INHIBITING TIGIT TO PROMOTE ANTI-TUMOR IMMUNITY

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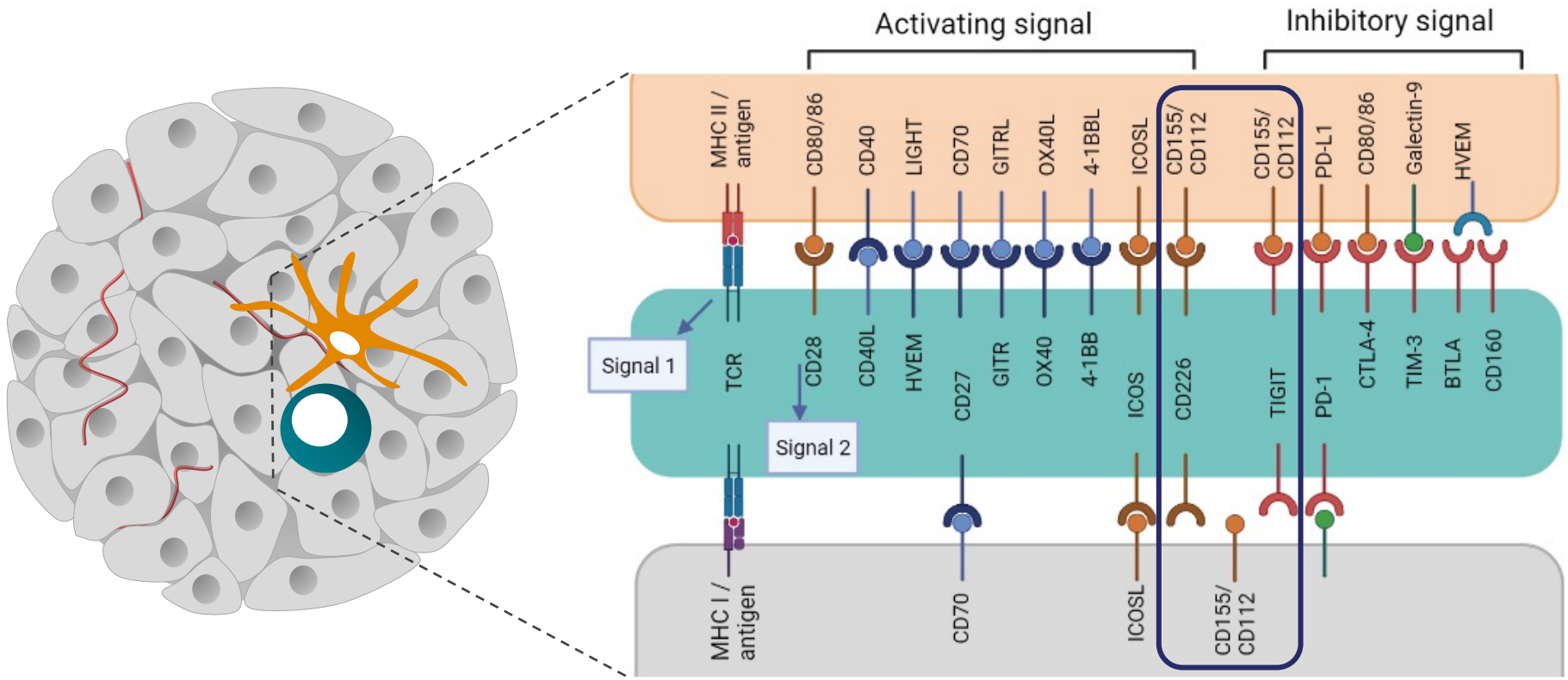
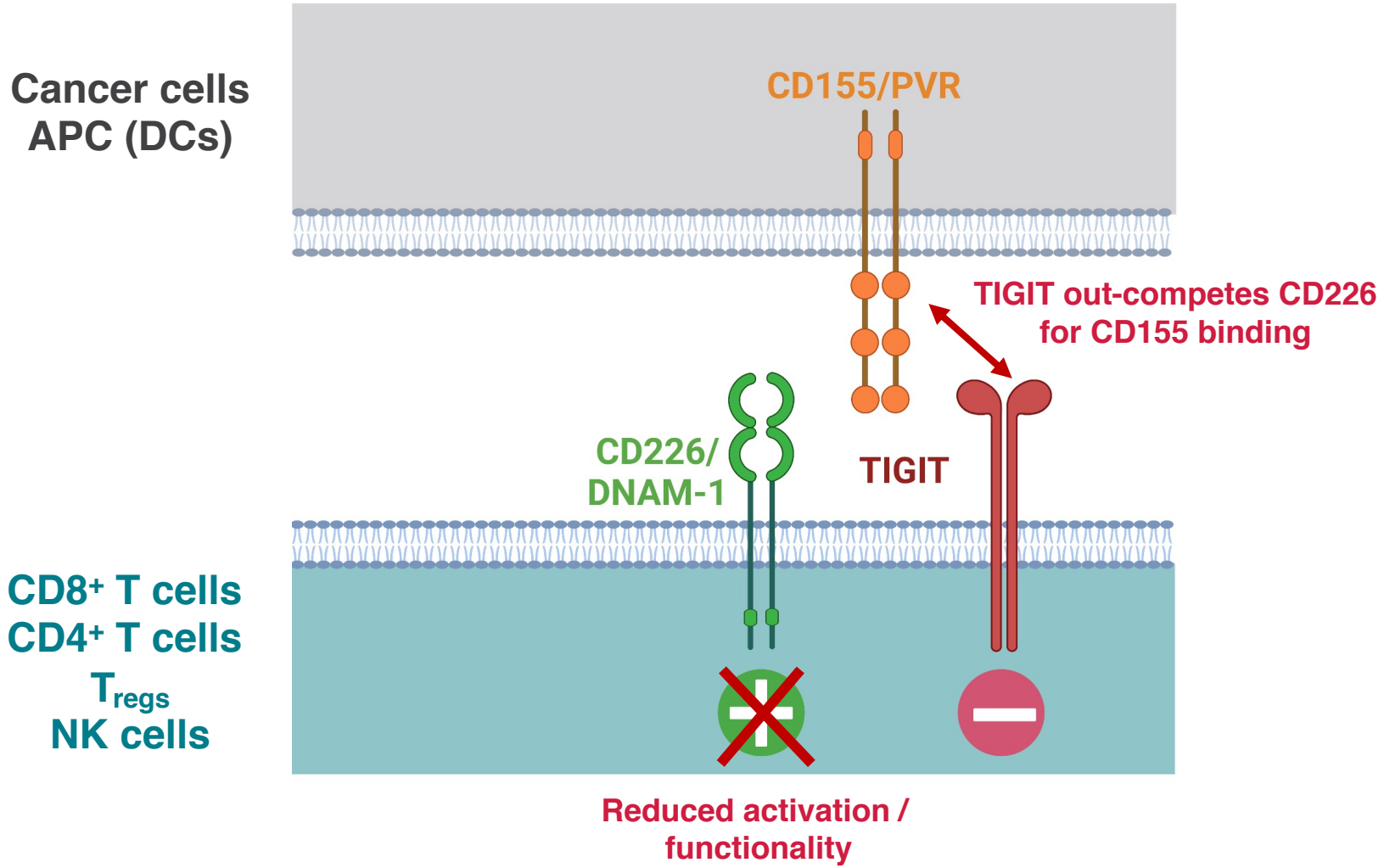
Molecular Suppression of T Cells in the Tumor Microenvironment: T Cell Inhibitory Receptors (Checkpoints)

