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FROM CODE TO CURE®

Rationalizing Combination Strategies to Maximize Clinical Response as Novel ICI Therapies Emerge

TIGIT Therapies Digital Summit

Eran Ophir, VP Research & Drug Discovery

October 2020

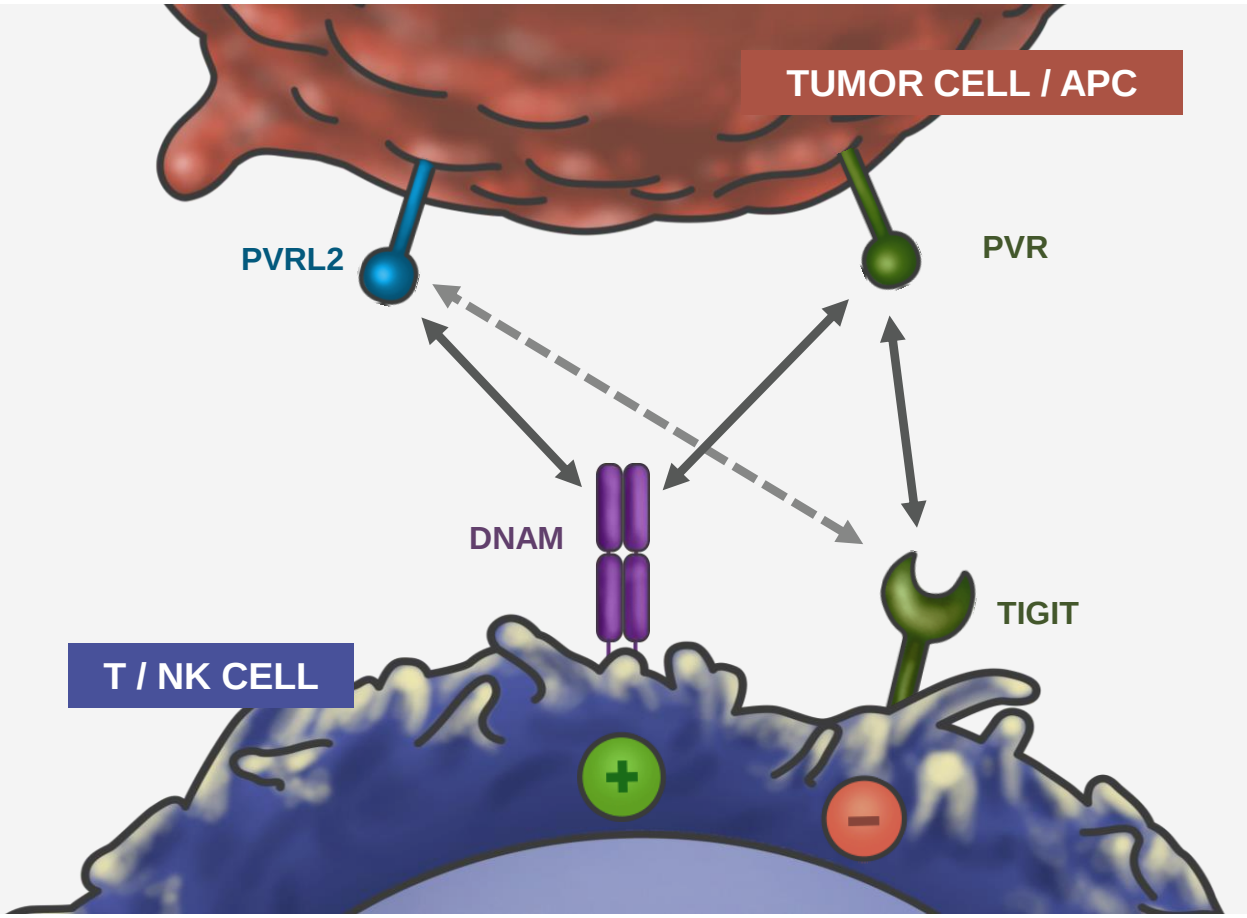
AGENDA

- TIGIT and PD-1 blockade combination: biological rational
- PVRIG: new checkpoint in the DNAM-1 axis
  - Biological rational for TIGIT:PD-1:PVRIG triple blockade
  - Preclinical data supporting TIGIT and PVRIG co-blockade
  - PVRL2 (PVRIG Ligand), expression pattern and potential clinical implications
- Perspectives

TIGIT AND DNAM-1 INTERPLAY

TIGIT mechanism of inhibition

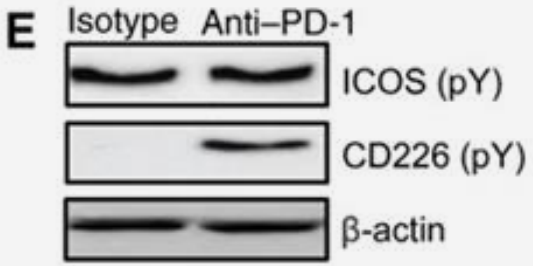
- TIGIT delivers direct inhibitory signal into T and NK cells
- TIGIT inhibits DNAM-1 co-stimulation
  - Decoy to PVR (higher affinity)
  - Dephosphorylation of DNAM-1
  - Interrupts DNAM-1 homo-dimerization



Martinet & Smyth, 2015 (modified)

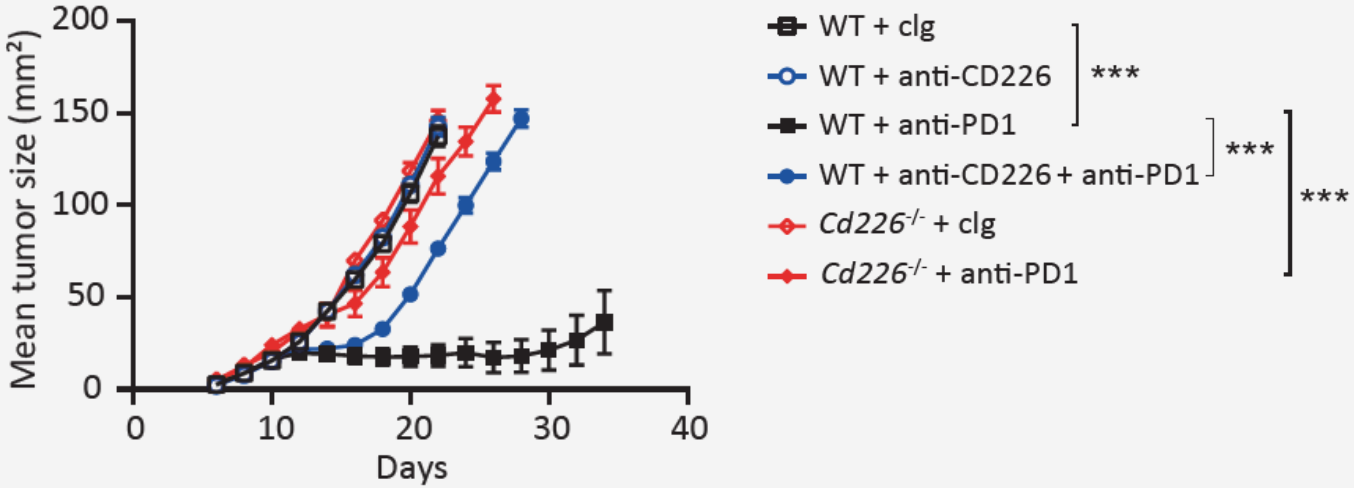
DNAM-1 INTERSECTS WITH THE PD-1 PATHWAY AND IS REQUIRED FOR IN-VIVO RESPONSE TO PD-1 BLOCKADE

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



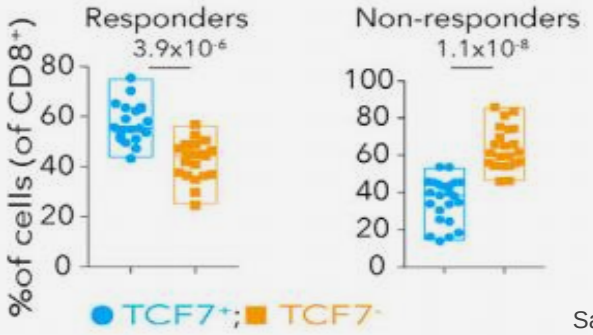
Weulersee et al. immunity 2019

NEW INSIGHTS INTO THE MECHANISM OF PD(L)1 BLOCKADE

- Upon PD1 blockade T stem-like memory T cells (T_{SCM}) proliferate, self-renew and give rise to differentiated cytotoxic effector T cells

