Fc-SILENT ANTI-TIGIT ANTIBODIES POTENTIATE ANTI-TUMOR IMMUNITY WITHOUT DEPLETING REGULATORY T CELLS

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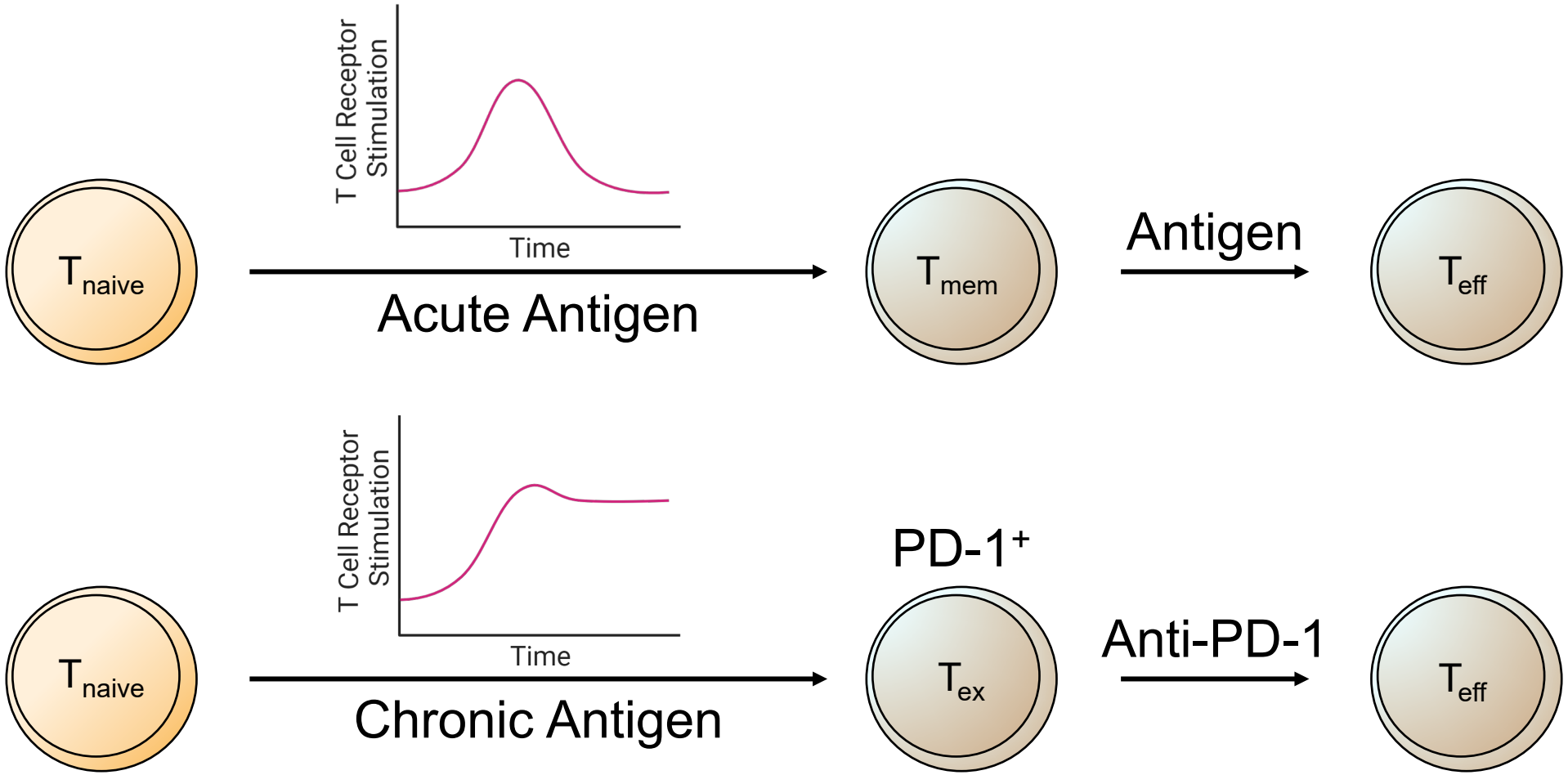