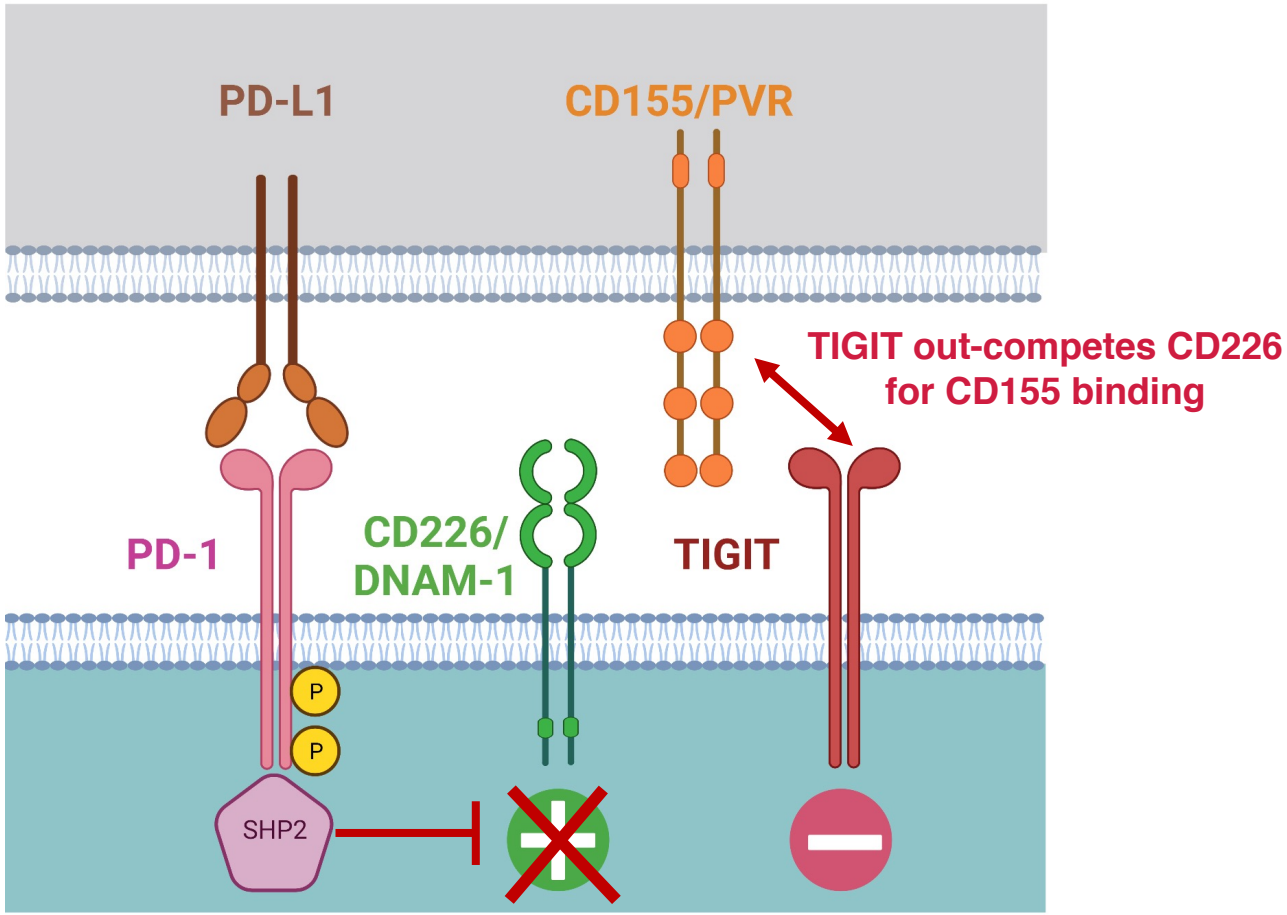


TIGIT is an Inhibitory Receptor That Out-Competes CD226 Activating Receptor for CD155 Binding, Resulting in Immunosuppression



Similar to the PD-1/CD28 Interaction, PD-1 Has Also Been Shown to Restrict CD226 Signaling

Cancer cells
APC (DCs)



CD8+ T cells
CD4+ T cells
T_{regs}
NK cells

Reduced activation / functionality

Banta *et al.* (2022) Immunity, DOI: 10.1016/j.immuni.2022.02.005

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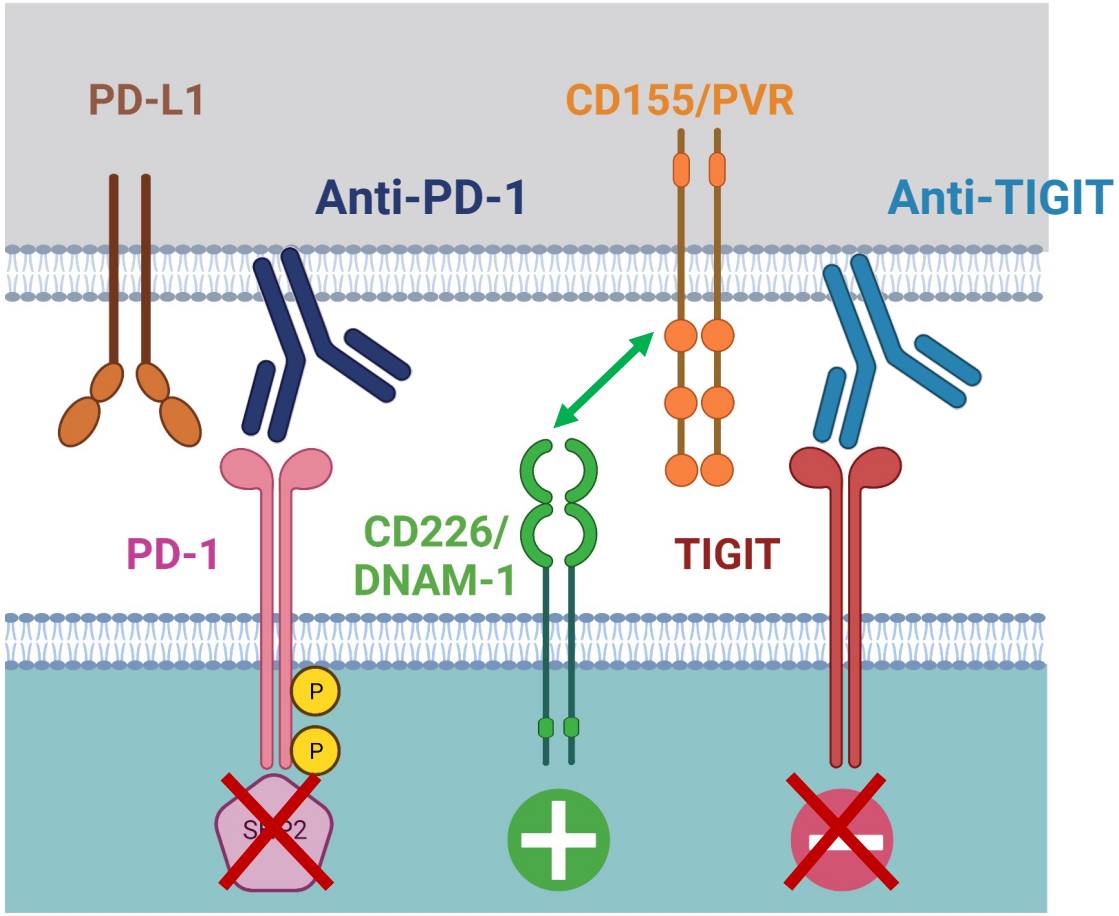
CD226 Signaling Can be Enhanced Through Co-blockade of PD-1 and TIGIT

