIGIT/CD96?)
- TIGIT and PVRIG deliver direct inhibitory signal into T and NK cells
- TIGIT/PVRIG has higher affinity to PVR/PVRL2 than DNAM-1 (decoy effect)

Alteber *et al.* Cancer Discov. 2021



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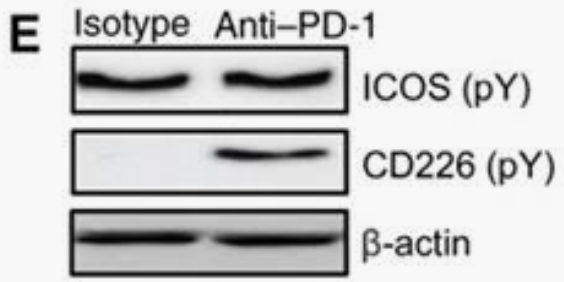
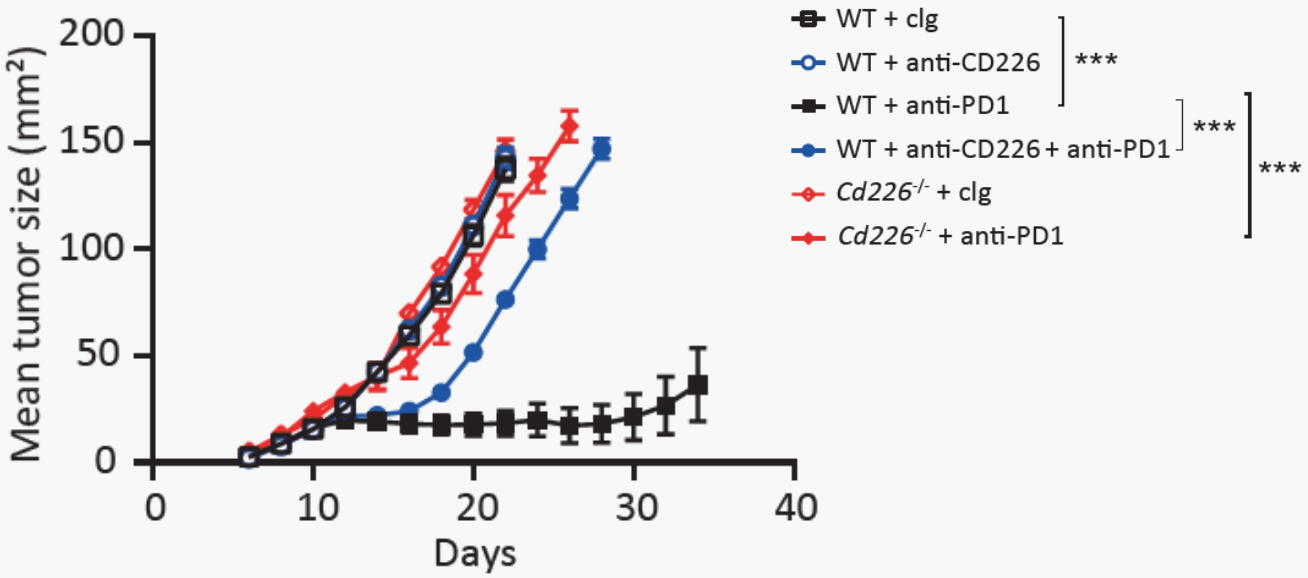
# DNAM-1 Intersects with the PD-1 Pathway and is Required for In-vivo Response to PD-1 Blockade

## PD-1 inhibition blocks DNAM-1 (CD226) dephosphorylation and inactivation




Wang et al., Science Immunology, 2018

## DNAM-1 KO or inhibition reverses a-PD-1 tumor growth inhibition




Weulersee et al. immunity 2019



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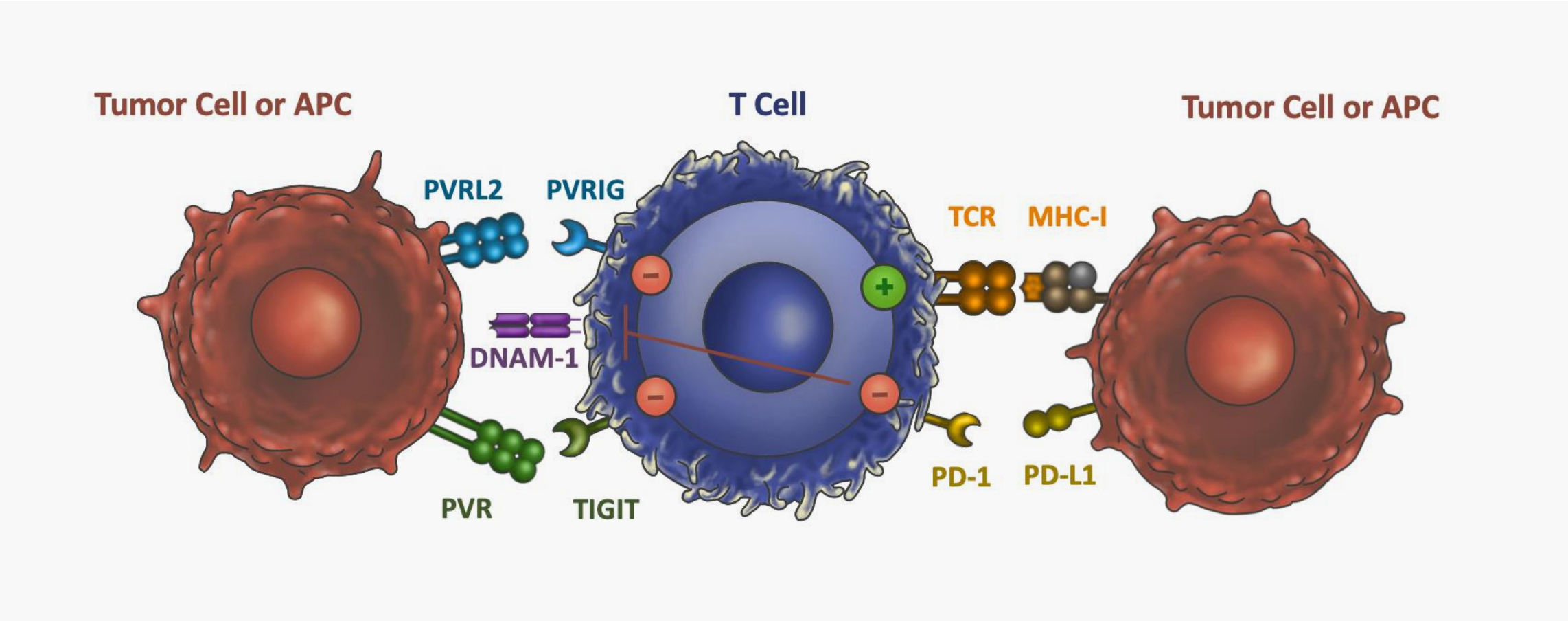
# PVRIG, TIGIT and PD-1 as Players in the DNAM-1 Axis




