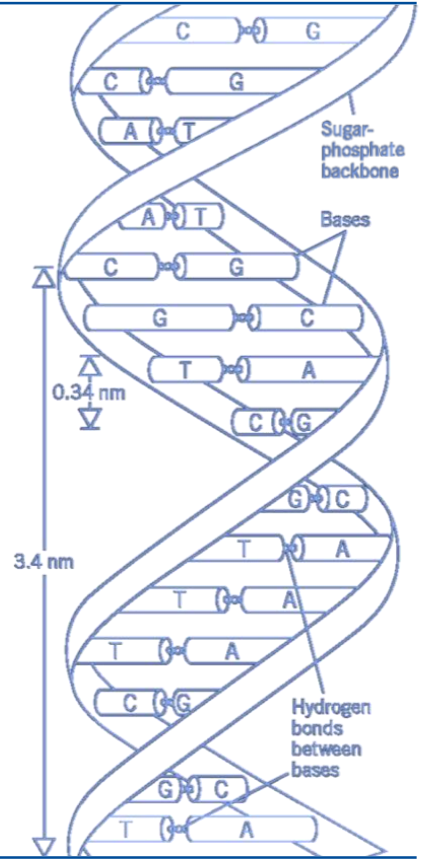
TIGIT OVERVIEW



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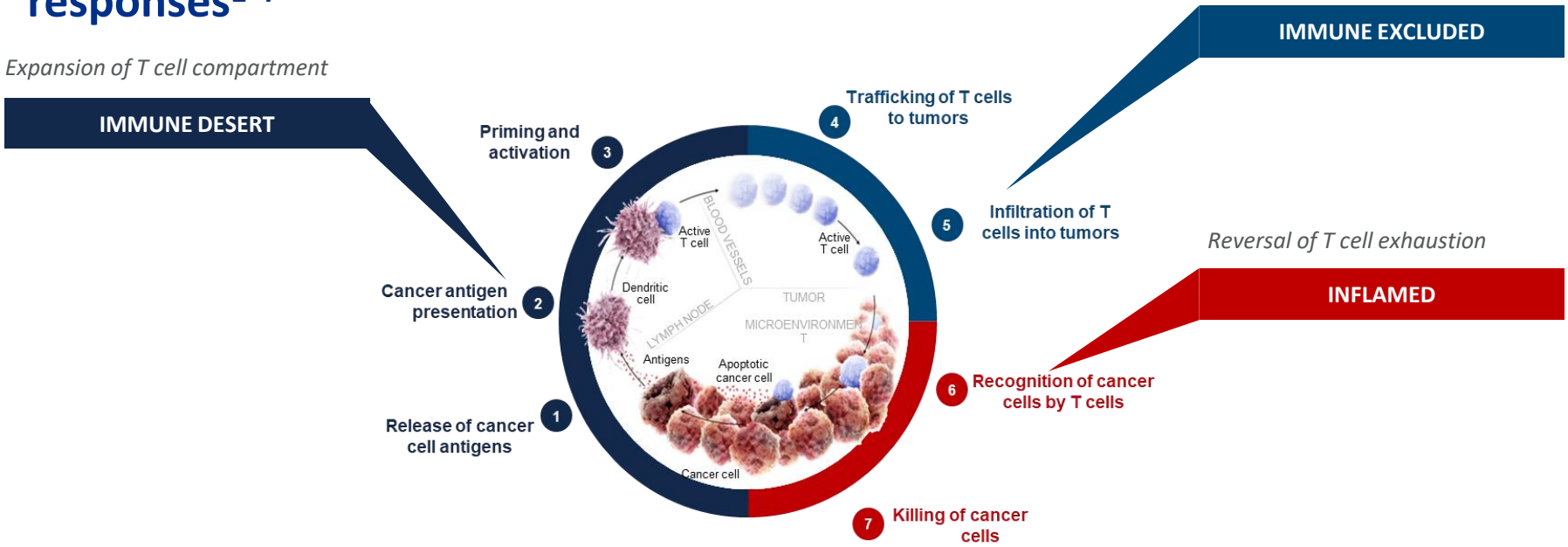
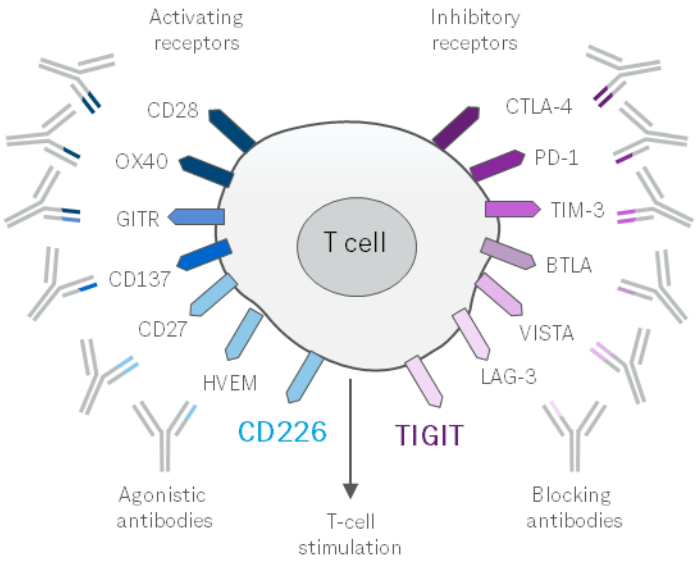
The cancer immunity cycle illustrates the potential of anti-tumor immune responses[1-4]