Cancer cells
APC (DCs)



CD8+ T cells
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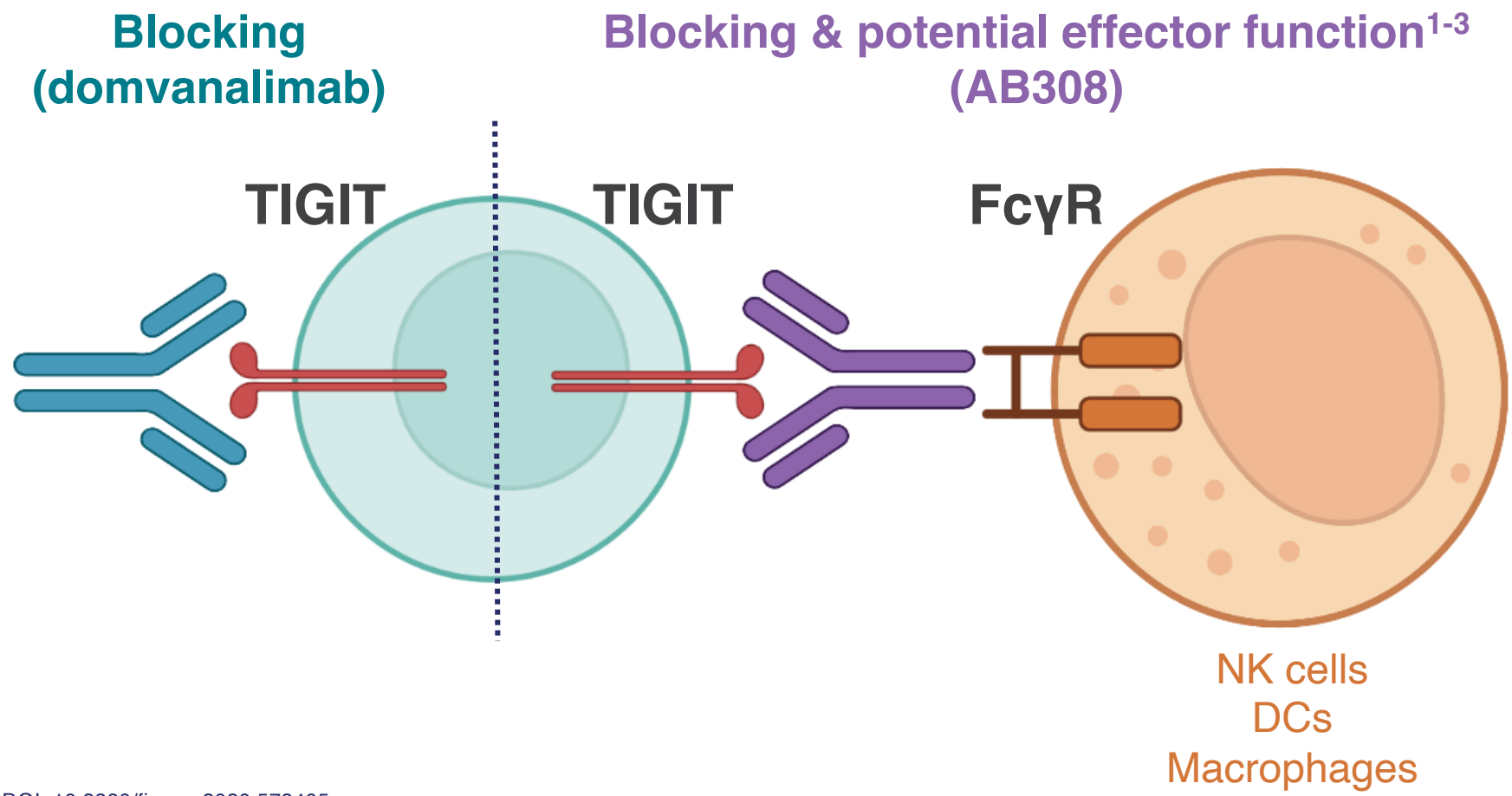
NK cells