Alteber *et al.* Cancer Discov. 2021



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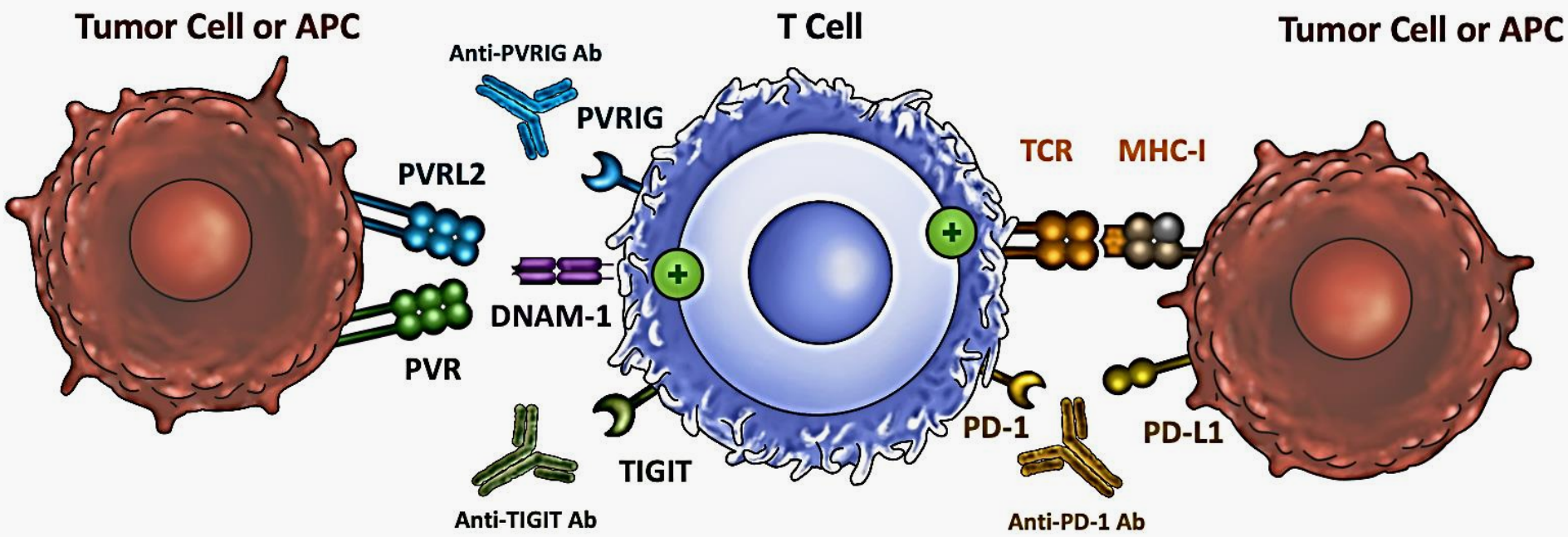
# Potential Intersection Between PVRIG/TIGIT and PD-1 Pathways Support Combination Approach to Overcome Immunotherapy Resistance




Alteber *et al.* Cancer Discov. 2021

**Different tumor types may respond to different combinations depending on dominance of the pathways**



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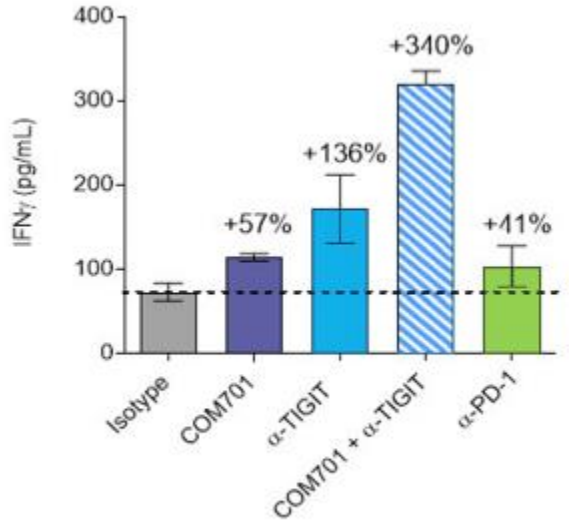
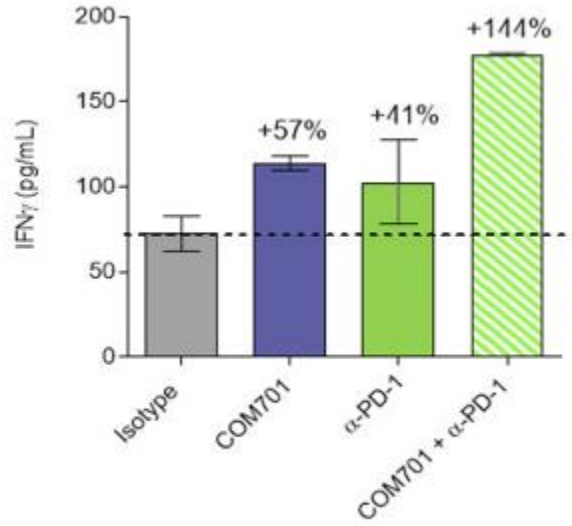
# Synergistic T Cell Activation With PVRIG, PD-1 and TIGIT Blockade

