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/CD226 Pathway
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

Banta et al. (2022) Immunity, DOI: 10.1016/j.immuni.2022.02.005
CD226 Signaling Can be Enhanced Through Co-blockade of PD-1 and TIGIT

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

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

**MC38**

- **Tumor Volume (mm³)**
  - Isotype
  - αPD-1
  - αTIGIT WT
  - αPD-1 + αTIGIT WT
  - αTIGIT FcS
  - αPD-1 + αTIGIT FcS

- **TIGIT expression levels**

**Days After Implantation**

WT = mlG2a  
Fc-silent (FcS) = mlG2a with L234A/ L235A / P329G mutations in heavy chain
In Human, Fc-enabled AB308 and tiragolumab Induce FcyR-mediated Signaling and Promote NK-mediated ADCC Against TIGIT-Expressing Target Cells

**FcyRllla V158 (high affinity)**

- AB308
- tiragolumab
- domvanalimab

**NK-mediated ADCC**

- pCHO
- hTIGIT-CHO

- Isotype
- Anti-TIGIT

**Target cell**

- TIGIT expression on target cells

- CD16 (FcyRIII)

**NK cell**

- TIGIT

**Tregs**

- ****

- ns

**CD8+ T cells**

- tiragolumab
- AB308
- domvanalimab

* 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/effect potential

Figure informed by:
Budimir et al. (2022) Cancer Immunol Res, DOI: 10.1158/2326-6066
Connolly et al. (2021) Science Immunol, DOI: 10.1126/sciimmunol.abg7
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

Stem-like

Terminally differentiated

% of CD8+ T cells

100
80
60
40
20
0
Stem-like
Terminally differentiated

% of CD8+ T cell subset

100
80
60
40
20
0

PD-1+
CD39+
GZMB+
GZMK+
CD103+

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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, 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 and that PD-1 and TIGIT can both suppress CD226 activity, further work is required to understand how co-blockade of PD-1 and TIGIT impacts PD-1⁺TIGIT⁺CD226⁺ stem-like CD8⁺ T cells

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