Increased activation / functionality

Banta *et al.* (2022) Immunity, DOI: 10.1016/j.immuni.2022.02.005

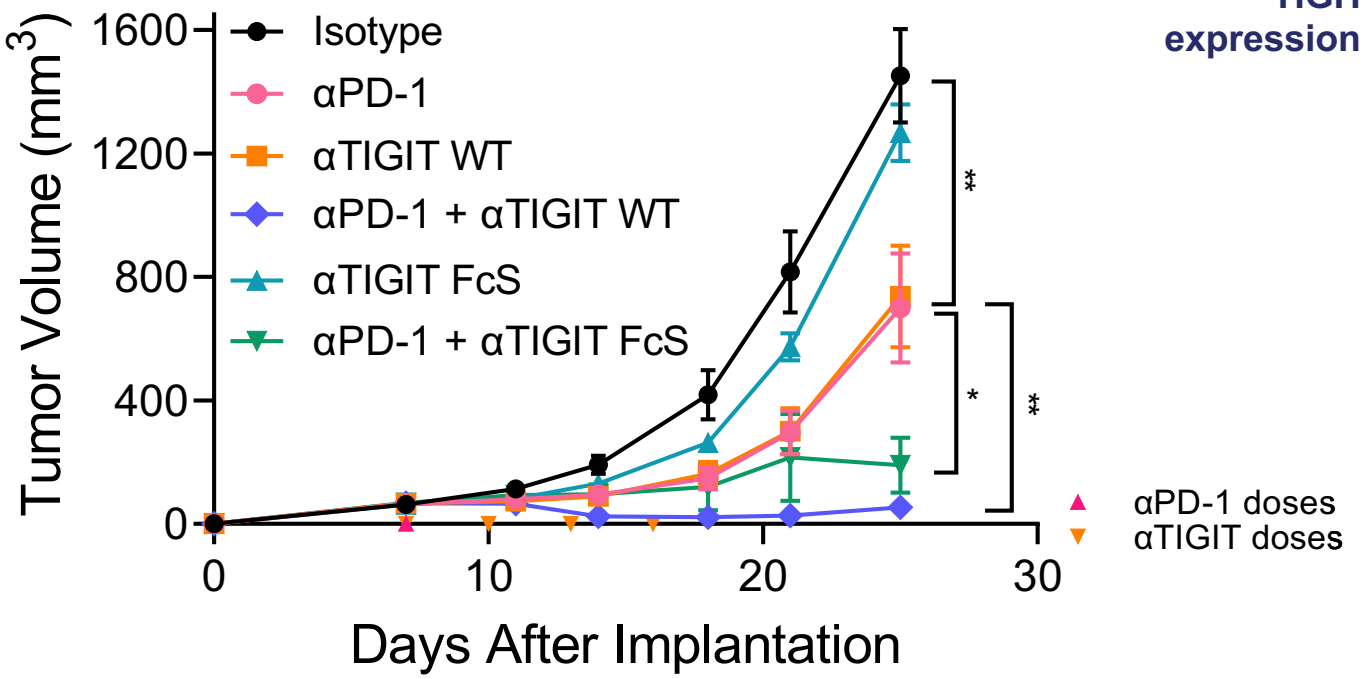
Domvanalimab (Fc-silent) and AB308 (Fc-enabled) are Potent Anti-TIGIT Antibodies Currently Being Evaluated in Cancer Patients



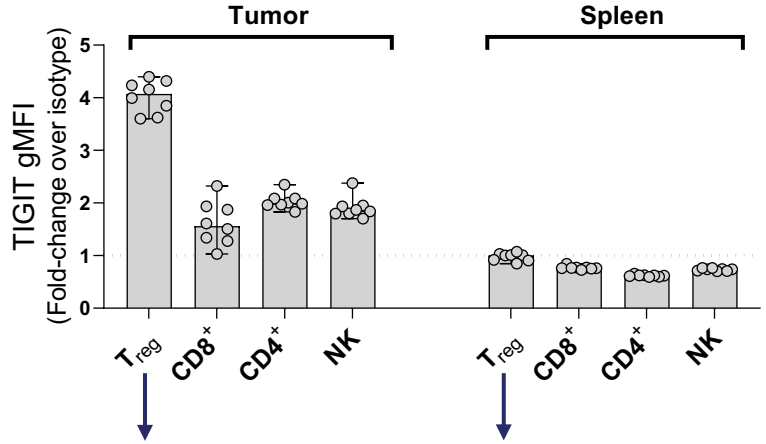
[1]Han *et al.* (2020) Frontiers in Immun. DOI: 10.3389/fimmu.2020.573405
[2]Waight *et al.* (2018) Cancer Cell. DOI: 10.1016/j.ccell.2018.05.005
[3]Chen *et al.* (2022) Frontiers in Immun. DOI: 10.3389/FIMMU.2022.828319/BIBTEX

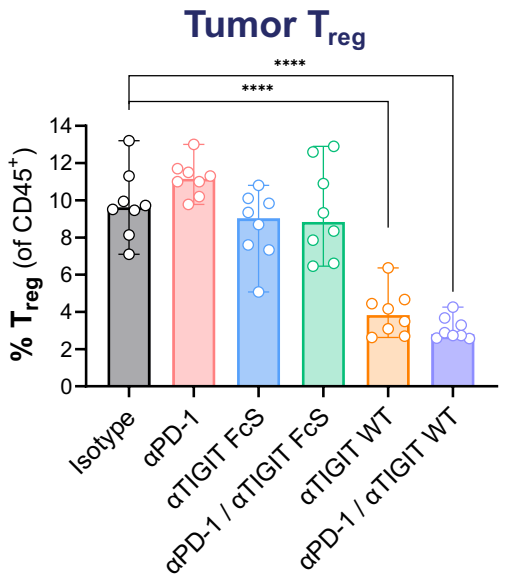
In Mice, Combination of α-PD-1 with Either Fc-Silent (FcS) or Fc-Enabled (WT) α-TIGIT Enhances Tumor Control

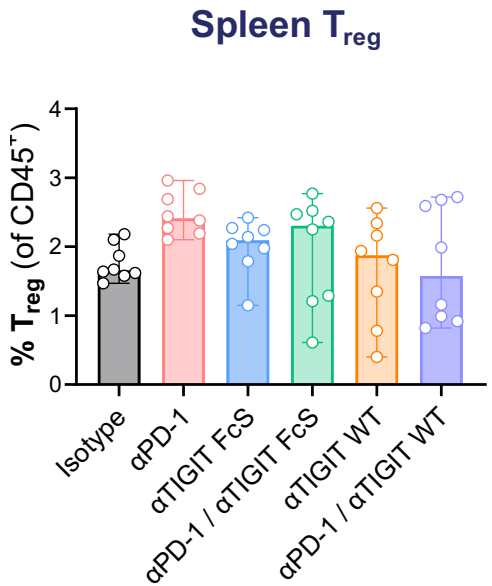
α-TIGIT-WT Associated With Intratumoral T_{reg} Depletion



TIGIT expression levels



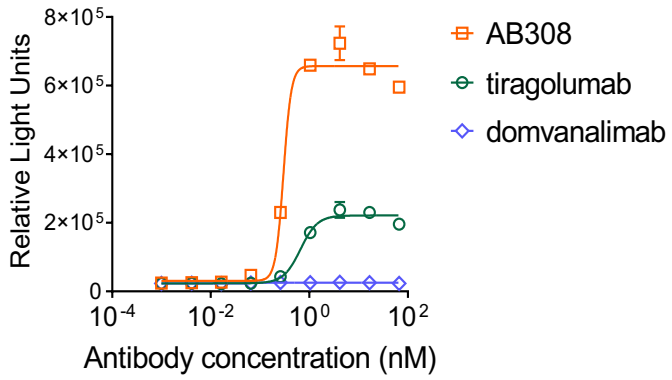


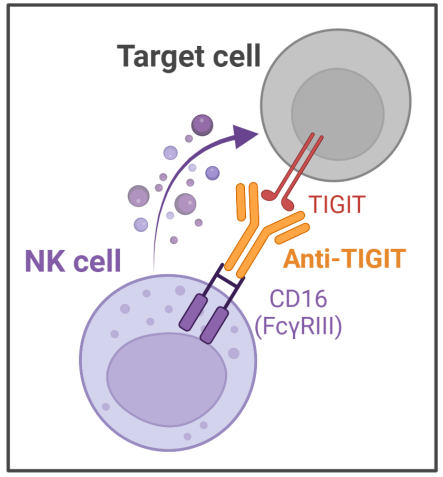


WT = mIgG2a
Fc-silent (FcS) = mIgG2a with L234A/ L235A / P329G mutations in heavy chain