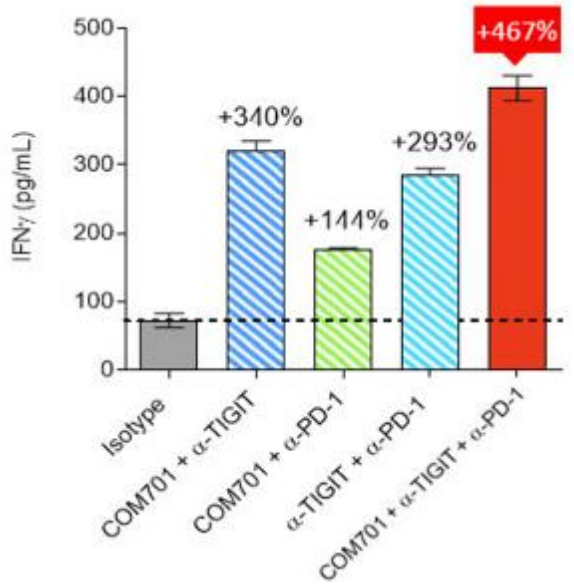
## COM701 +/- anti-TIGIT




## COM701 +/- anti-PD-1




## Triple combination




COM701 –PVRIG blocking antibody

Whelan, et al., Cancer Immunol Res. 2019



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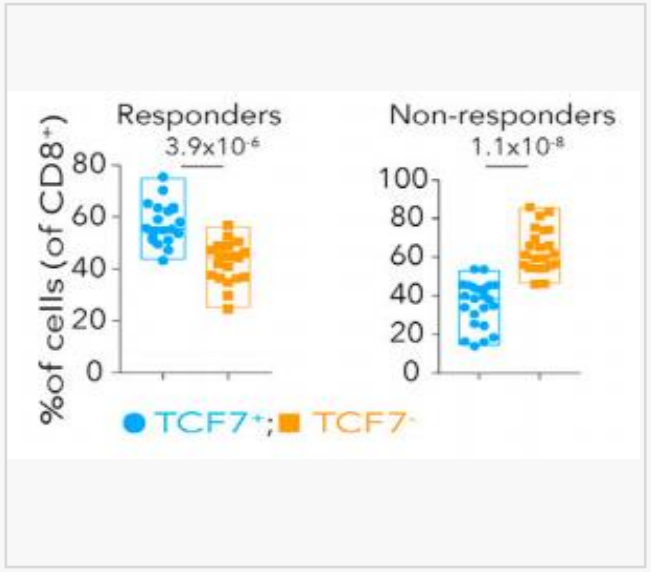
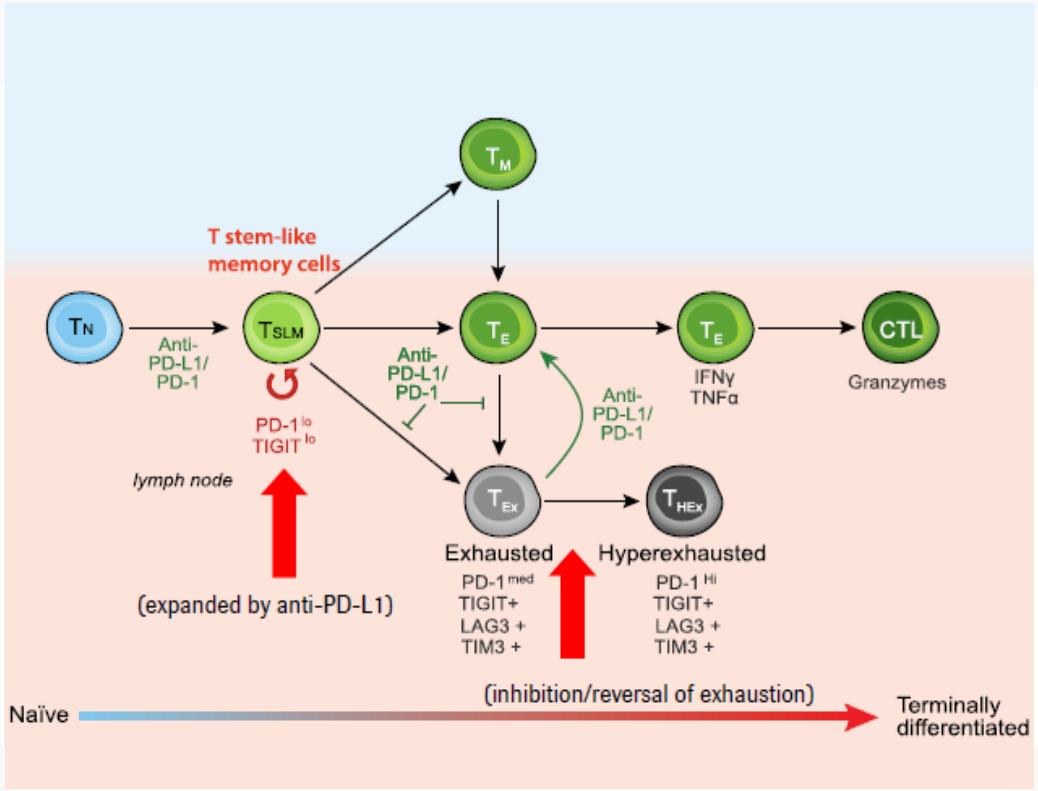
# Growing Evidence of T stem-like Cells Importance in IO

## Fraction of TCF7+ cells is a predictive of PD-1 response in melanoma




Sadeh-Feldman et al., 2018, Cell




Modified from Chen and Mellman Nature 2017

- Anti-PD-L1 expands a key population of PD-1-positive Tscm which also express TIGIT
- TIGIT and PD-1 co-blockade might enable optimal Tscm activation and DNAM-1 co-stimulation



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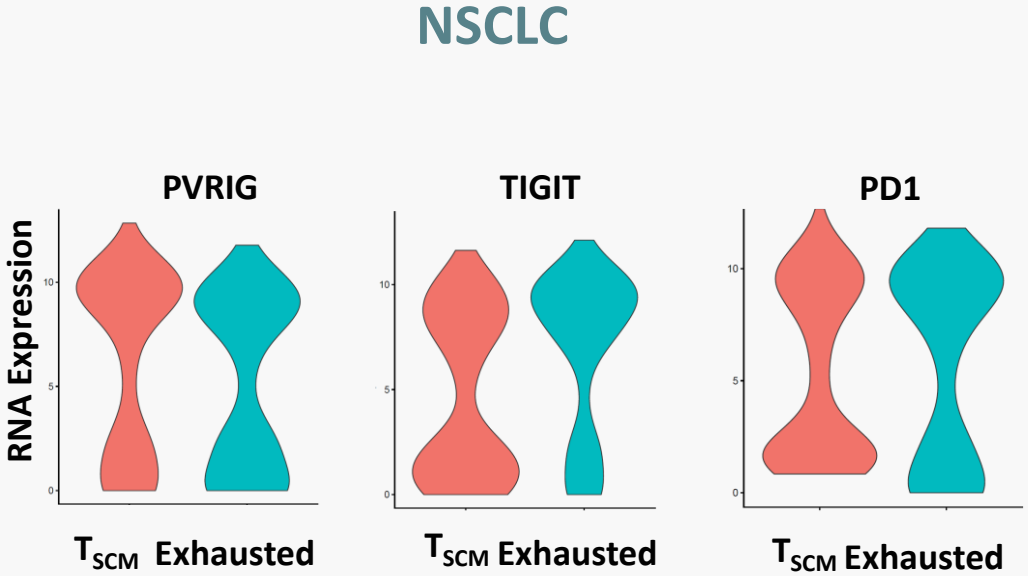
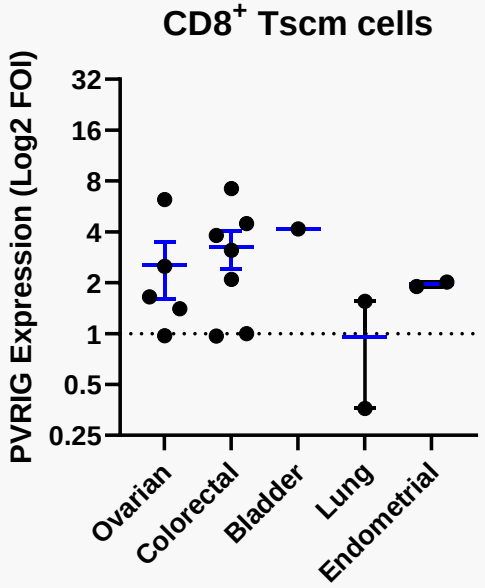
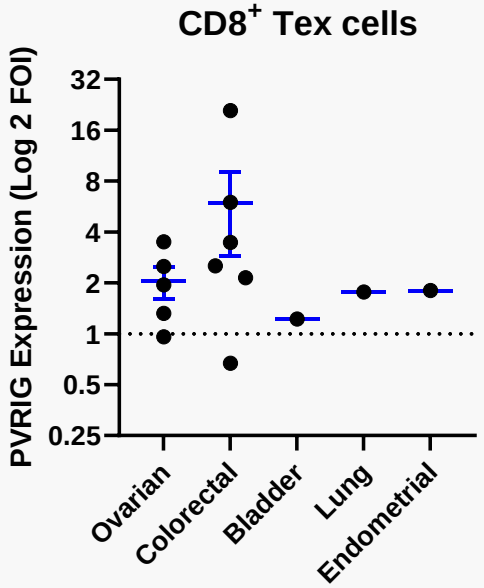
# PVRIG is Expressed by T Stem-like Cells