  Siddiquie et al. Immunity 2019

  - Predictive of PD-1 response



Sadeh-Feldman et al. Cell 2018

- PD-L1 expression by Dendritic cells is a key regulator of immunity in cancer

  Oh et al. Nature Cancer 2020

  - 'Activated DC' program is triggered following antigen uptake and associated with efficient T cell activation in LNs, limited by PD-L1

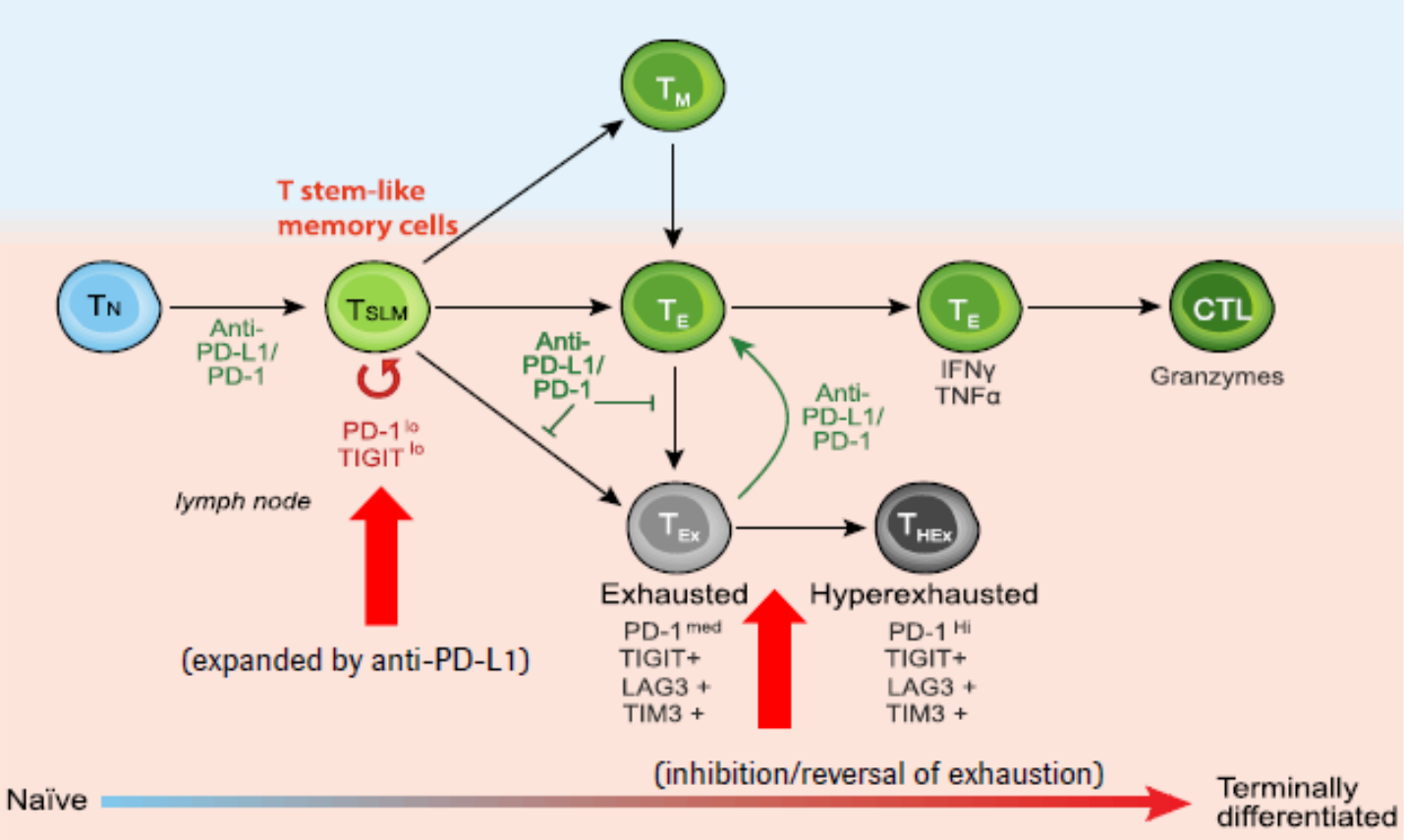
    Maier et al Nature 2020

- Tertiary lympoid structures (TLS) are Lymphoid Structures in the tumor bed in which Local T cell Priming occur
  - Predictive of PD1 response

    Helmink et al Nature 2020

TIGIT AND PD-1: DOMINANT CHECKPOINTS EXPRESSED BY T_{SCM}

Anti-PD-L1 expands a key population of PD-1-positive T stem-like cells, which also express TIGIT



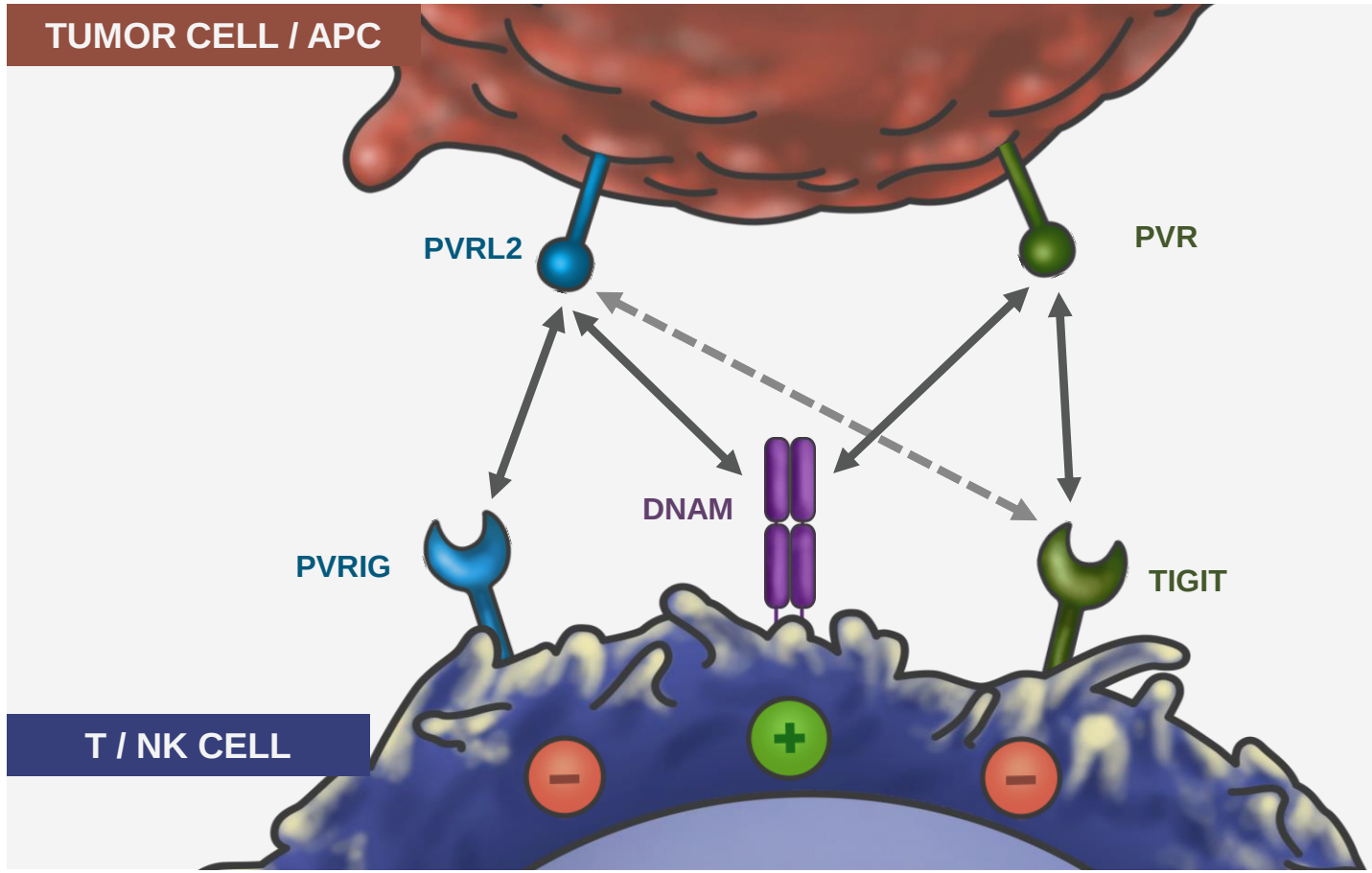
Modified from Chen and Mellman Nature 2017