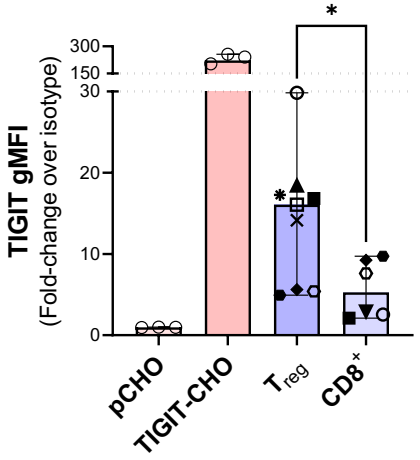
In Human, Fc-enabled AB308 and tiragolumab Induce FcγR-mediated Signaling and Promote NK-mediated ADCC Against TIGIT-Expressing Target Cells

FcγRIIIa V158 (high affinity)

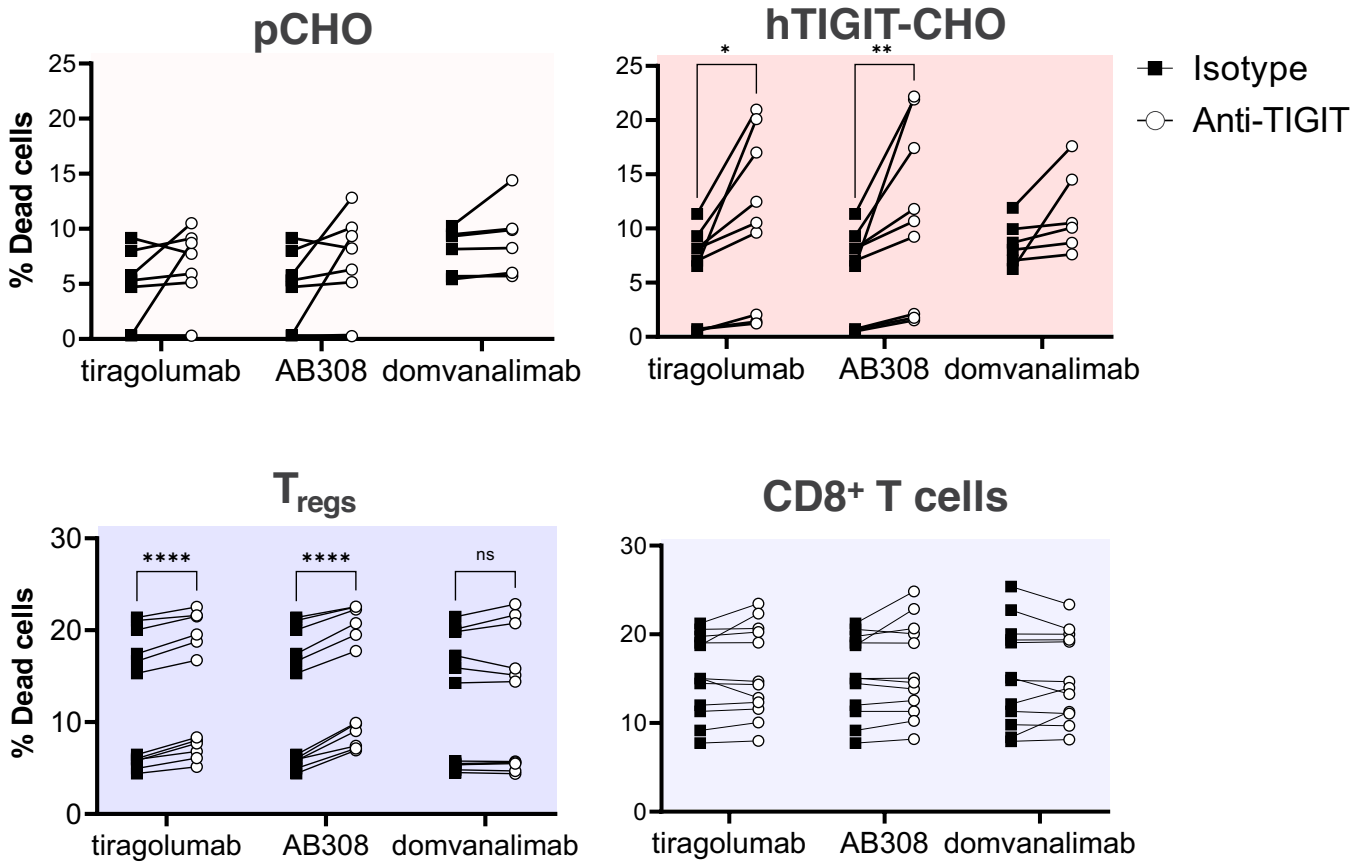




TIGIT expression on target cells



NK-mediated ADCC



tiragolumab synthesized by Arcus based on INN publication

What is the Identity of TIGIT-expressing T cells Modulated by Treatment with Anti-TIGIT Antibodies?

Pre-dysfunctional/Stem-like CD8⁺ T cells activated by anti-PDx are also probable targets for anti-TIGIT

Increased pool of T cells capable of differentiating into cells with enhanced cytotoxic/effector potential