scRNA analysis of Gau et al. Nat Med 2018

Internal FLOW cytometry Data

**Potential for optimal Tscm activation, expansion and generation of effector T cells**



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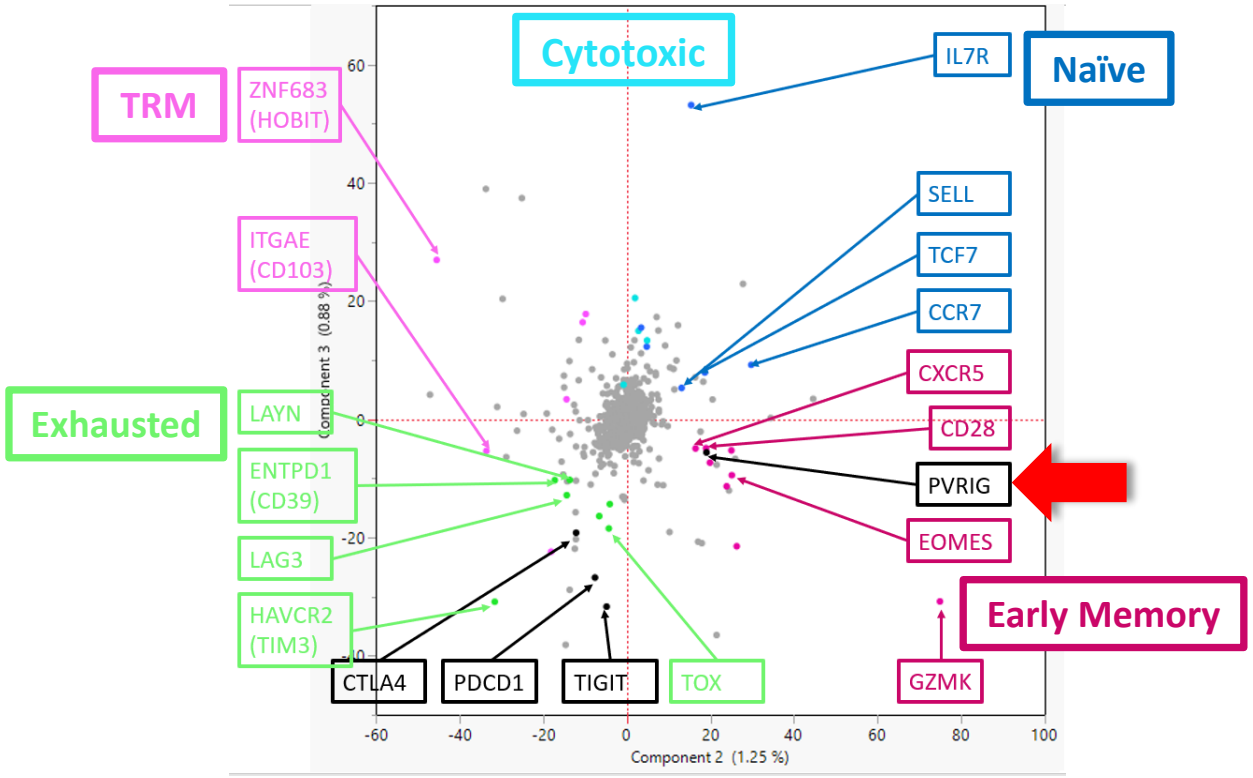
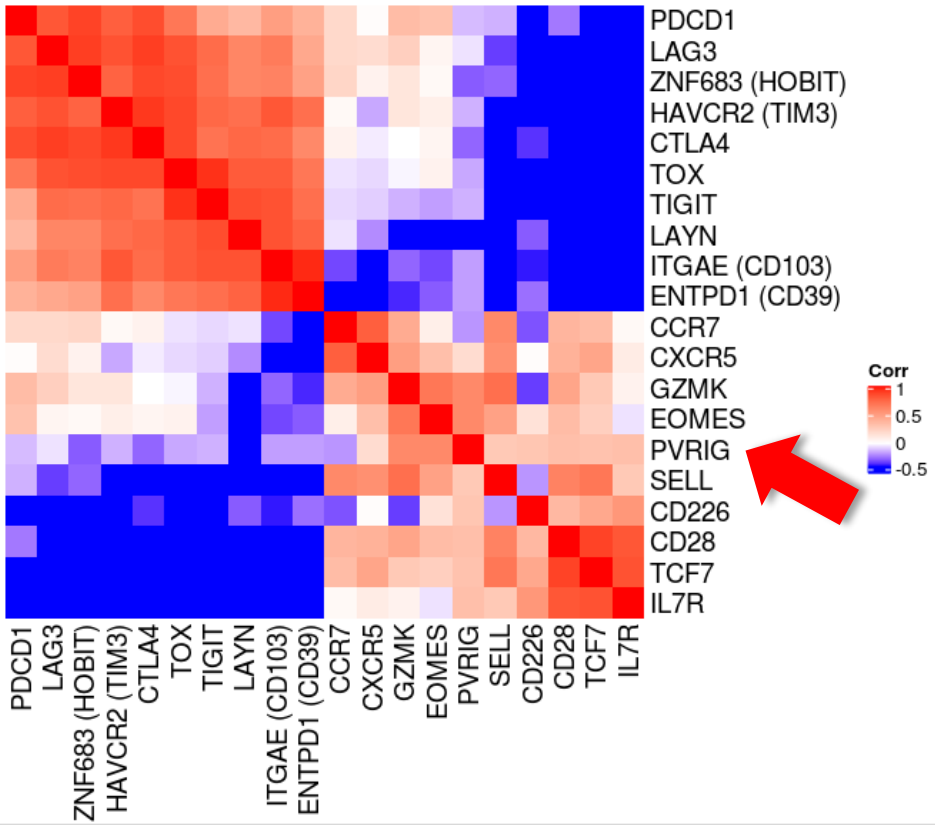
# PVRIG Uniquely Clusters with Early Memory Differentiation/ Stem-like Genes