TIGIT and PD-1 co-blockade might enable optimal T_{SCM} activation and DNAM-1 co-stimulation

TIGIT and PD-L1 co-blockade: a validated clinical combination (CITYSCAPE randomized trial)

Genentech Investor call Feb 2020

PVRIG: A NOVEL CHECKPOINT TARGET IN THE TIGIT/DNAM-1 AXIS

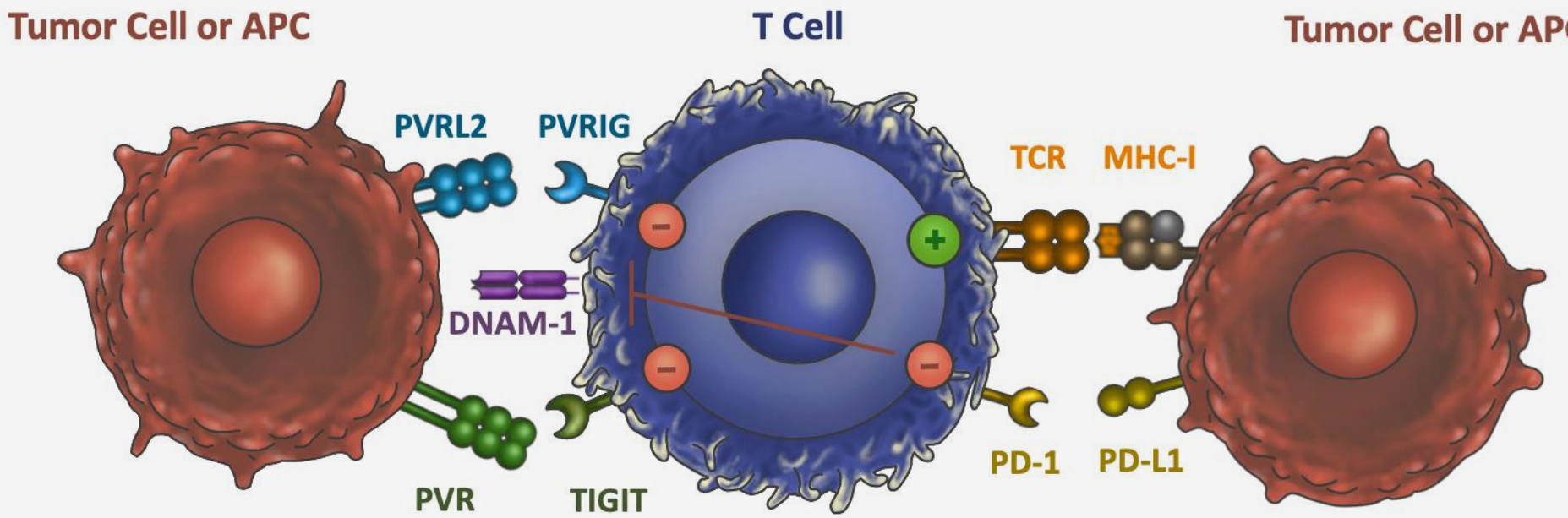


- PVRIG binds PVRL2 as a functional ligand (TIGIT binding to PVRL2 is of low affinity)
- Similarly to TIGIT/PVR/DNAM, PVRIG has higher affinity to PVRL2 than DNAM-1 (decoy effect)
- DNAM-1 axis – two parallel and complementary inhibitory pathways (PVRIG & TIGIT)

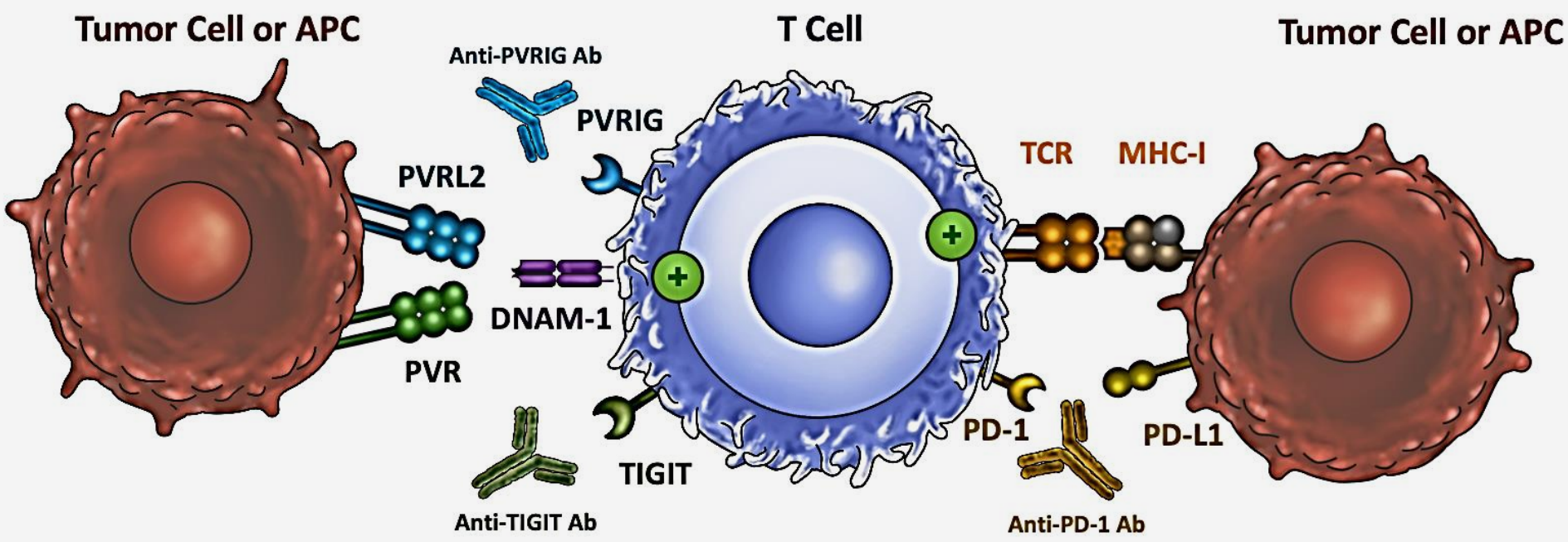
Martinet & Smyth, 2015 (modified)