In some cases, targeting of one negative regulator may enable cancer immunity. Other cases may require additional strategies to enable cancer immunity.

1. Chen DS, Mellman I. *Immunity*. 2013;39(1):1-10. 2. Kim JM, Chen DS. *Annals Oncol*. 2016;27(8):1492-1504. 3. Hedge PS, et al. Clin Cancer *Res*. 2016;22(8):1865-1874. 4. Chen DS, Mellman I. *Nature*. 2017; 541(7631):321-330.

There are many T cell checkpoints to combine with PD-1/L1 blockade, why choose TIGIT?



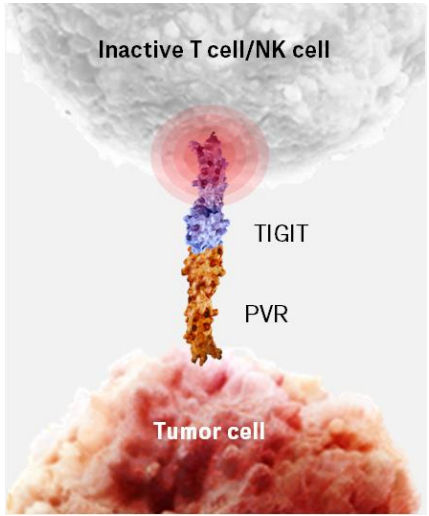
- TIGIT is a novel checkpoint inhibitor that is expressed on multiple immune cells, including CD8+, CD4+, regulatory T cells, and NK cells[2-6]
  - TIGIT has a co-inhibitory receptor role and counterbalances the co-stimulatory function of CD226
- TIGIT binds with high affinity to PVR and competes with CD226
  - After binding with PVR, TIGIT “turns off” the immune response by inhibiting T cell activation

ITIM=immunoreceptor tyrosine-based inhibition motif; NK=natural killer; PVR=poliovirus receptor; TIGIT=T-cell immunoglobulin and ITIM domain.

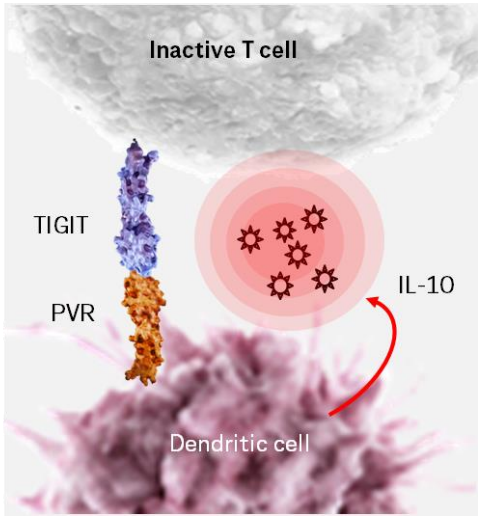
1. Figure adapted from Mellman I et al. *Nature* 2011. 2. Yu X et al. *Nature Immuno*. 2009;10(1):48-57. 3. Manieri et al. *Trends Immunol* 2017;38(1):20-28. 4. Rotte et al. *Annals of Oncol*. 2018;29:71-83. 5. Johnston et al. *Cancer Cell*. 2014;26:923-937. 6. Chiang and Mellman. *J Immunother Cancer* 2022;10(4):e004711.