## PCA Analysis of CD8+ T cell genes, NSCLC




GSE99254_NSCLC Dataset internally analyzed

## Unsupervised correlation analysis of scRNA, CRC




GSE108989_CRC Dataset internally analyzed



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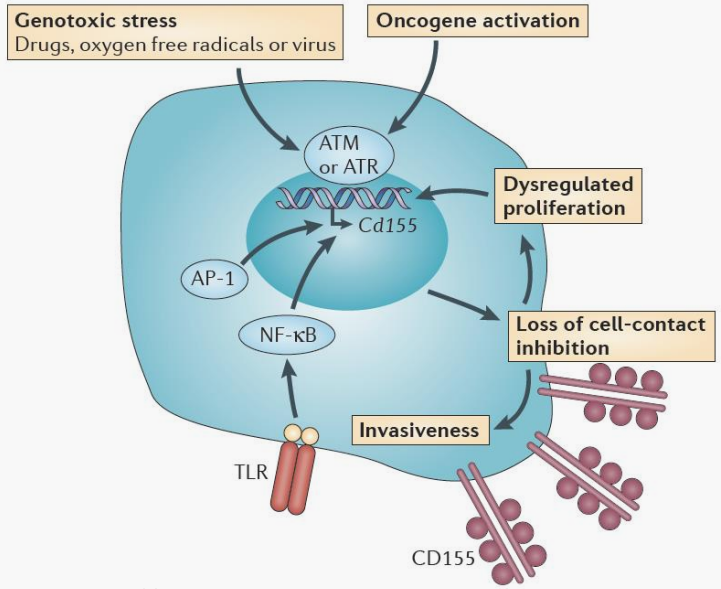
# PVR and PVRL2 are Expressed in Inflamed and Non-Inflamed Tumors

## PVR/PVRL2 on tumor cells induced by:

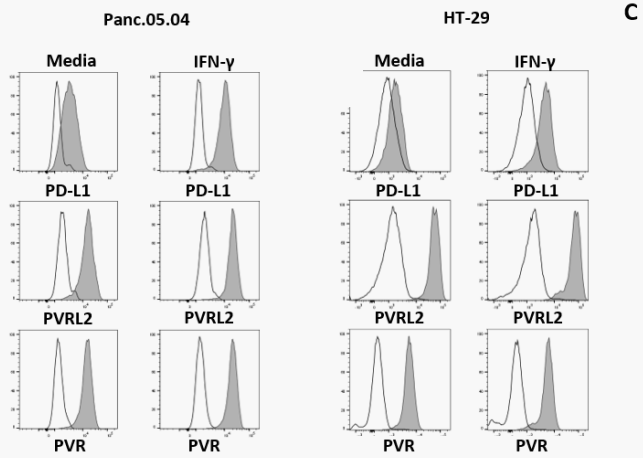
1. Genotoxic stress (DNA damage, oxidative stress)
2. Tumorigenesis (loss of contact inhibition/increased invasiveness)




Martinet et al. Nature Rev. Imm. 2015

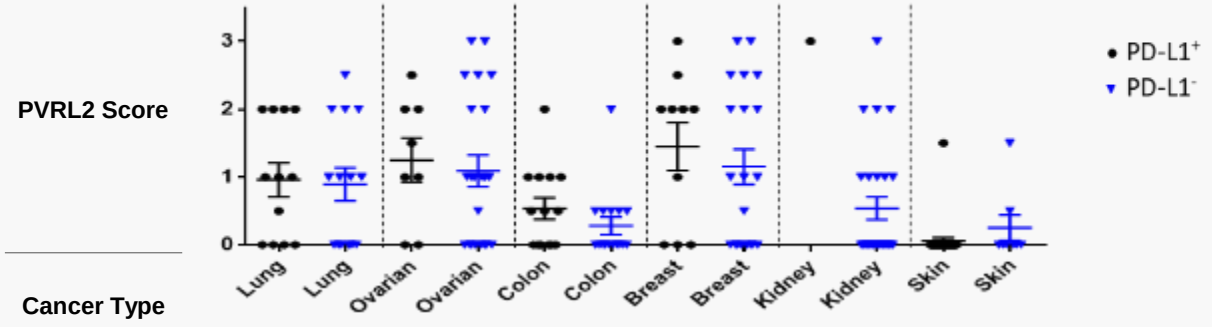
**PVRIG+TIGIT blockade may address PD-L1$^{low}$ non-inflamed indications**