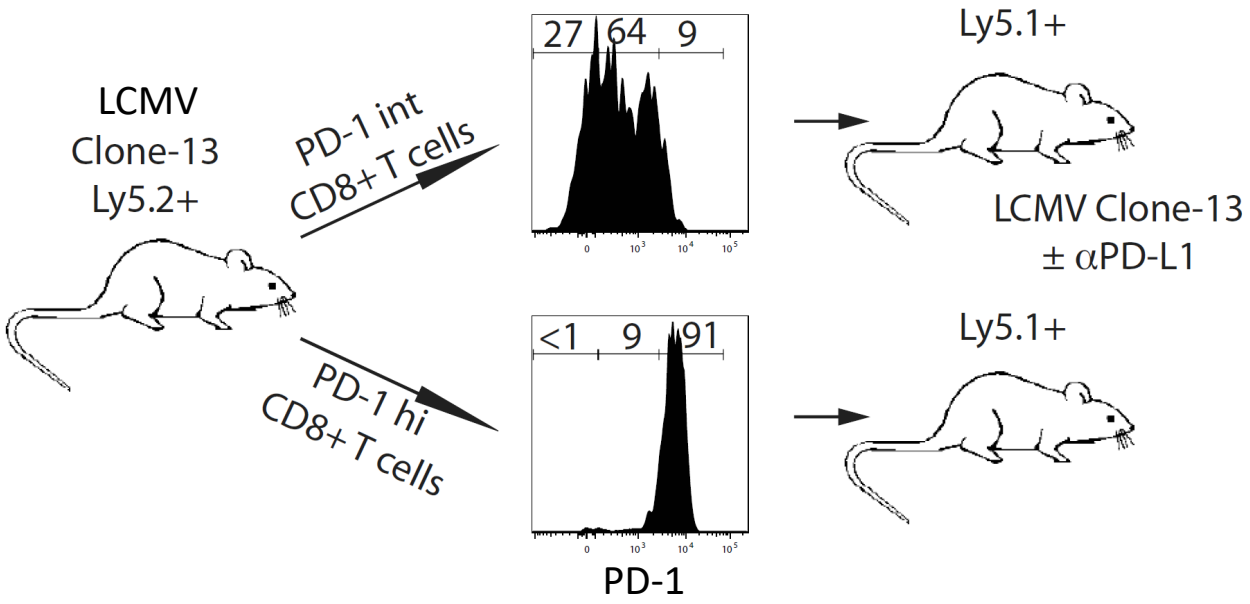
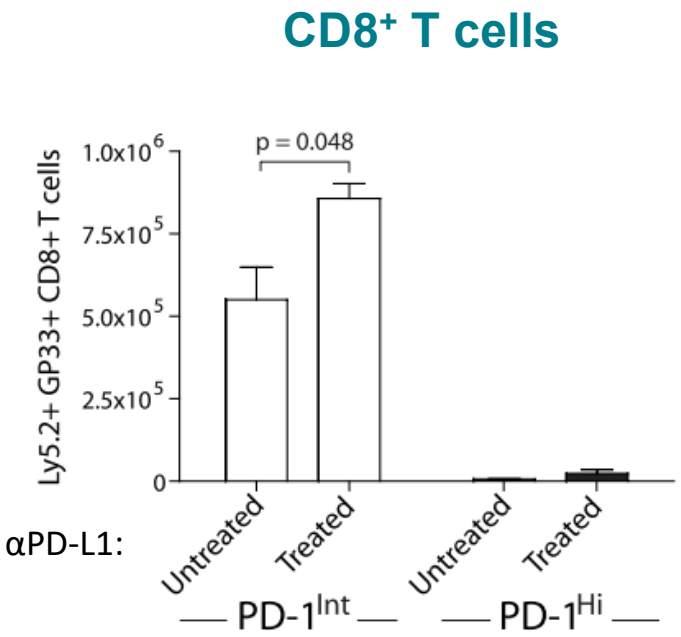
T Cell Exhaustion is a Distinct Differentiation Pathway in Response to Chronic Antigen Exposure