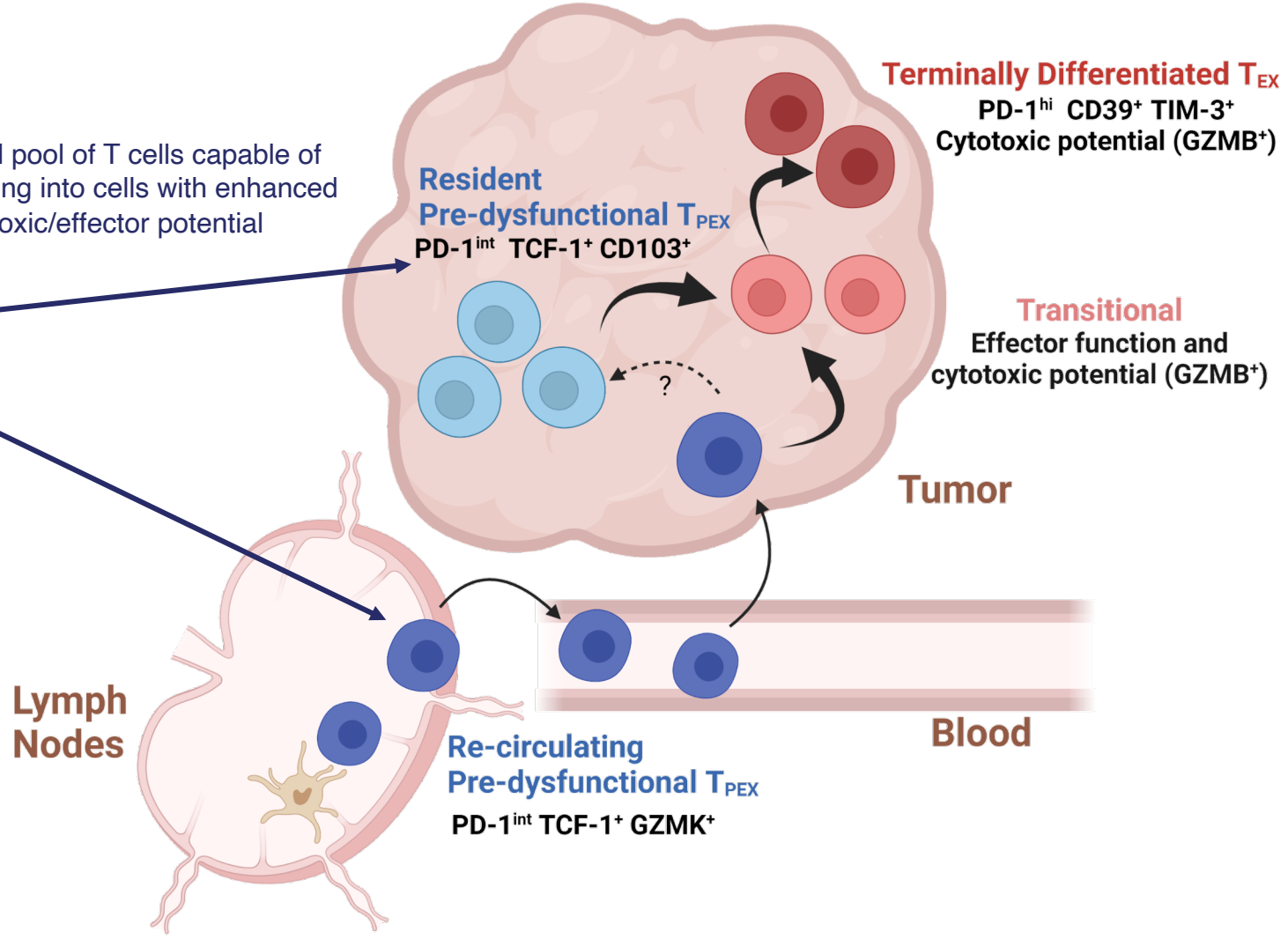
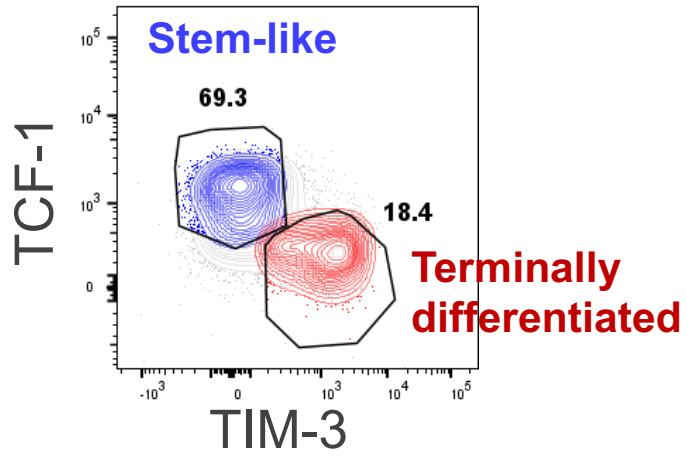


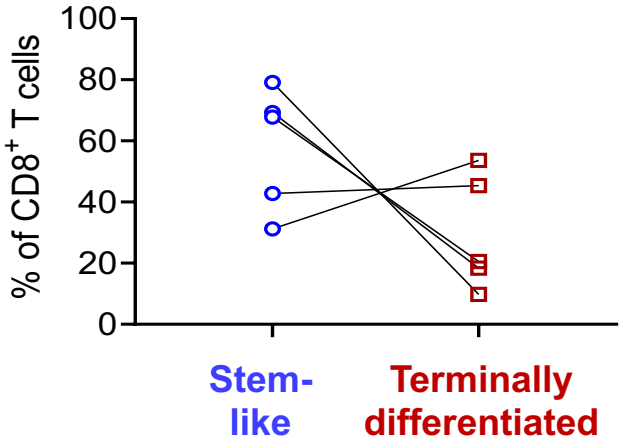
Figure informed by:

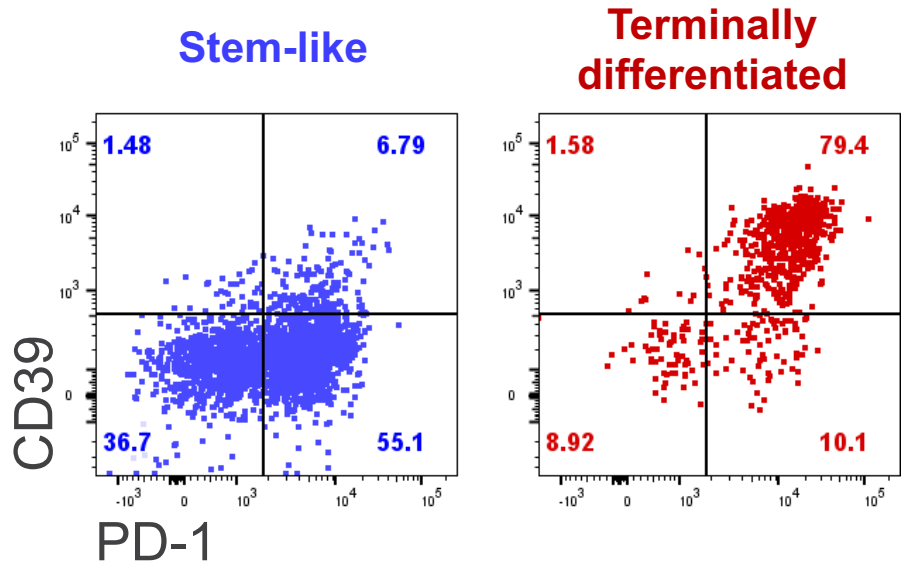
Budimir *et al.*(2022) Cancer Immunol Res, DOI: 10.1158/2326-6066
Siddiqui *et al.* (2019) Immunity, DOI: 10.1016/J.IMMUNI.2018.12.021
Sade-Feldman *et al.* (2018) Cell, DOI: 10.1016/J.CELL.2018.10.038
Connolly *et al. (*2021) Science Immunol, DOI: 10.1126/sciimmunol.abg7
Jansen *et al. (*2019) Nature, DOI: 10.1038/s41586-019-1836-5
Miller *et al.* (2019) Nat Immunol, DOI: 10.1038/s41590-019-0312-6