TIGIT is proposed to inhibit T cell activation via three mechanisms

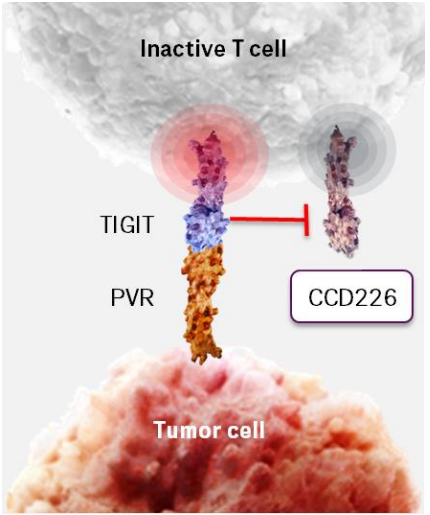
1 TIGIT inhibits T and NK cells by binding to PVR[2]



2 TIGIT down-modulates APCs to enhance production of immunosuppressive IL-10[1-4]



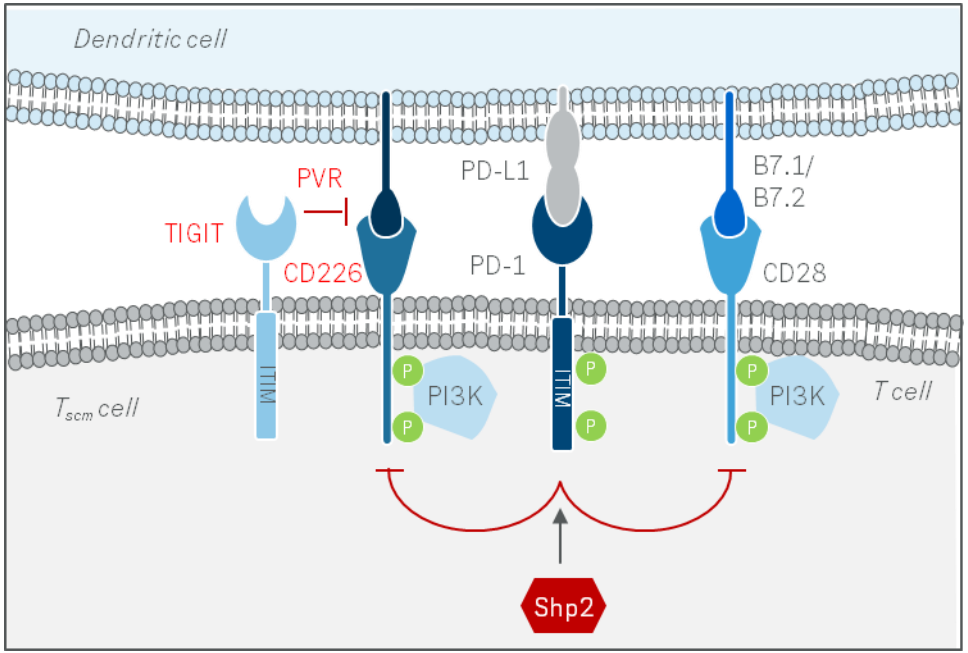
3 TIGIT inhibits positive signaling by the co-stimulatory CD226 receptor by binding to PVR at a higher affinity[1-7]



APC=antigen presenting cells; IL=interleukin; ITIM=immunoreceptor tyrosine-based inhibition motif; NK=natural killer; PVR=poliovirus receptor; TIGIT=T-cell immunoglobulin and ITIM domain.

1. Figure adapted from Manieri et al. *Trends Immunol*. 2017;38(1):20-28. 2. Yu X et al. *Nature Immuno*. 2009;10(1):48-57. 3. Dardalhon et al. *J Immunol*. 2005;175:1558–1565. 4. Carlsten et al. *Cancer Res.* 2007; 67:1317-25. 5. Levin et al. *Eur J Immunol*. 2011;s41(4):902-15. 6. Chiang and Mellman. *J Immunother Cancer* 2022;10(4):e004711.
7. Banta et al. *Immunity*. 202255:512-526.

The convergence of the TIGIT and PD-1 pathways



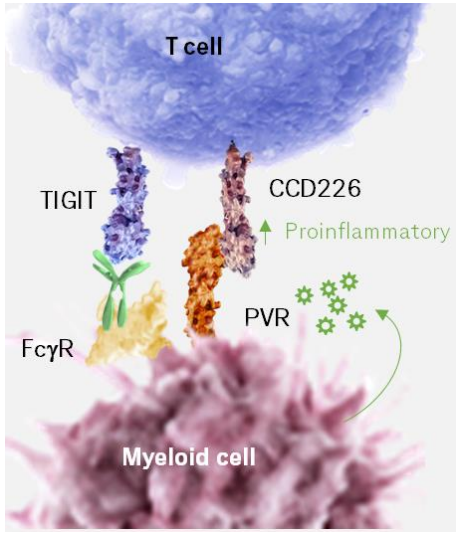
- The TIGIT pathway has a distinct but complementary effect to the PD-L1:PD-1 pathway on the immune response
- TIGIT and PD-1 inhibitory pathways converge to inactivate CD226, a key activating receptor required for full CD8+ T cell effector function
- PD-1 mediates dephosphorylation of both CD28 and CD226, thereby suppresses T cell function
- Optimal activation of costimulation requires coordinated inhibition of both TIGIT and PD-1

ITIM=immunoreceptor tyrosine-based inhibition motif; PD-1/PD-L1=programmed death protein-1/programmed death ligand-1; TIGIT=T-cell immunoglobulin and ITIM domain.