## PVR/PVRL2 on Tumor Cells are not Modulated by IFN-γ




Whelan, et al., Cancer Immunol Res. 2019

## PVR/PVRL2 Commonly Expressed in PD-L1 Negative Tumors




SITC, November 2017, Whelan, et al., poster presentation



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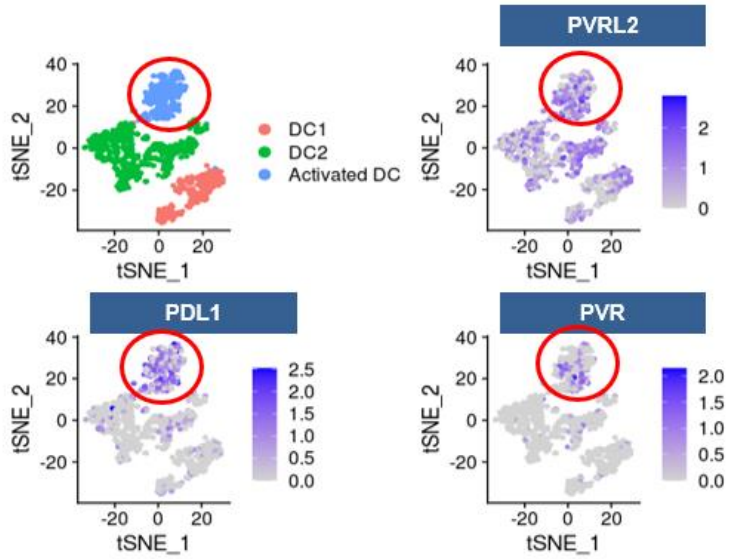
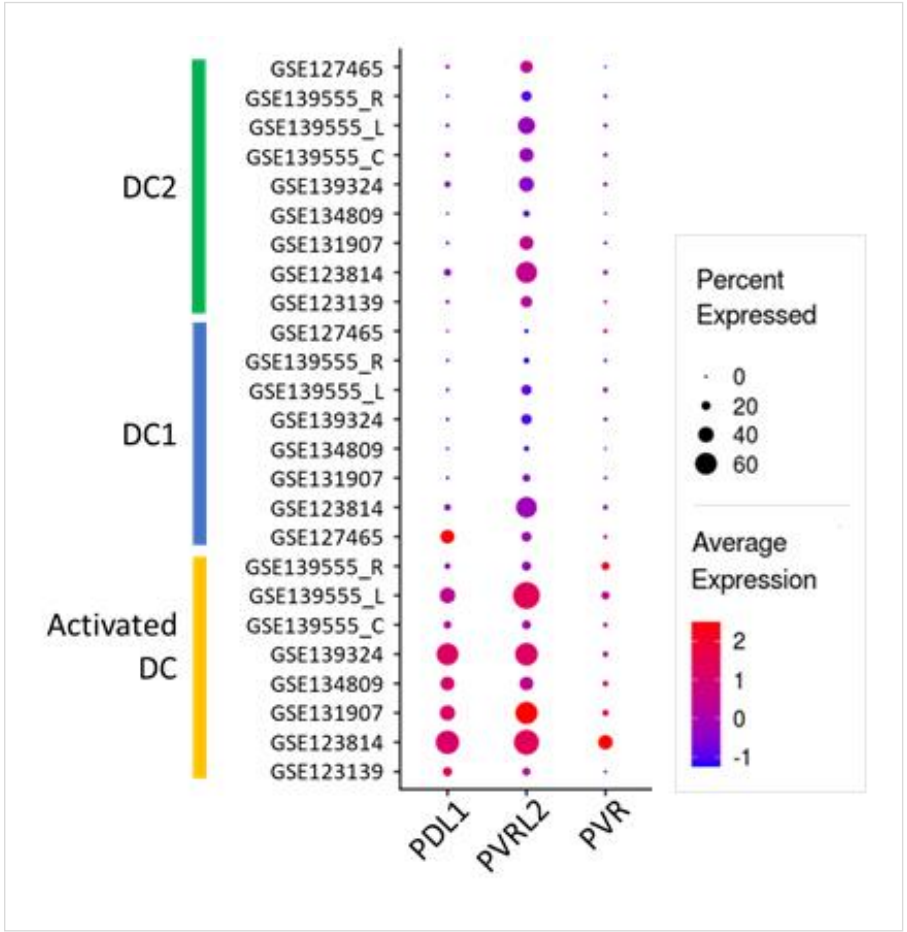
# PVRL2 Has A Dominant Expression on Dendritic Cells

## DC Population in SCC/BCC




GSE123814 Dataset internally analyzed




PVRIG blockade may enhance interaction and activation of Tscm by DCs in PD-L1$^{low}$ non-inflamed indications



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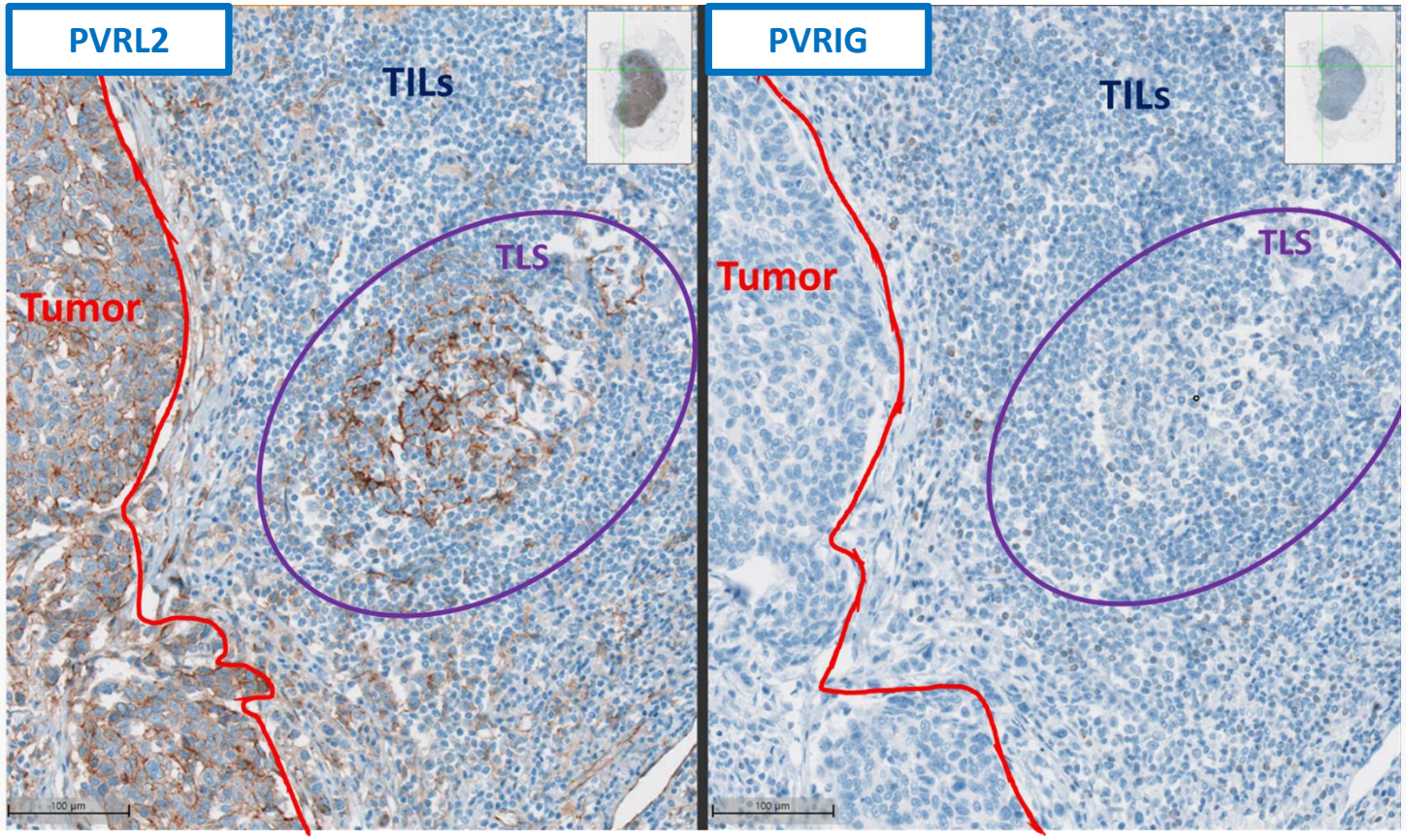
# PVRL2 and PVRIG Expression in Tertiary Lymphoid Structures