Whelan, et al., Cancer Immunol Res. 2019

PVRIG, TIGIT AND PD-1 AS PLAYERS IN THE DNAM-1 AXIS

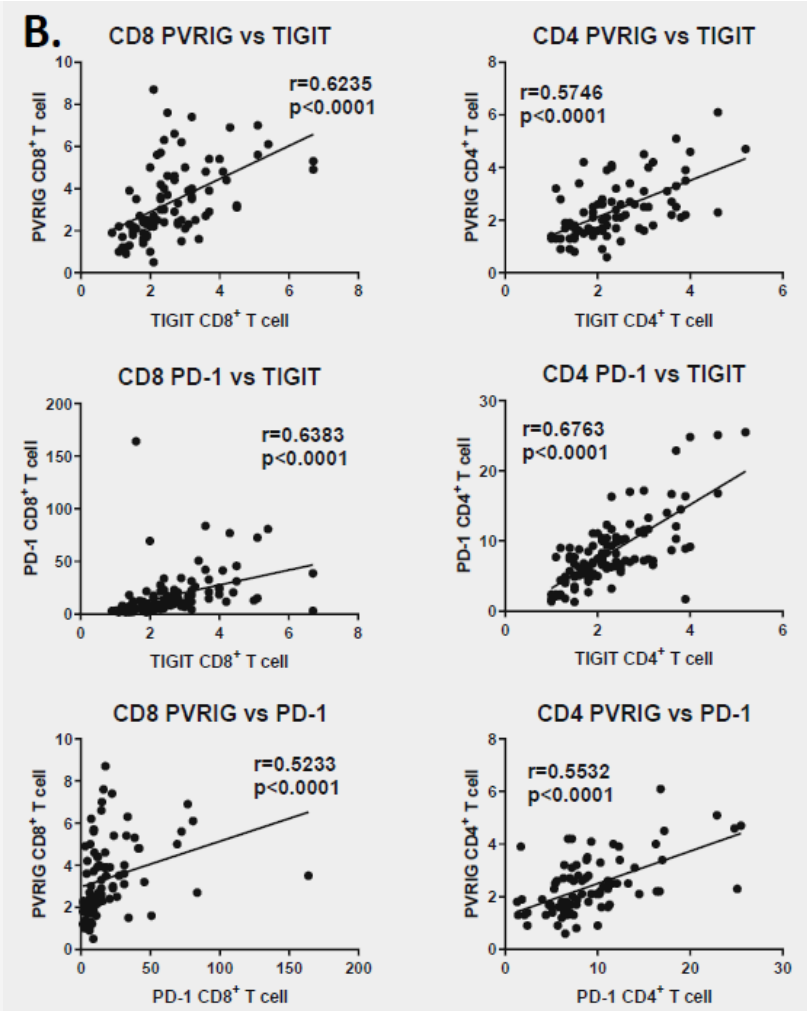


POTENTIAL INTERSECTION BETWEEN PVRIG/TIGIT AND PD-1 PATHWAYS SUPPORT COMBINATION APPROACH TO OVERCOME IMMUNOTHERAPY RESISTANCE



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

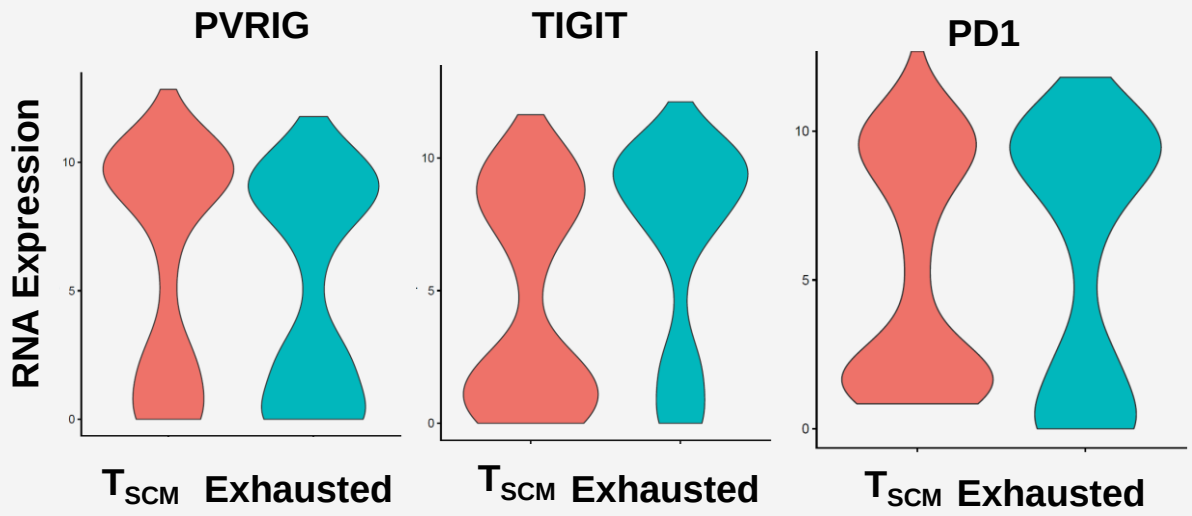
PVRIG, TIGIT AND PD-1 ARE CO-EXPRESSED IN TUMOR INFILTRATING T CELLS ACROSS TUMOR INDICATIONS



Logronio et al., SITC 2019 poster presentation

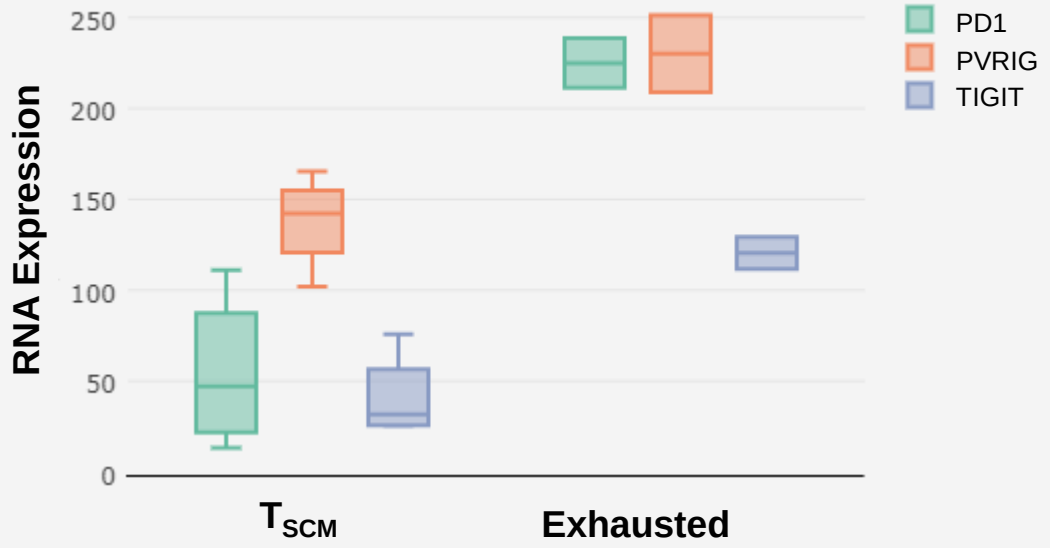
PVRIG IS EXPRESSED BY T_{SCM} (SIMILAR TO TIGIT AND PD-1)

NSCLC



Single cell RNA analysis of Gau et al Nat Med 2018

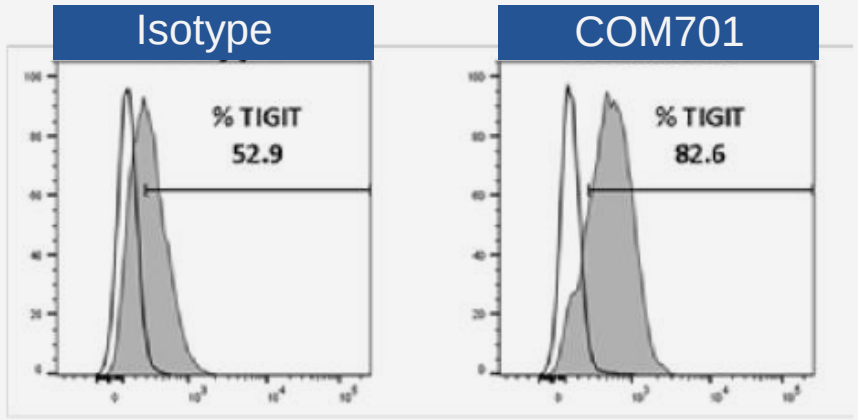
Bladder Cancer

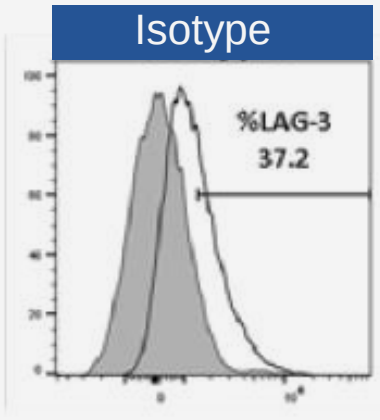


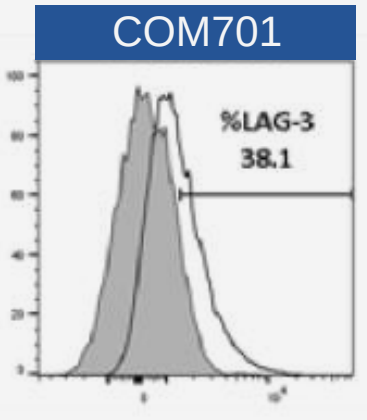
RNA seq Analysis of Jansen et al. Nature 2019

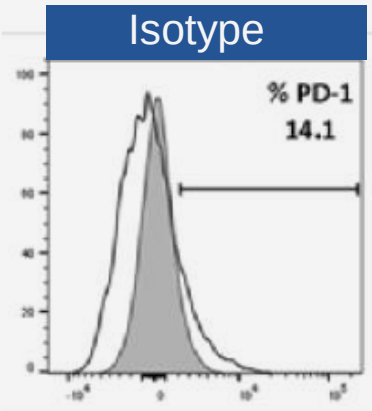
Potential for optimal T_{SCM} activation, expansion and generation of effector T cells