Not All Exhausted T Cells Are Created Equal

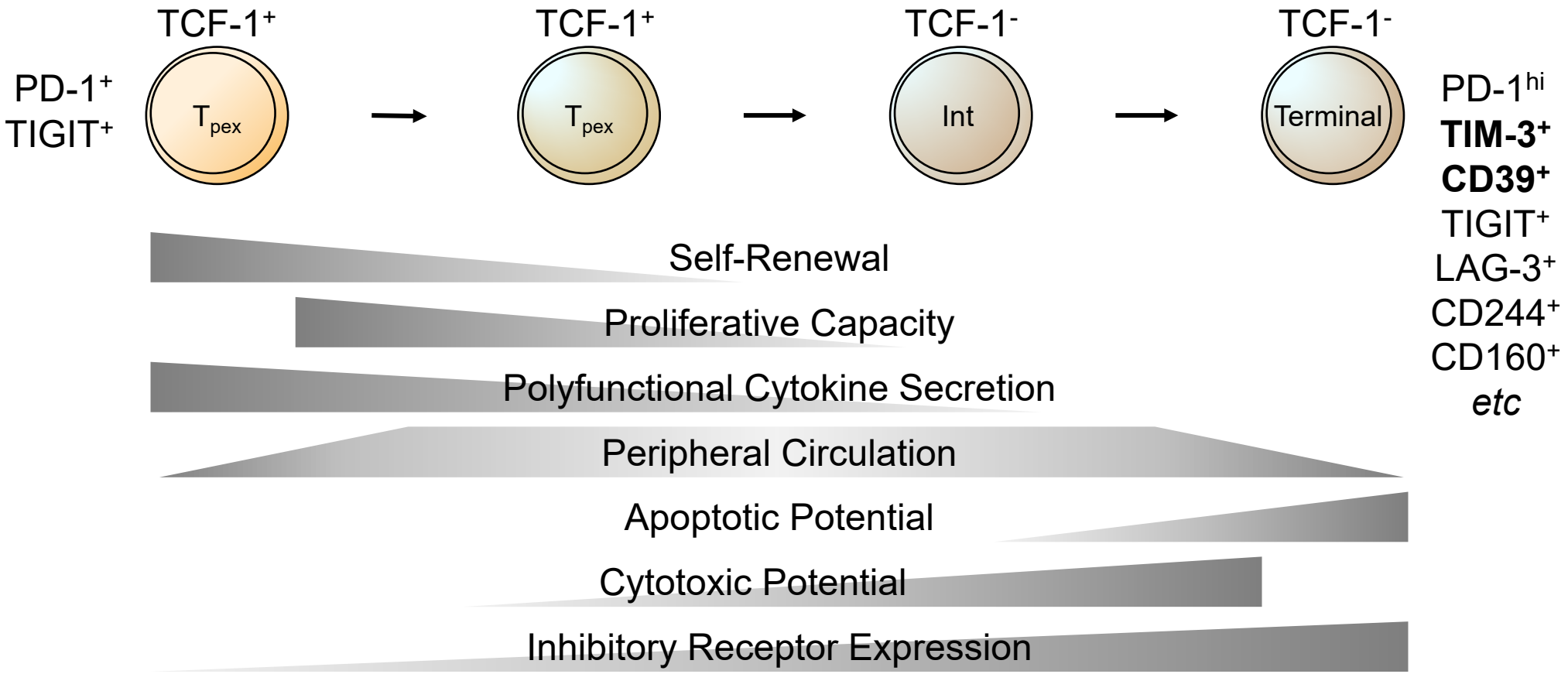




Modified from: Blackburn *et al* (2008) PNAS

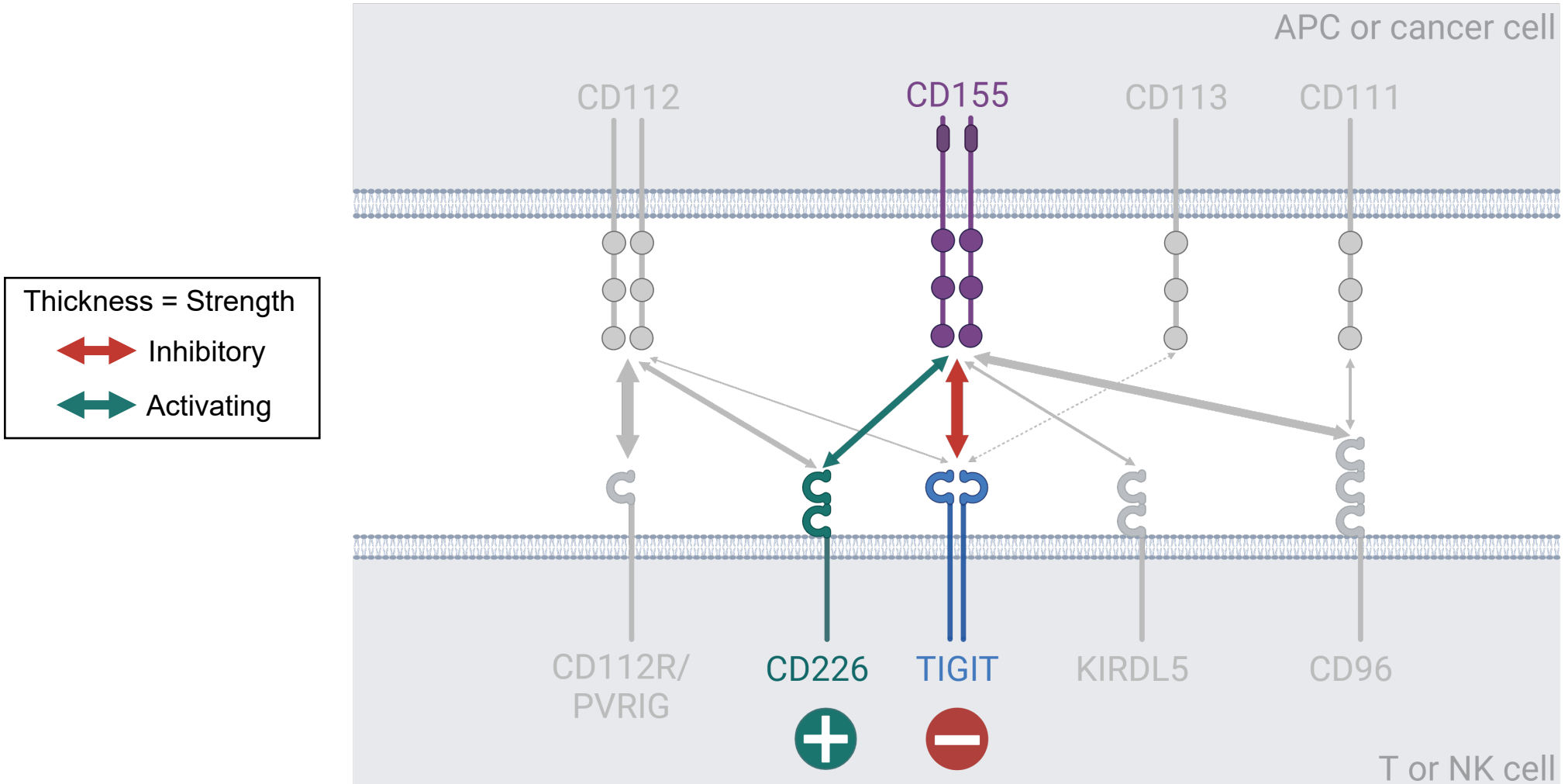
Pre-exhausted T Cells (T_{pex}) are Targets for Anti-PDx

Exhausted T cell Differentiation is a Continuum of Functional States



Beltra *et al* (2020) Immunity; McLane, Abdel-Hajeem, & Wherry (2019) Ann Rev Immunol

Receptors and Ligands in the TIGIT Pathway Participate in Complex Molecular Cross-talk