**Tertiary lymphoid structures are Lymphoid Structures in the tumor bed in which local T cell activation occur**

- **Predictive of PD1 response**

TNBC Sample, Internal Data

Helmink et al Nature 2020

**Potential of PVRIG blockade to enhance T cell proliferation at the tumor bed**



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# COM701 Clinical Program

## Phase 1 Arm A - Monotherapy

| | |
|---|---|
| Monotherapy<br>Dose Escalation | Monotherapy Cohort Expansion<br>(20 patients; progressed on SOC) |
| All-comers<br>(progressed on SOC) | NSCLC, Ovarian, Breast, Endometrial, Colorectal |

## Phase 1 Arm B – Dual Combination

| | |
|---|---|
| Dual Combination: Escalating doses of COM701 with fixed dose of Opdivo® (Up to 20 patients) | Dual combination Cohort Expansion<br>(progressed on SOC) |
| All-comers (progressed on SOC) | Ovarian, Breast, Endometrial and MSS-CRC |

## Phase 1/2 - Triple Combination

| | |
|---|---|
| Triple Combination Dose Escalation<br>Escalating doses of COM701 with fixed doses of Opdivo® + BMS-986207 | Triple Combination<br>Cohort Expansion |
| All-comers (progressed on SOC)<br>Study ongoing | Ovarian, Endometrial, additional tumor types with high PVRL2 expression |

**COM701 - First PVRIG blocker tested clinically**



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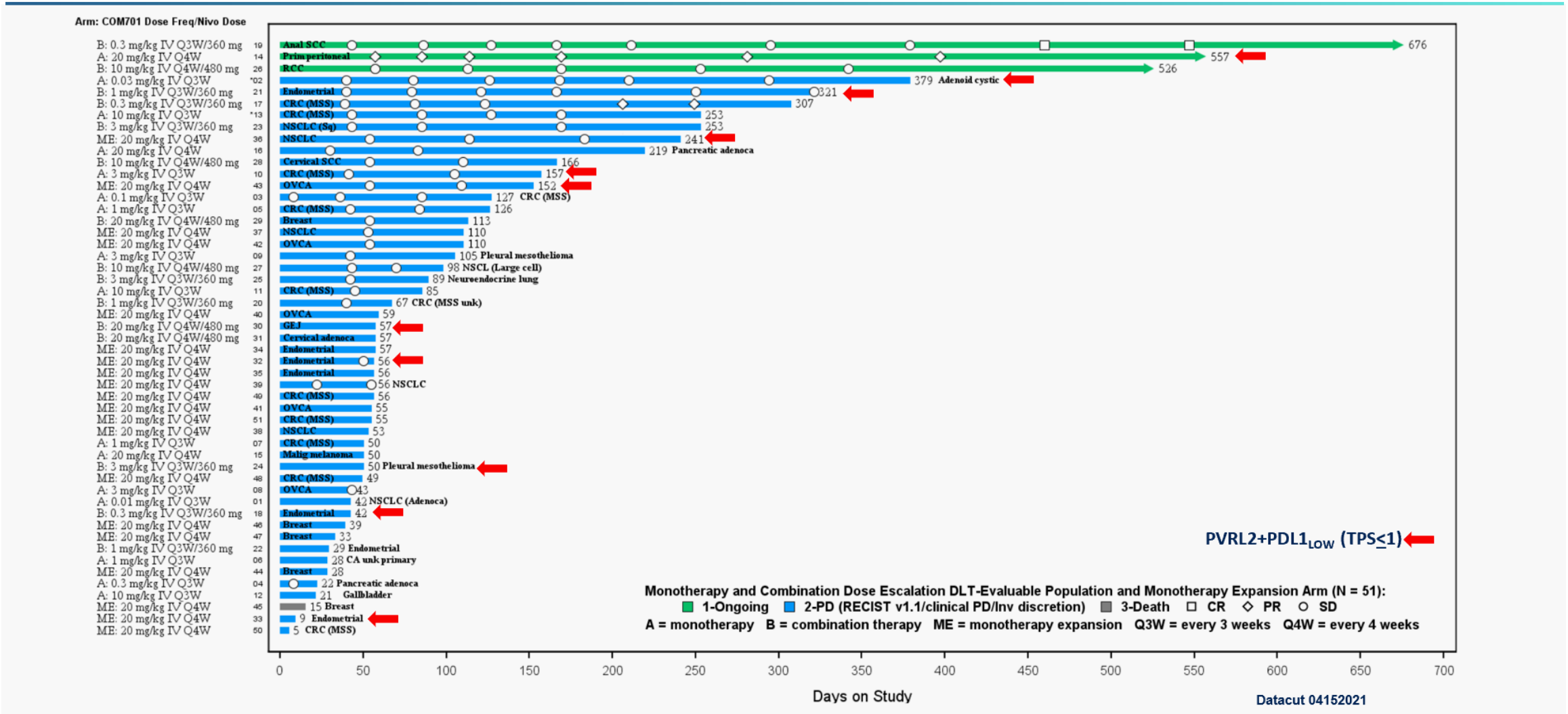
# COM701 Monotherapy and Nivolumab Combination Therapy: SWIMMER PLOT