1. Banta K et al. *Immunity*. 2022;55:512-526.

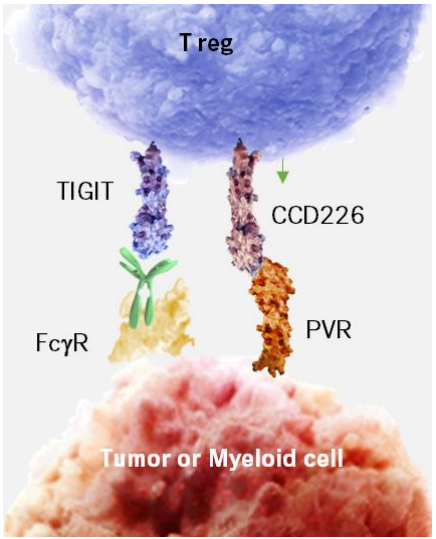
TIGIT activity may also reflect modulation of myeloid cells, CD226 suppression of Tregs, NK cell activation

Modulation of myeloid (dendritic) cells creates proinflammatory tumor microenvironment[1-3]



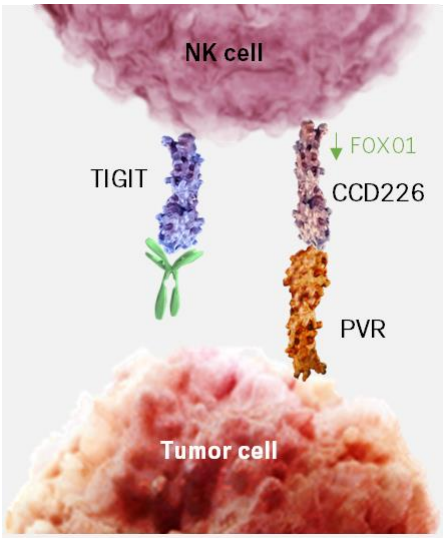
↑ Activation

CD226 signaling may dampen T_{reg} suppression, promote effector phenotype[2-4]



Reprogramming, Effector/inflammatory Treg depletion

TIGIT is also expressed by NK cells, unlike PD-1[4]



↑ Enhanced effector

1. Roche Analyst Event ASCO 2021 Presentation. Available at: https://www.roche.com. 2. Patil N, et al. Presented at SITC 2022. #P475. 3. Patil N et al. Presented at AACR 2023. Abst 57123. 4. Chiang and Mellman. *J Immunother Cancer* 2022;10(4):e004711.

Summary

- TIGIT expression is elevated in human cancers and strongly correlates with PD-1 expression and CD8+ T-cell infiltration. TIGIT expression in lung cancer samples suggests that TILs, particularly exhausted CD8+ T-cells, may express high levels of TIGIT and PD-1[1]
- PD-1 pathway inhibition may reactivate tumor-specific T-cells in lymph nodes, and combination with TIGIT inhibition could increase IFN-γ production and killing at the tumor site[2]
- Co-blockade of TIGIT and PD-L1 helps restore CD226 signaling and optimal anti-tumor CD8+ T cell activation and responses, and[3-5]
- Co-blockade of TIGIT and PD-L1 may lead to reprogramming of suppressive mechanisms in the tumor microenvironment to promote expansion and activation of CD8+ T-cells[6]

IFN=interferon; ITIM=immunoreceptor tyrosine-based inhibition motif; PD-1/PD-L1=programmed death protein-1/programmed death ligand-1; TIGIT=T-cell immunoglobulin and ITIM domain; TIL=tumor infiltrating lymphocytes

1. Johnston et al. *Cancer Cell*. 2014;26:923-937. 2. Yu X et al. *Nature Immuno*. 2009;10(1):48-57. 3 Manieri et al. *Trends Immunol* 2017;38(1):20-28. 4. Banta K et al. *Immunity*. 2022;55:512-526. 5. Chiang and Mellman. *JITC*. 2022;10:e004711. 6. Patil N, et al. Presented at SITC 2022. #P475.