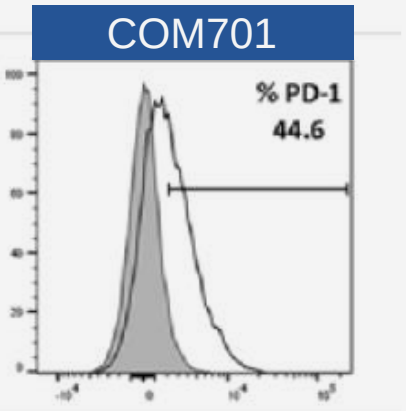
PVRIG BLOCKADE SELECTIVELY INDUCES TIGIT AND PD-1 EXPRESSION ON T CELLS

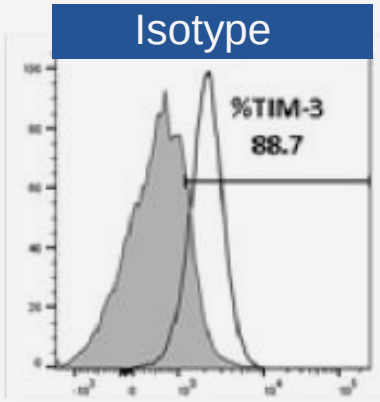


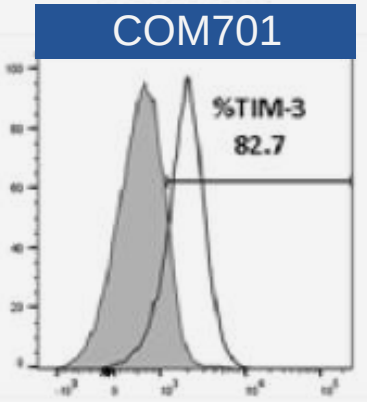










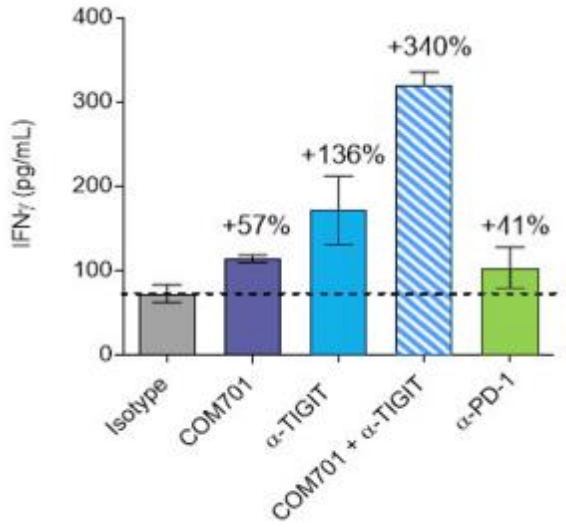


COM701
PVRIG blocking antibody

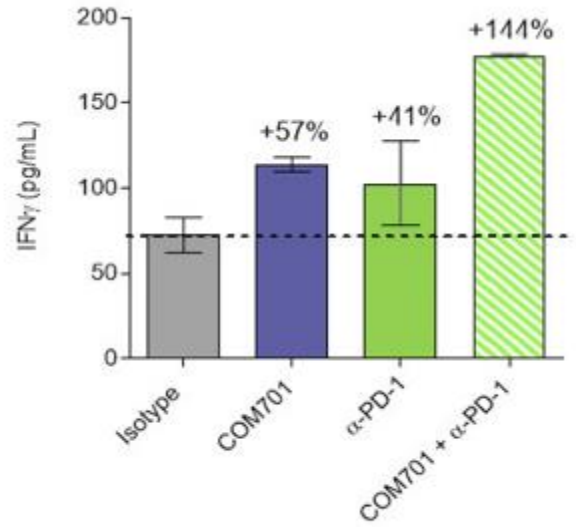
Adopted from Whelan, et al., Cancer Immunol Res. 2019

SYNERGISTIC T CELL ACTIVATION WITH PVRIG, PD-1 AND TIGIT BLOCKADE

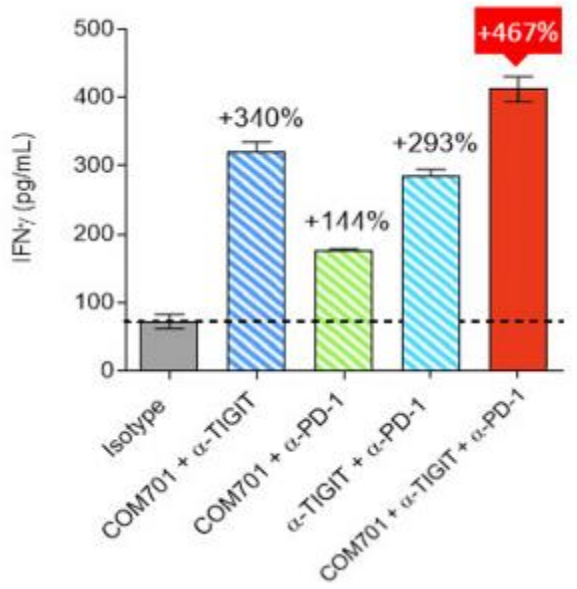
COM701 +/- anti-TIGIT



COM701 +/- anti-PD-1



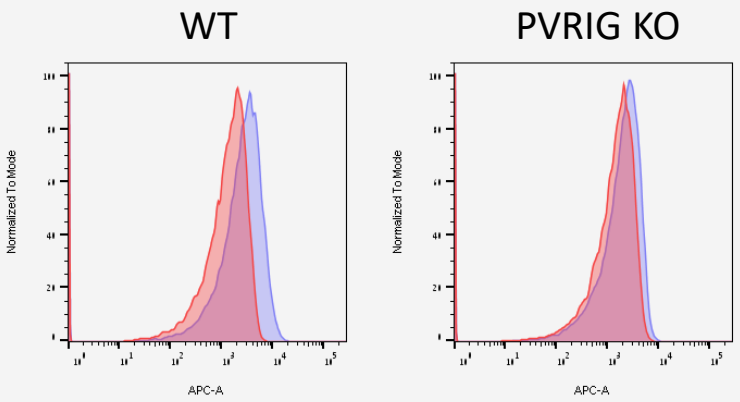
Triple combination

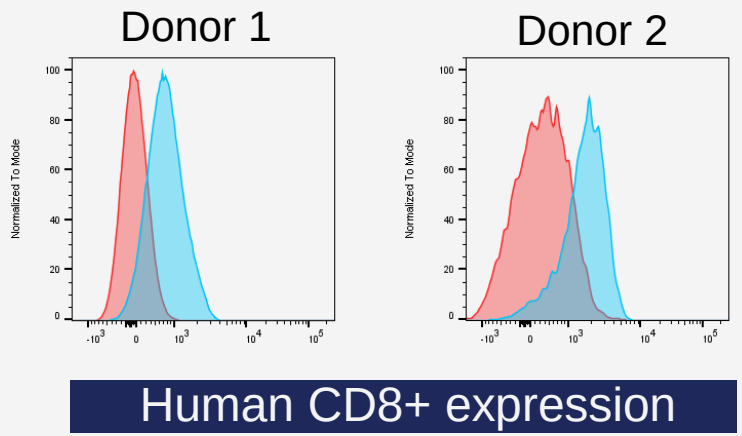


Whelan, et al., Cancer Immunol Res. 2019

COM701
PVRIG blocking antibody

MOUSE PVRIG IS EXPRESSED AT LOWER LEVELS THAN, AND IS STRUCTURALLY DIFFERENT FROM, HUMAN PVRIG



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Human     SGVLLFGCVYLLHLLRRHKHRPAPRLQPSRTSPQAPRARAWAPSQASQAALHVPYATINT
Macaca    SGVLLFGCGYLLHLLRRQKHRPTPRLQPSHTNSQALTAQAWAPSQASQAALHDPYATINT
Mouse     SGVFLFGFIFILCLRWQQRHWCLSKSQPSLTSTQ----------------------------
          ***:***  ::* *  :::*   .: *** *..*