ASCO, June 2021, Vaena et al., Oral presentation

**Preliminary anti-tumor activity also in patients with PVRL2+PDL1$_{low}$ tumors**



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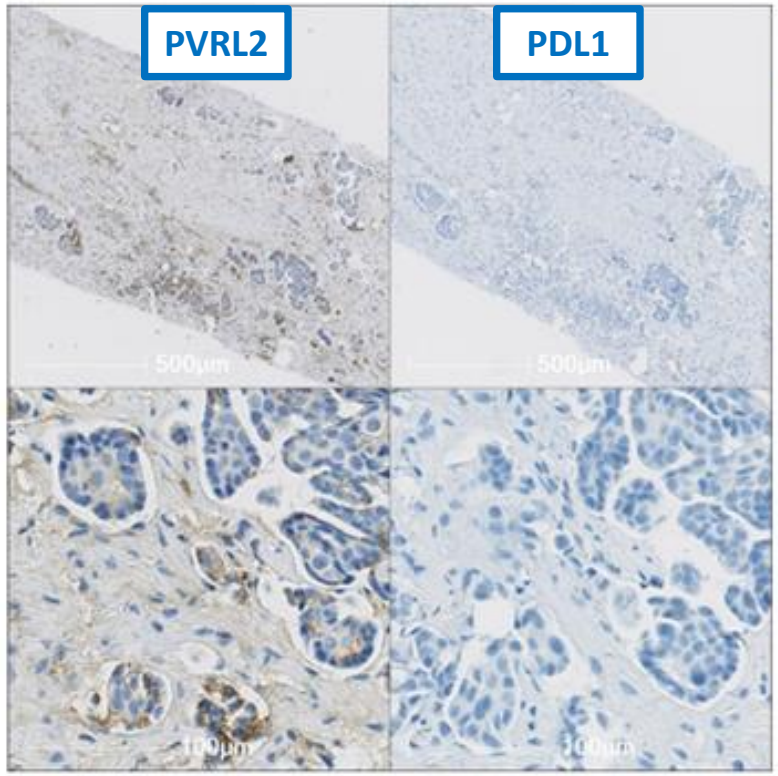
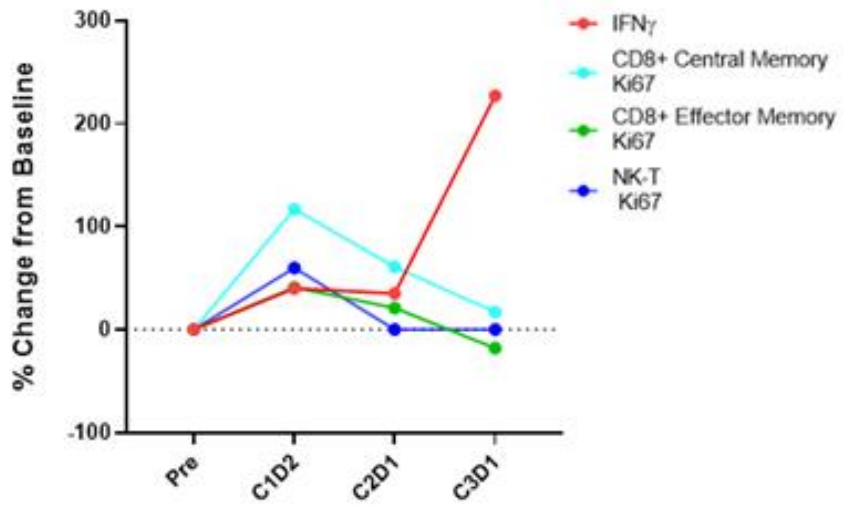
# Confirmed Partial Response in Patient with Primary Peritoneal PD-L1 Negative Cancer Treated with COM701 Monotherapy




- Pre-treatment Archival biopsy (>1 year)
- Negative PD-L1 staining
- PVRL2 expression found on tumor and endothelial cells
- Immune "desert": no immune cells detected in biopsy




**Increased immune cells proliferation and IFN-gamma induction in peripheral blood**

ASCO, June 2021, Vaena et al., Oral presentation

**PR in patient with non-inflamed TME demonstrating immune activation in peripheral blood following COM701 monotherapy**



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# Summary

- PVRIG is a novel checkpoint in the DNAM-1 axis, co-expressed with PD-1 and TIGIT in Tscm and exhausted T cells but uniquely clusters with early memory differentiation/ stem-like genes
- PVRIG blockade show synergistic activity with TIGIT and PD-1 blockade in pre-clinical studies
- PVRL2 and PVR are expressed in $PDL1_{low}$ and $PD\text{-}L1_{high}$ tumor types
- PVRL2 has abundant expression across DC types and in TLS
- COM701 blockade could potentially mediate an interaction between DCs & Tscm in the tumor bed (TLS) and lymphoid organs. A potential mechanism which could lead to increase T cell expansion and infiltration into less 'inflamed' tumors
- Preliminary signals for COM701 antitumor activity in patients with $PVRL2{+}PD\text{-}L1_{low}$ tumors
- PVRIG, TIGIT and PD1 combination might expand CPI treatment to patient's population not responding to currently approved CPIs.

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This presentation contains “forward-looking statements” within the meaning of the the Securities Act of 1933 and the Securities Exchange Act of 1934, as amended, and the safe-harbor provisions of the Private Securities Litigation Reform Act of 1995. Forward-looking statements can be identified by the use of terminology such as “will,” “may,” “expects,” “anticipates,” “believes,” “potential,” “plan,” “goal,” “estimate,” “likely,” “should,” and “intends,” and similar expressions that are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements involve known and unknown risks and uncertainties that may cause the actual results, performance or achievements of Compugen to be materially different from any future results, performance or achievements expressed or implied by such forward-looking statements, including statements regarding the timing and success of our clinical trials, enrollment of patients, type of clinical trials, presentation of data and our cash position and expenditures. Among these risks: Compugen’s operations could be affected by the outbreak and spread of COVID-19, Compugen’s business model is substantially dependent on entering into collaboration agreements with third parties, and Compugen may not be successful in generating adequate revenues or commercialize its business model or control its expenditures. Compugen also may not meet expected milestones in its development pipeline and may also be unable to enroll patient to its clinical trials or to present data. Moreover, clinical development involves a lengthy and expensive process, with an uncertain outcome and Compugen may encounter substantial delays or even an inability to begin clinical trials for any specific product or may not be able to conduct or complete its trials on the timelines it expects. These and other factors, including the ability to finance the Company, are more fully discussed in the "Risk Factors" section of Compugen’s most recent Annual Report on Form 20-F as filed with the Securities and Exchange Commission (“SEC”) as well as other documents that may be subsequently filed by Compugen from time to time with the SEC. In addition, any forward-looking statements represent Compugen’s views only as of the date of this presentation and should not be relied upon as representing its views as of any subsequent date. Compugen does not assume any obligation to update any forward-looking statements unless required by law. Certain studies and data presented herein have been conducted for us by other entities as indicated where relevant. Intellectual property, including patents, copyrights or trade secret displayed in this presentation, whether registered or unregistered, are the intellectual property rights of Compugen. Compugen's name and logo and other Compugen product names, slogans and logos referenced in this presentation are trademarks of Compugen Ltd. and/or its subsidiary, registered in the U.S.A., EU member states and Israel.

# Our Vision

Transforming patient lives by developing first-in-class therapeutics based on Compugen's computational target discovery platform

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# Thank you.