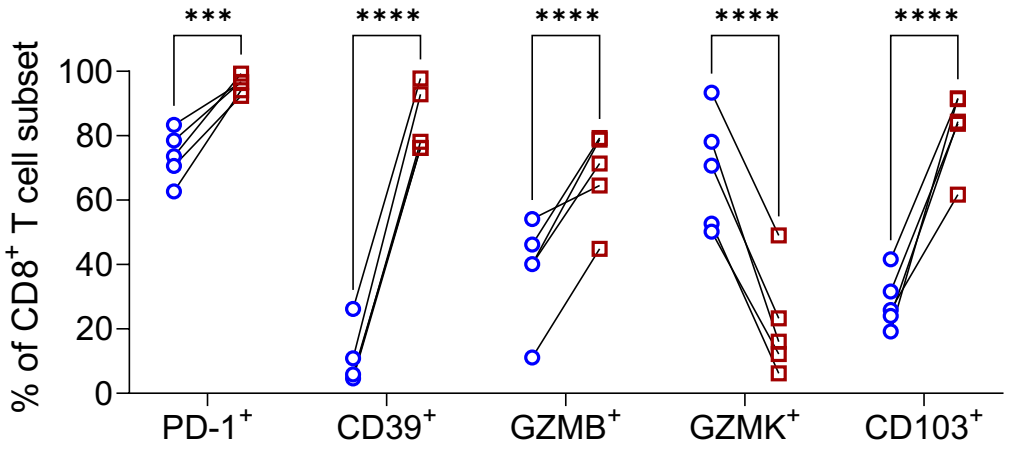
Stem-like (TCF-1+) and Terminally Differentiated (TIM-3+) CD8+ T Cells are Present in NSCLC Tumors