Human     SCRPATLDTAHPHGGPSWWASLPTHAAHRPQGPAAWASTPIPARGSFVSVENGLYAQAGE
Macaca    SFCPATLDTAHPNG----WASLPTHAAHQPQGPAASASTPILARGSFVSVENGLYTQAGE
Mouse     ----AQVETQPPH----------------------LAST----HSSFISMENGLYALA--
              * ::*  *:                         ***    :.**:*:*****: *

Human     RPPHTGPGLTLFPDPRGPRAMEGPLGVR
Macaca    RPPHTGPGLTLFPDCRGPRALEGRFGVR
Mouse     ----------------------------
```

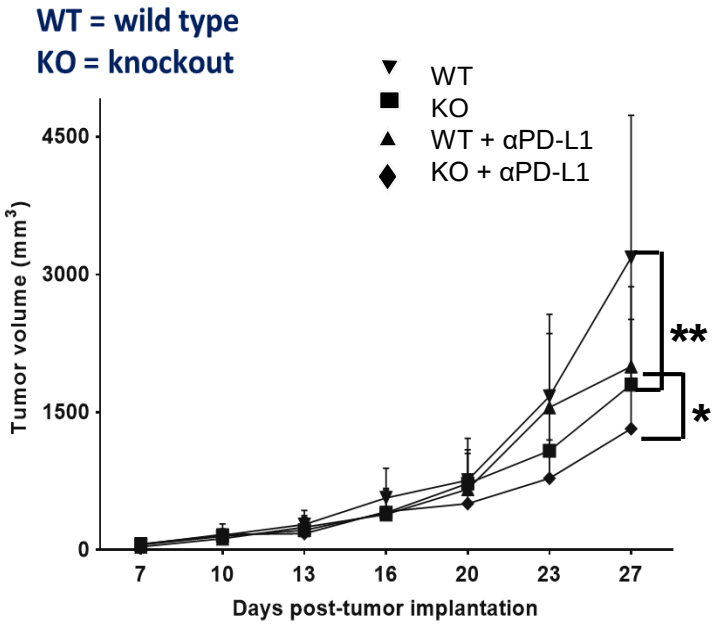
ITIM

Transmembrane
Optional Ser/Tyr-Phosphorylation

Mouse in vivo data may underestimate human effects

PVRIG KNOCKOUT OR INHIBITION REDUCES TUMOR GROWTH IN COMBINATION WITH PD-L1 OR TIGIT BLOCKADE IN MOUSE MODELS

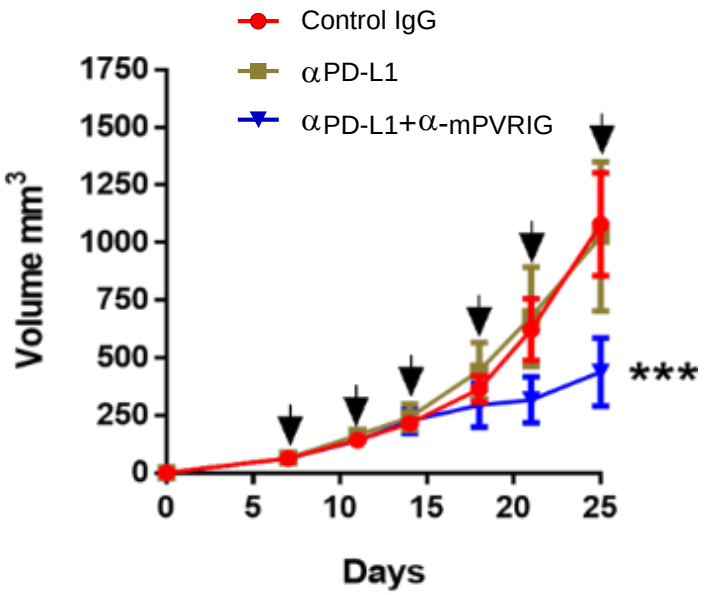
PVRIG KO MICE (MC38)



Reduced tumor growth in KO mice

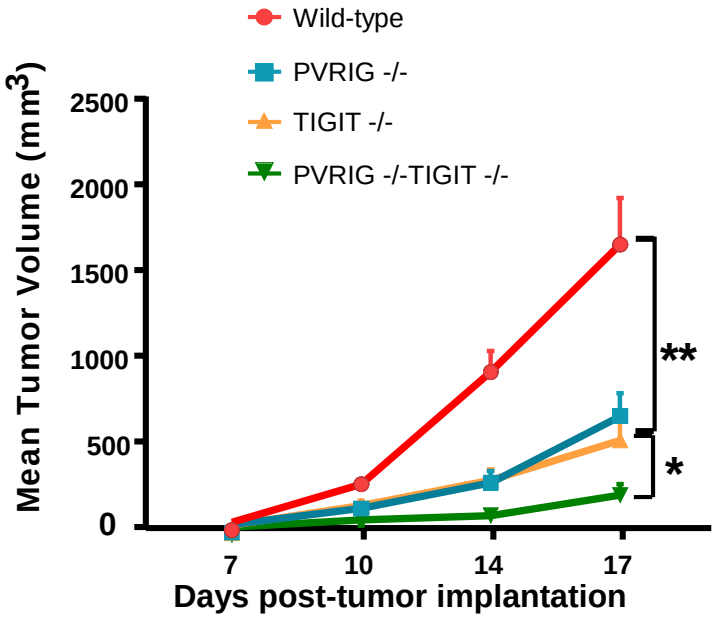
Ganguly and Pardoll, Johns Hopkins Univ. MC38 model

anti-PVRIG + anti-PD-L1 (CT26)



Synergistic tumor growth inhibition with anti-PD-L1

PVRIG + TIGIT Double KO (B16)



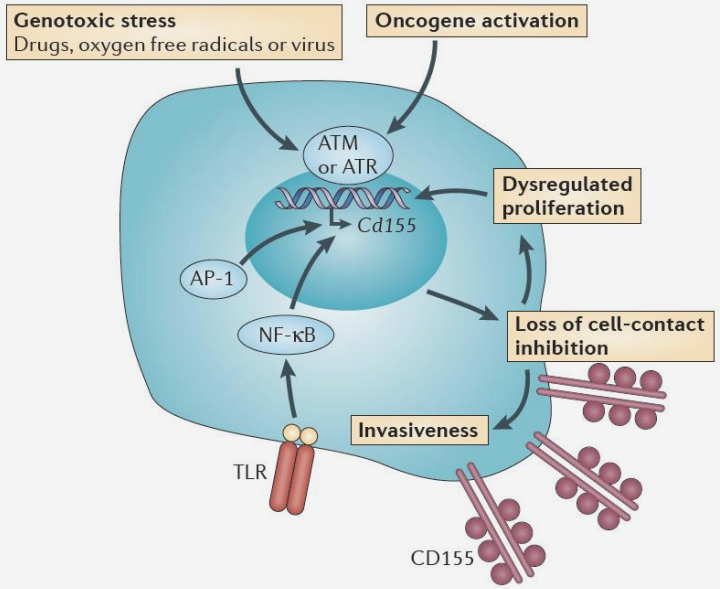
Reduced tumor growth in PVRIG + TIGIT double KO mice

SITC, November 2016, Hunter, et al., oral presentation
SITC, November 2019, Logronio, et al., poster presentation

PVR AND PVRL2 ARE EXPRESSED IN INFLAMED AND NON-INFLAMED TUMORS

PVR/PVRL2 on tumor cells induced by:

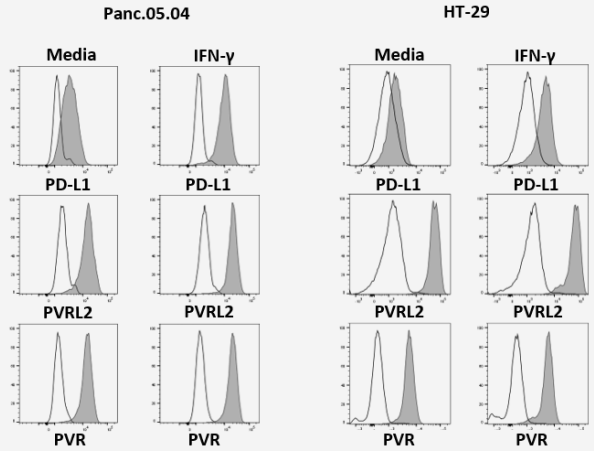
1. Genotoxic stress (DNA damage, oxidative stress)
2. Tumorigenesis (loss of contact inhibition/increased invasiveness)



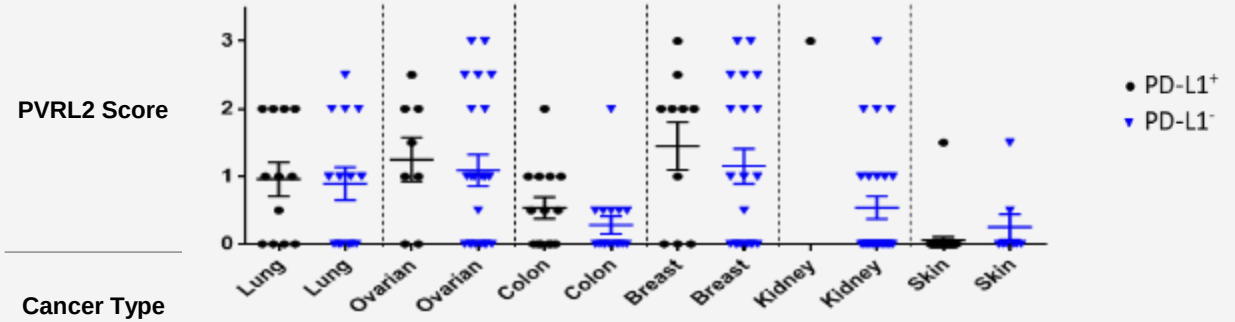
Martinet et al. Nature Rev. Imm. 2015

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

PVR/PVRL2 on Tumor Cells is not Modulated by IFN-g