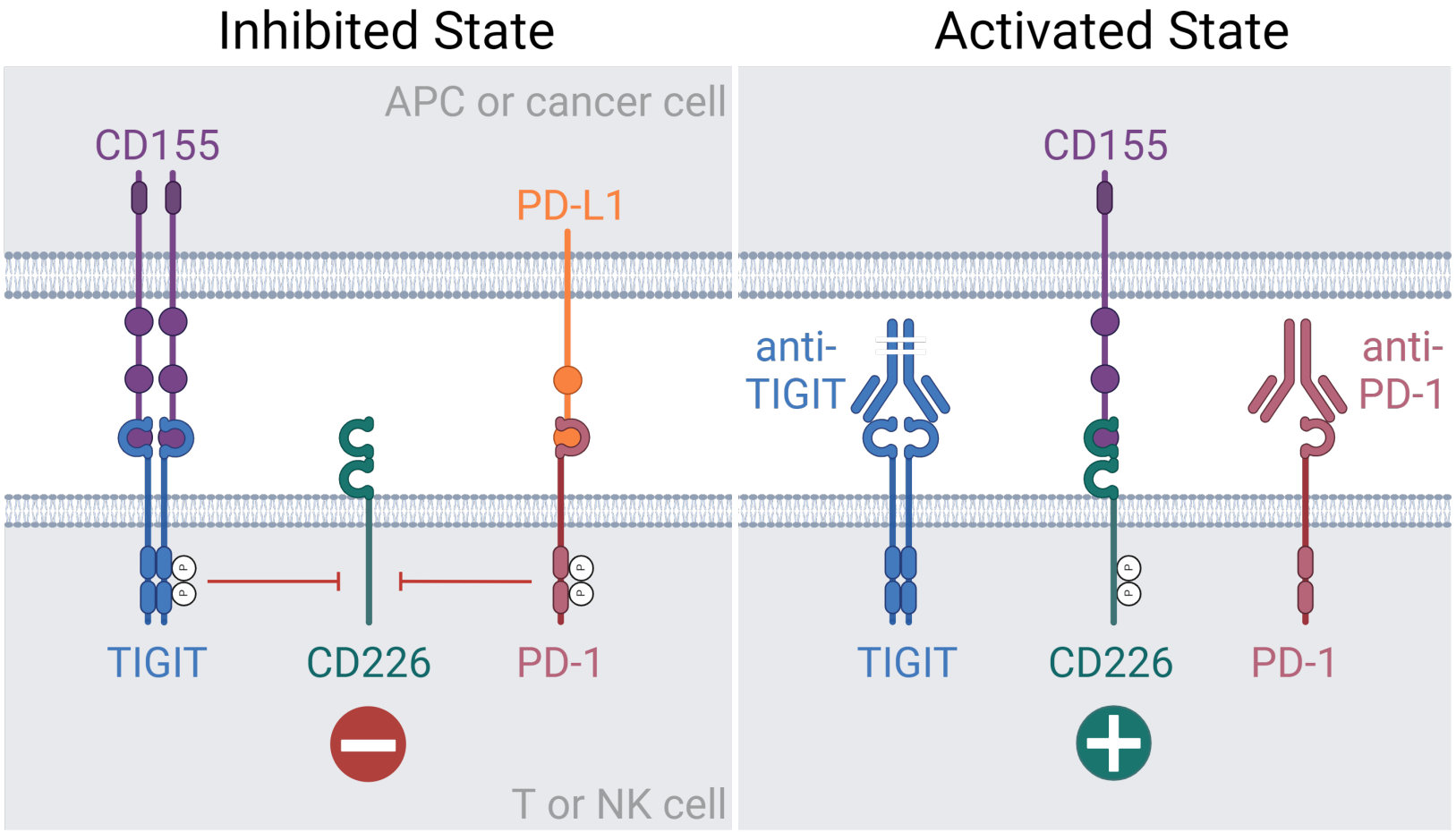


Adapted from: Chauvin & Zarour (2020) JITC, Holder & Grant (2020) Front Cell Inf Microbiol

Simultaneously Blocking TIGIT↔CD155 & PD-1↔PD-L1 Interactions Promotes Effector Cell Activation

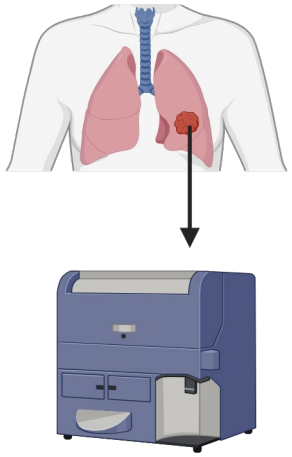
- **TIGIT and PD-1 play distinct, yet complementary roles in suppressing anti-tumor responses**

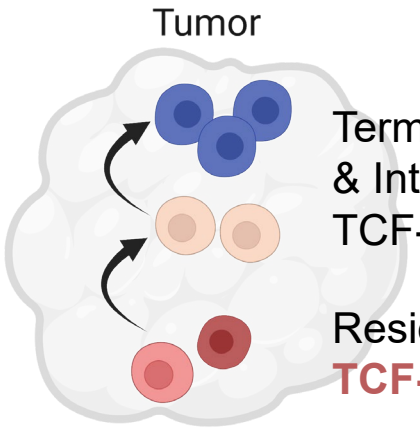
Do T_{pex} subsets in the NSCLC tumor microenvironment co-express TIGIT, PD-1, and CD226?



Wang *et al* (2018) Sci Immunol; Banta *et al* (2022) Immunity;
Jin *et al* (2020) Cancer Immunol Res; Worboys *et al* (2023) Nat Comm

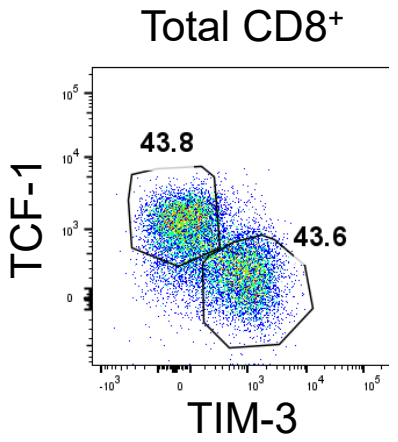
Exhausted T-cell Subsets in Human NSCLC Tumors Express PD-1, TIGIT, and CD226