Gated on CD8+ T cells

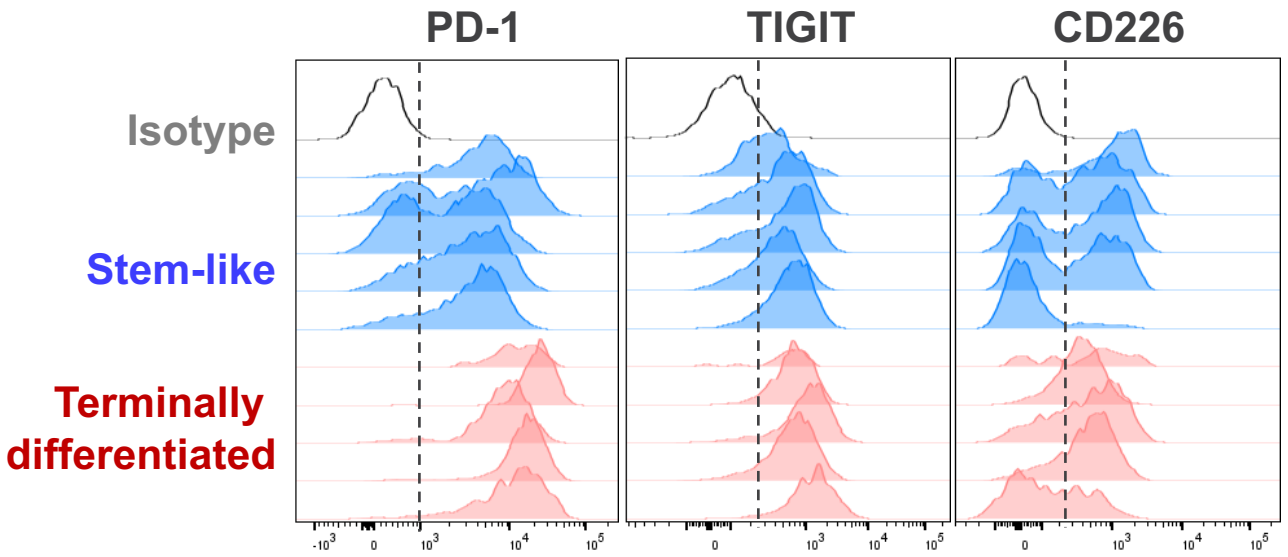


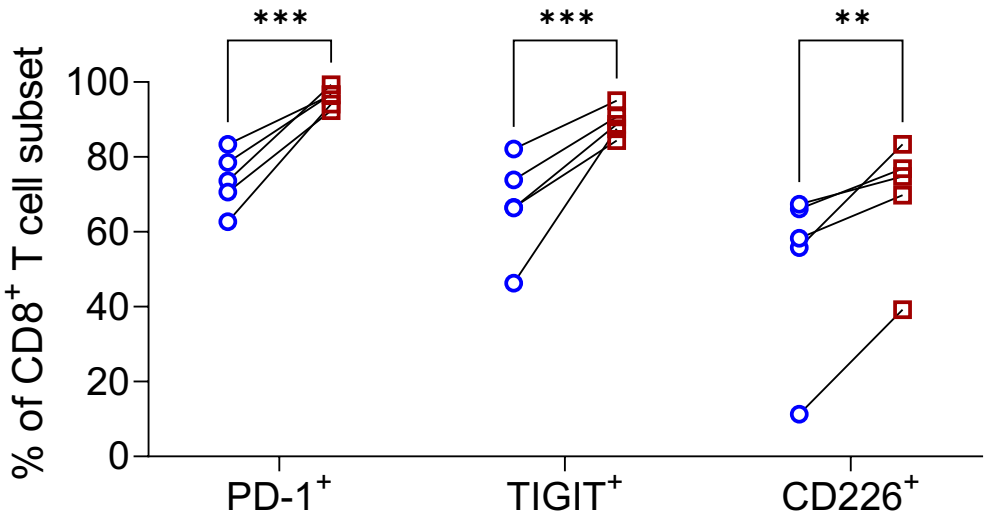




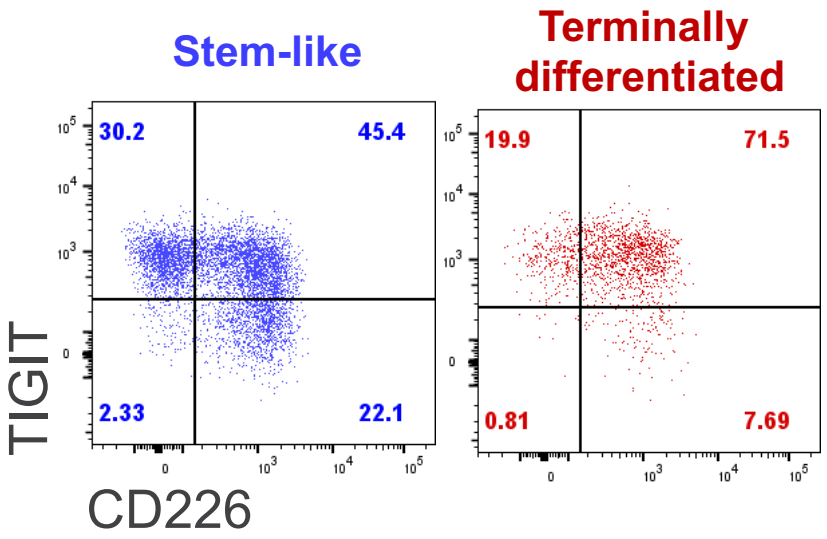


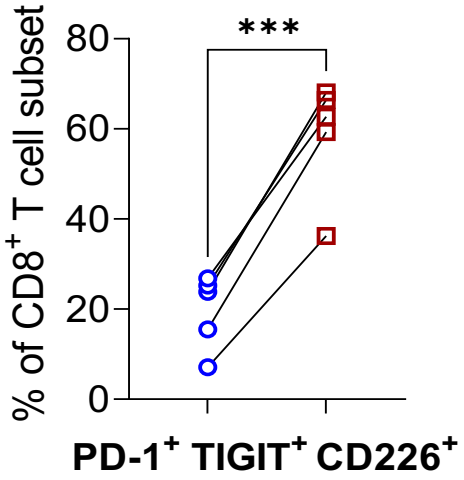
In NSCLC Tumors, PD-1, TIGIT, and CD226 are Expressed on a High Proportion of Both Stem-like and Terminally Differentiated CD8+ T Cells

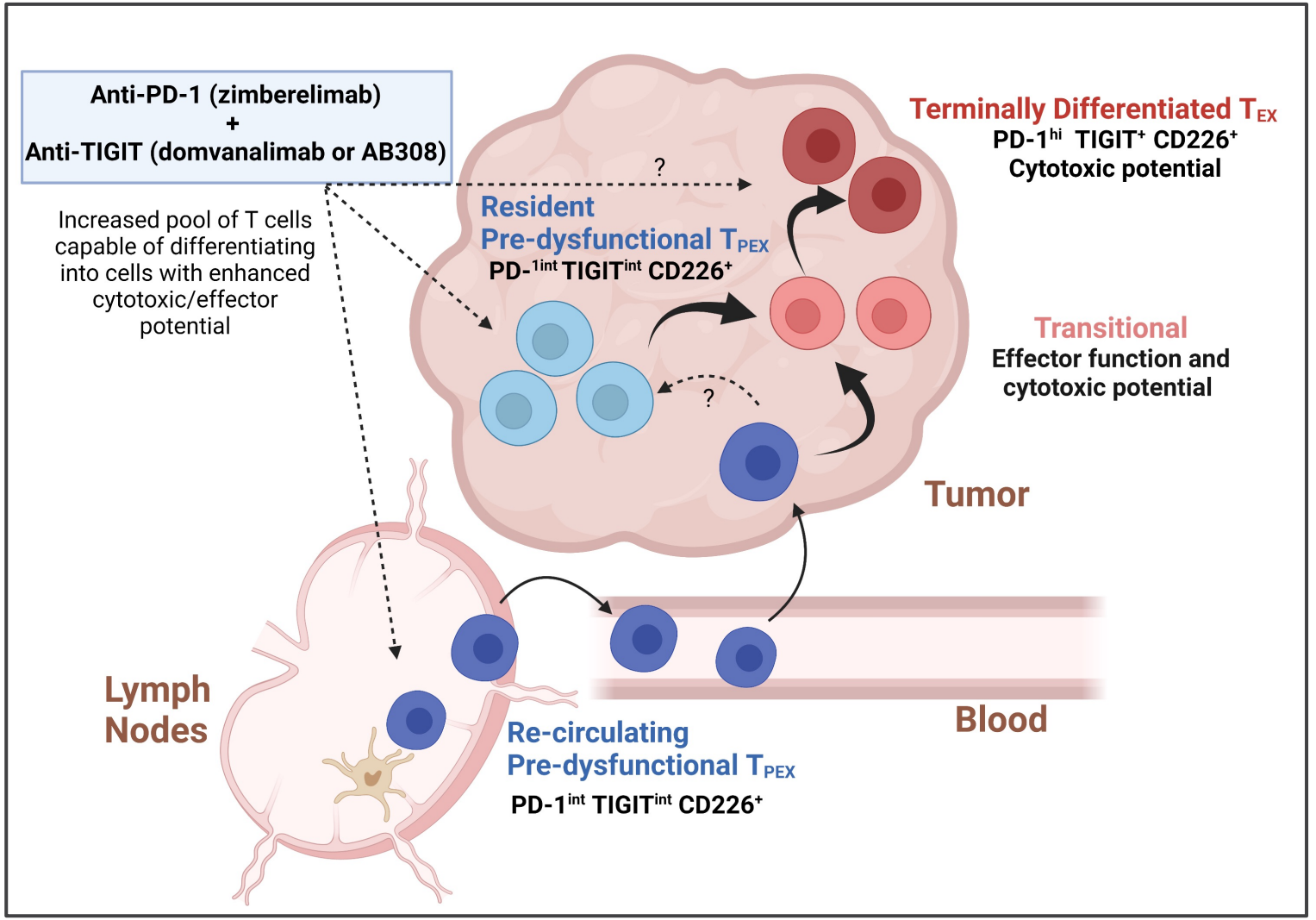




PD-1+TIGIT+CD226+ Stem-like CD8+ T cells are Probable Targets for Co-blockade of PD-1 and TIGIT







Conclusions and Future Directions

- **Fc-enabled AB308, but not Fc-silent domvanalimab, has the capacity to bind Fcγ receptors and promote NK-mediated ADCC**
- **PD-1, TIGIT, and CD226 are co-expressed on both stem-like and terminally differentiated intratumoral $CD8^+$ T cell subsets in NSCLC subjects**
- **Akin to reported cellular targets of anti-PD-(L)1[1], PD-1, TIGIT, and CD226 co-expressing stem-like $CD8^+$ T cells are probable targets for anti-TIGIT therapy**
- **Given that stem-like $CD8^+$ T cells are essential for anti-tumor responses[1] and that PD-1 and TIGIT can both suppress CD226 activity[2], further work is required to understand how co-blockade of PD-1 and TIGIT impacts $PD\text{-}1^+TIGIT^+CD226^+$ stem-like $CD8^+$ T cells**

[1]Budimir *et al.*(2022) Cancer Immunol Res, DOI: 10.1158/2326-6066
[2]Banta *et al.* (2022) Immunity, DOI: 10.1016/j.immuni.2022.02.005

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