PVR/PVRL2 Commonly Expressed in PD-L1 Negative Tumors

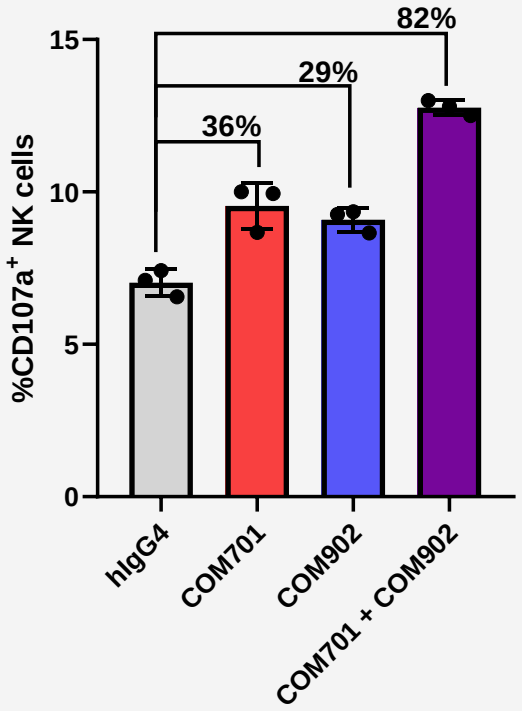


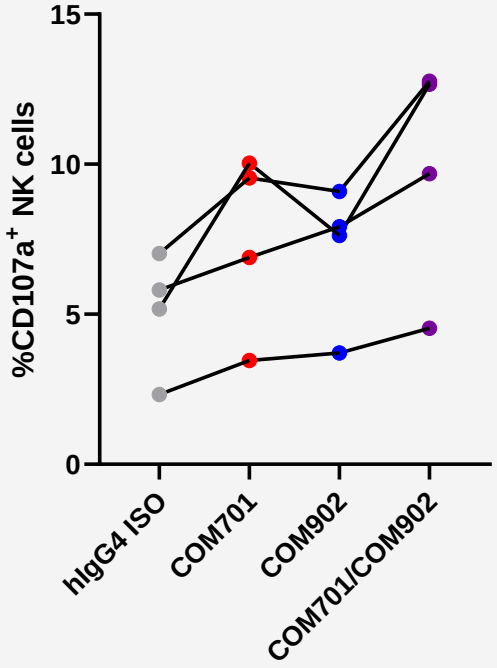
Whelan, et al., Cancer Immunol Res. 2019

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

PVRIG AND TIGIT CO-BLOCKADE ENHANCES NK CELL ACTIVATION

COM701
PVRIG Blocking antibody
COM902
TIGIT Blocking antibody



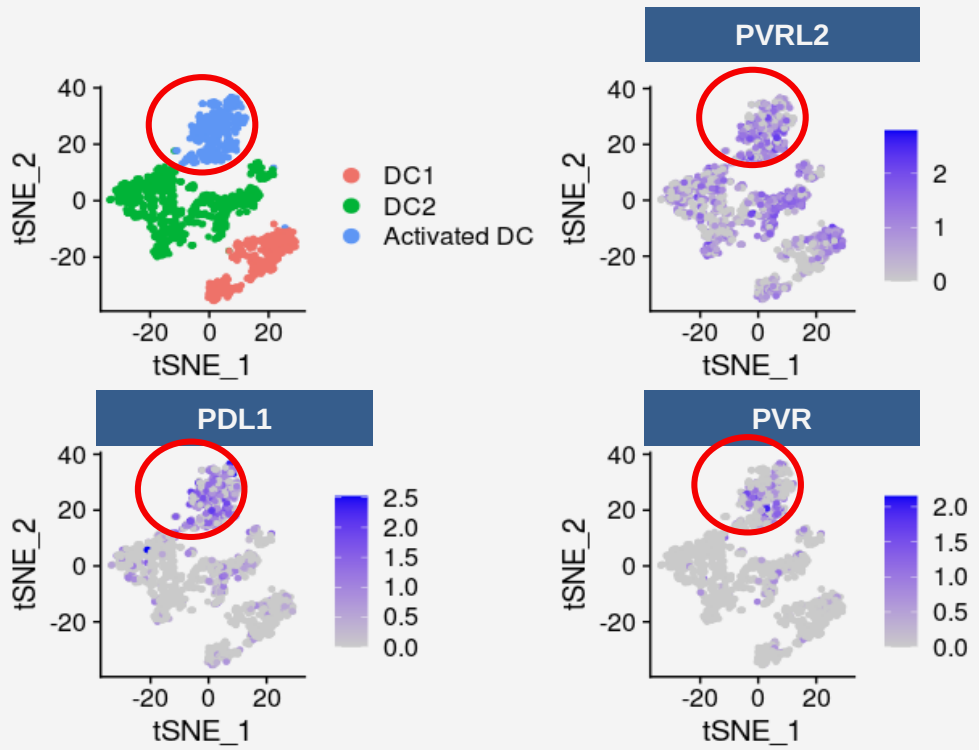


Hanssen et al, Manuscript submitted

Opportunity to activate NK cells in tumors with low T cell infiltration

PVR/PVRL2/PD-L1 ARE CO-EXPRESSED IN 'ACTIVATED' DENDRITIC CELLS ACROSS MULTIPLE TUMOR TYPES

DC Population in SCC/BCC



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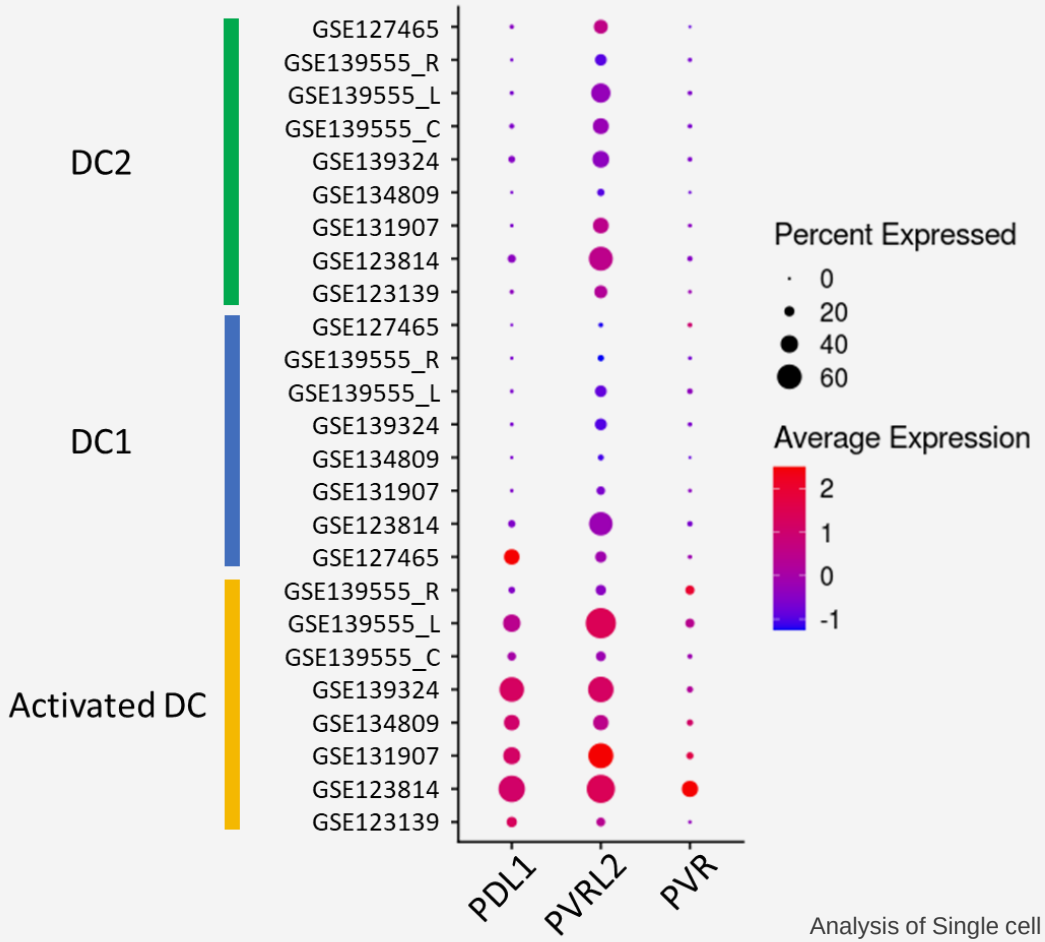
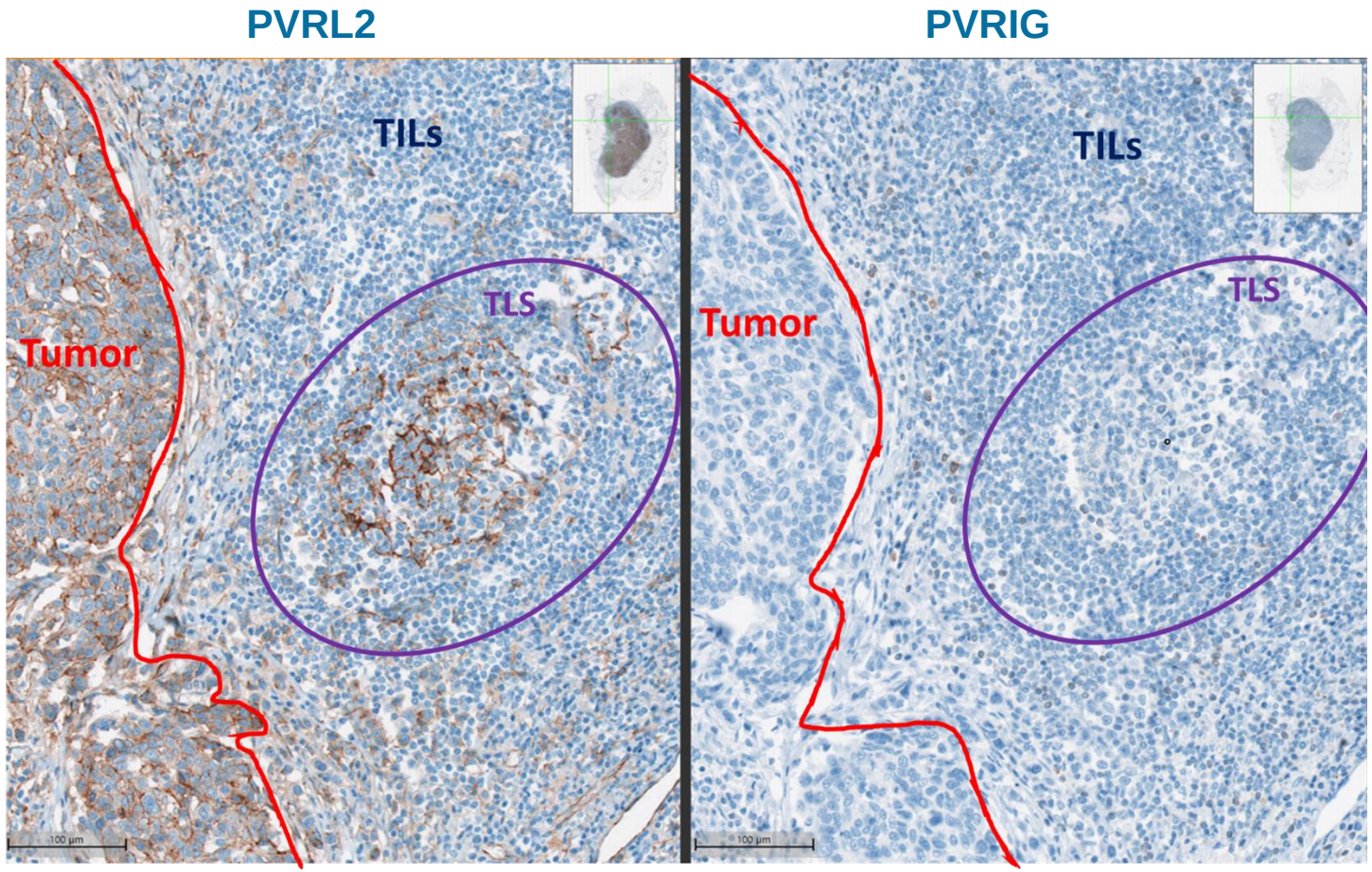


Analysis of Single cell Public Data

PVRL2 is abundant across DC subsets

PVRL2 AND PVRIG EXPRESSION IN TERTIARY LYMPHOID STRUCTURES (TLS)



TNBC Sample, Internal Data

Potential of COM701 to enhance T cell proliferation at the tumor bed

ANTI-PVRIG COM701 CLINICAL PROGRAMS

Phase 1 Arm A

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

Phase 1 Arm B

Dual Combination Escalating doses of COM701 with fixed dose of Opdivo® (Up to 20 patients)
All-comers (progressed on SOC)

Phase 1/2

Triple Combination Dose Escalation Escalating doses of COM701 with fixed doses of Opdivo® + BMS-986207 (Anti-TIGIT Ab)
All-comers (progressed on SOC); Study ongoing

Triple Combination Cohort Expansion
Ovarian, Endometrial, additional tumor types with high PVRL2 expression

Study Objectives

- Safety & Tolerability
- PK/PD