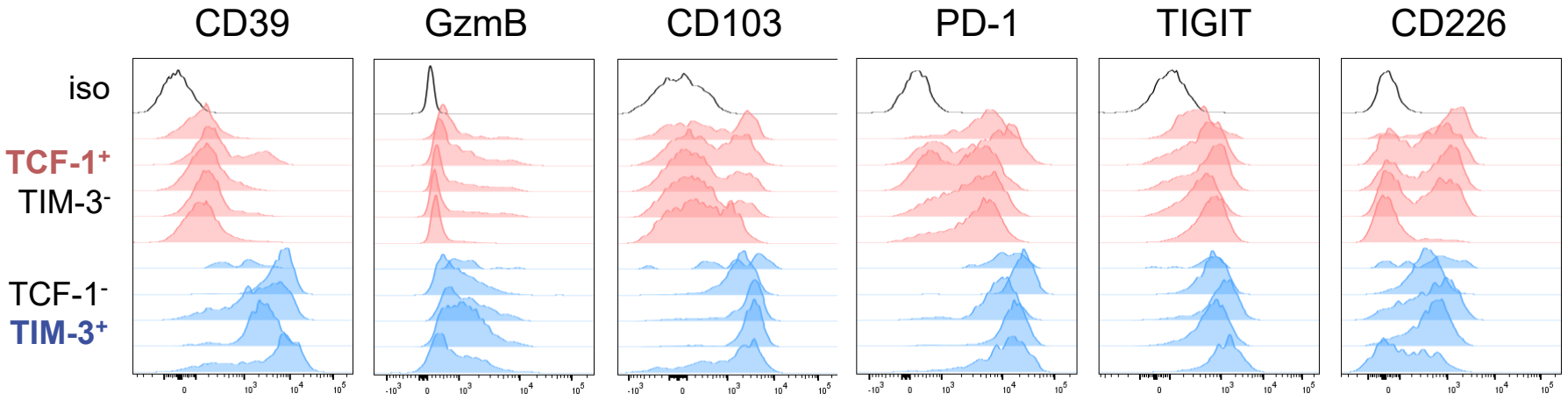


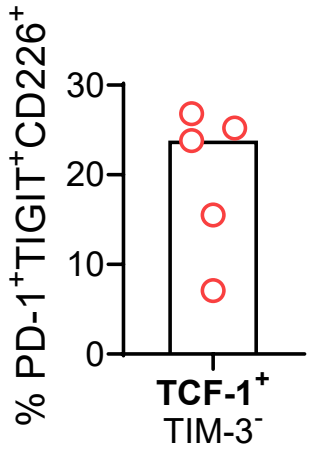


Terminally Differentiated & Intermediate
TCF-1^{-}**TIM-3^{+}**

Resident & Circulating (T_{pex})
TCF-1^{+}TIM-3^{-}

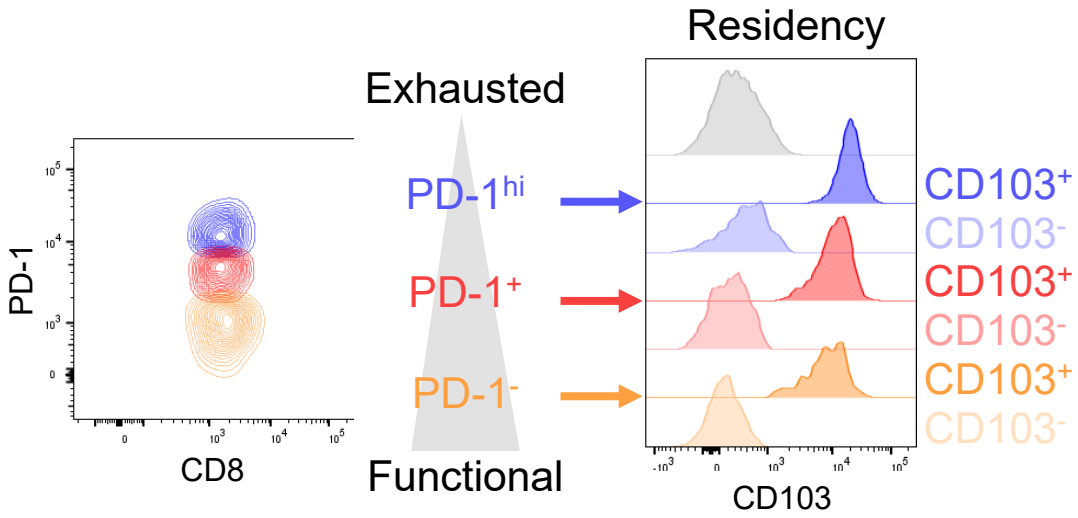


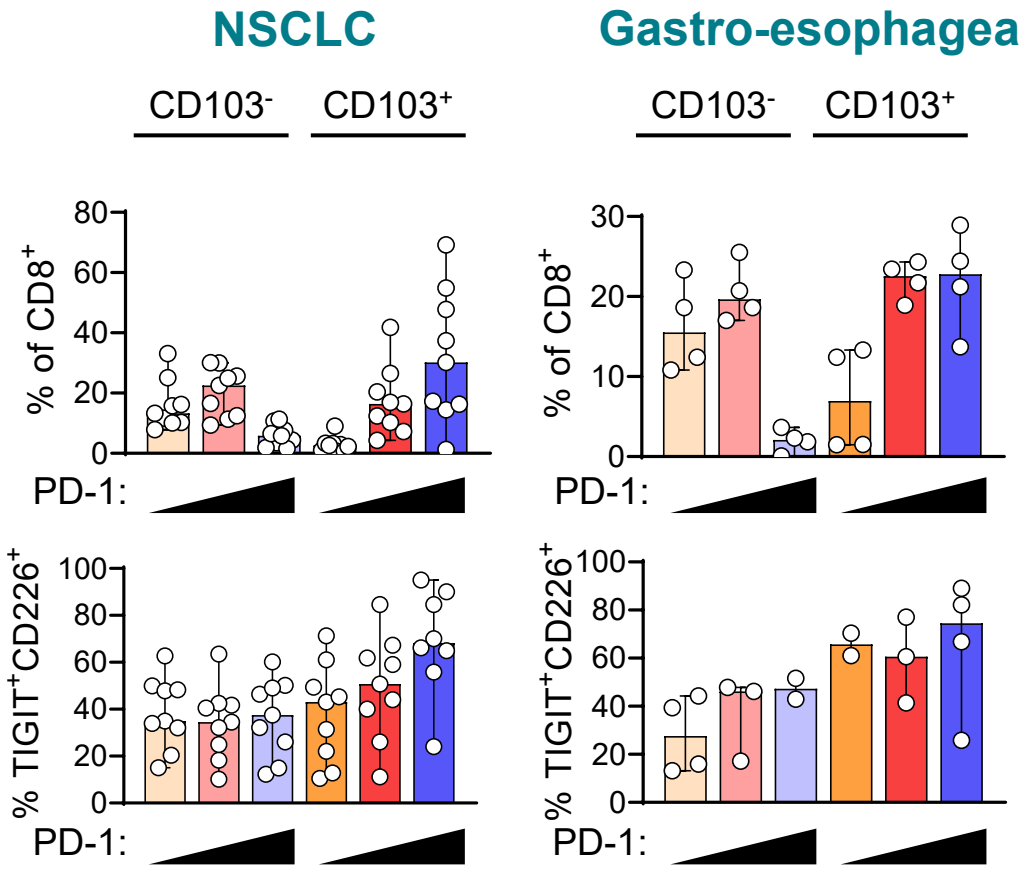




TCF-1^{+} and TIM-3^{+} subsets are highly heterogenous and contain multiple cell subsets

Exhausted T-cell Subsets in Human NSCLC Tumors Express PD-1, TIGIT, and CD226

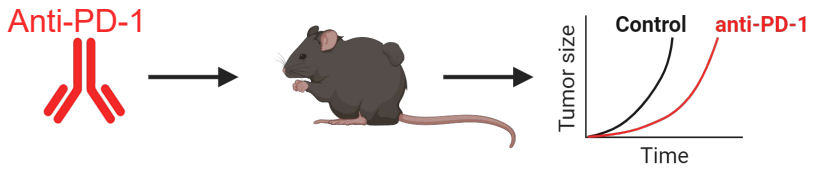




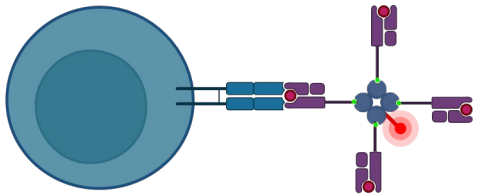
Does TIGIT blockade enhance activation of T_{pex} and tumor control in the context of anti-PD-1?

Identification of an Ideal Experimental Model to Evaluate Anti-PD-1 Combination Parters

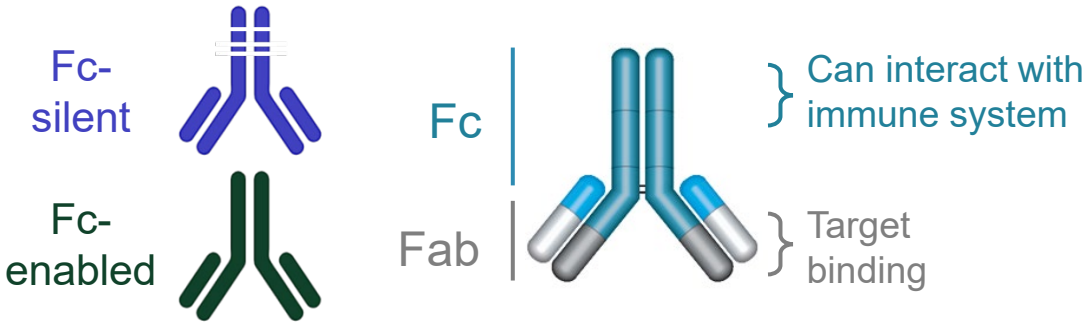
- **The MC38 colon carcinoma model is T-cell infiltrated and anti-PD-1 responsive**
  - Modeling “hot” tumors



- **Tools exist to monitor endogenous MC38-specific CD8⁺ T cells responses**
  - p15E MHC class I tetramers

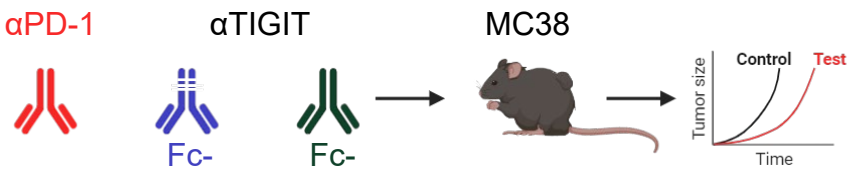


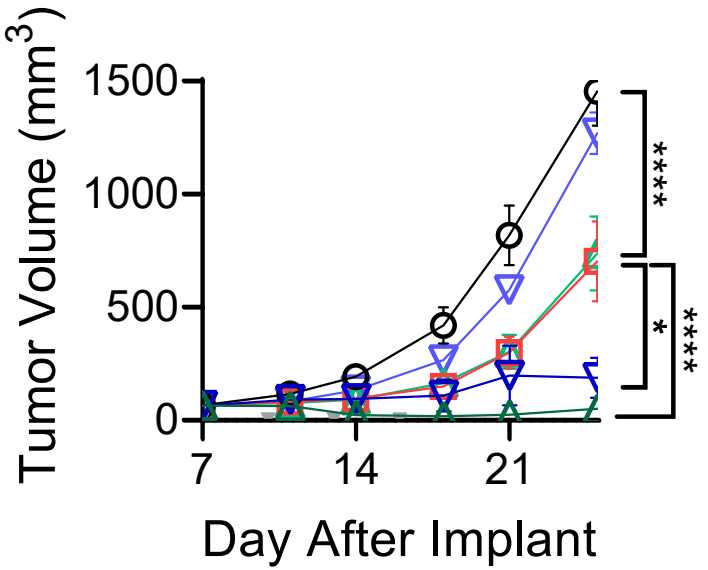
- **Critical design feature of anti-TIGIT antibodies: Fc-domain selection**
  - Engaging Fcγ receptors can trigger
    - T_{reg} depletion by ADCC[1]
    - Non-specific myeloid cell activation[2]
    - Potential for immune synapse enhancement[3]