- Clinical activity – COM701 monotherapy and in combination

Biomarker Strategy

- Expression of DNAM axis members
- Additional indications based on biomarker analysis

COM701: INITIAL CLINICAL DATA

Monotherapy and Combination Dose Escalation Study (AACR Data Presentation, April 2020)

Safety Profile	• COM701 well-tolerated, no DLTs reported as monotherapy and in combination with Opdivo® • 16 patients in Arm A; 12 patients in Arm B

Anti-Tumor Activity	• ***Two confirmed partial responses***: both patients on treatment at cutoff date
	  • A patient with ***platinum-resistant MSS primary peritoneal cancer*** (a type of ***ovarian cancer***) from monotherapy dose escalation study
	  • A patient with ***MSS-CRC*** from combination dose escalation study
	• ***High disease control rate*** of 69% (11/16) for monotherapy and 75% (9/12) for combination
	• 50% of patients in Arm B remain on study, some with continued responses beyond 200 days
	• ***Durable responses*** for over six months in 21% of patients across treatment arms

Signs of anti-tumor activity in non-inflamed indications

SUMMARY

- DNAM-1 intersects with the PD-1 pathway and is required for In-Vivo response to PD-1 blockade
- PVRIG is a novel checkpoint in the DNAM-1 axis, co-expressed with PD-1 and TIGIT in T_{SCM} and exhausted T cells
- 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 Tertiary Lymphoid Structures (TLS)
- COM701 blockade could potentially mediate an interaction between DCs & T_{SCM} in the tumor bed (TLS) and lymphoid organs. A potential mechanism which could lead to increase T cell priming and infiltration into less ‘inflamed’ tumors