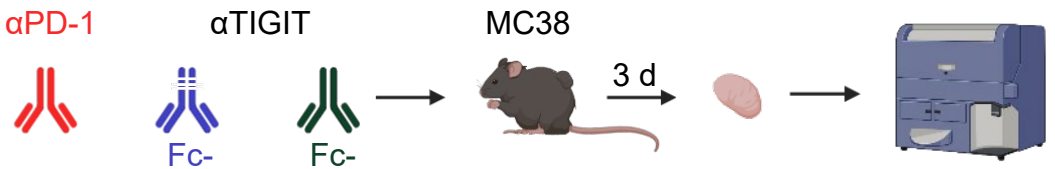
[1]Preillon *et al* (2021) Mol Cancer Ther; Chen *et al* (2022) Front Immunol;
[2]Han *et al* (2020) Front Immunol; [3]Waight *et al* (2018) Cancer Cell

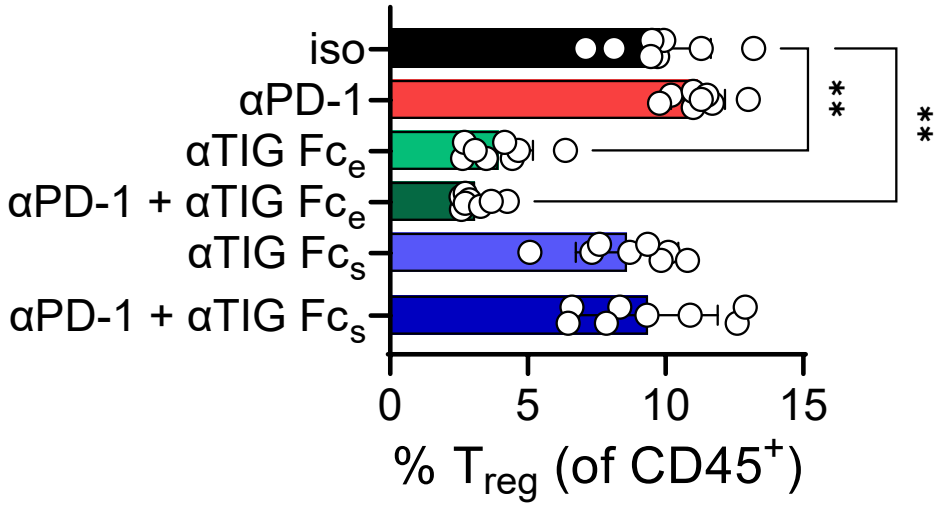
Fc-silent Anti-TIGIT Promotes Anti-tumor Immunity Without Regulatory T Cell (T_{reg}) Depletion





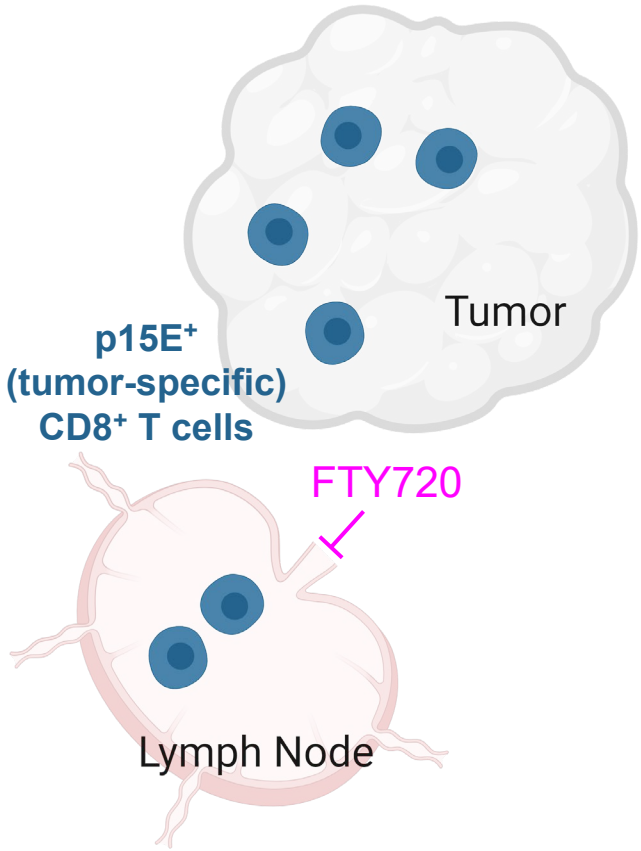
isotype
αPD-1
Fc_e = Fc-enabled — αTIG Fc_e — αPD-1 + αTIG Fc_e
Fc_s = Fc-silent — αTIG Fc_s — αPD-1 + αTIG Fc_s

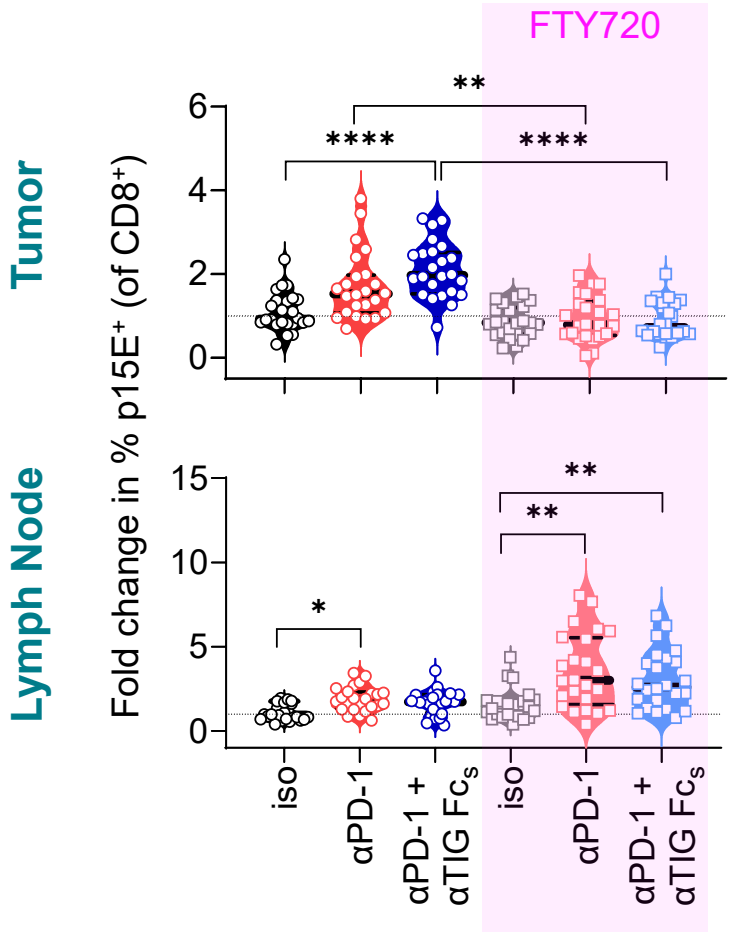


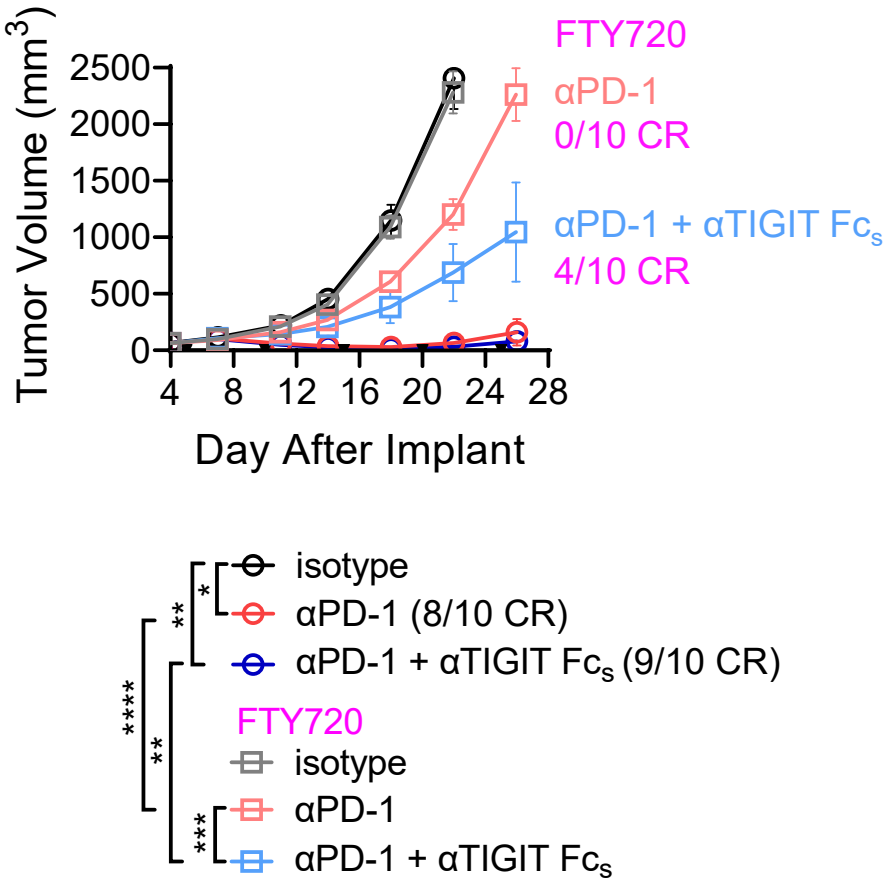


How does Fc-silent anti-TIGIT promote anti-tumor immunity?

Fc-silent Anti-TIGIT Potentiates Expansion of Tumor-specific CD8⁺ T Cells and Tumor Control

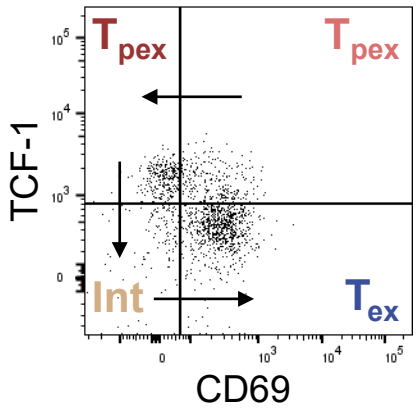


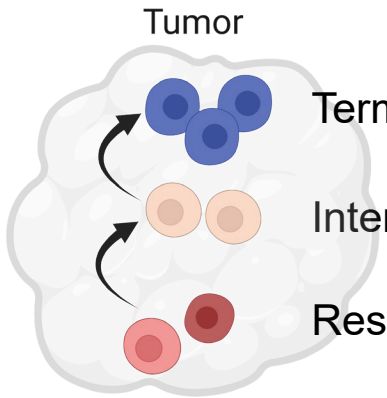




12 TIL assessment 3 days post first dose

Fc-silent Anti-TIGIT Potentiates Pre-exhausted Tumor-specific T-cell Activation and Differentiation

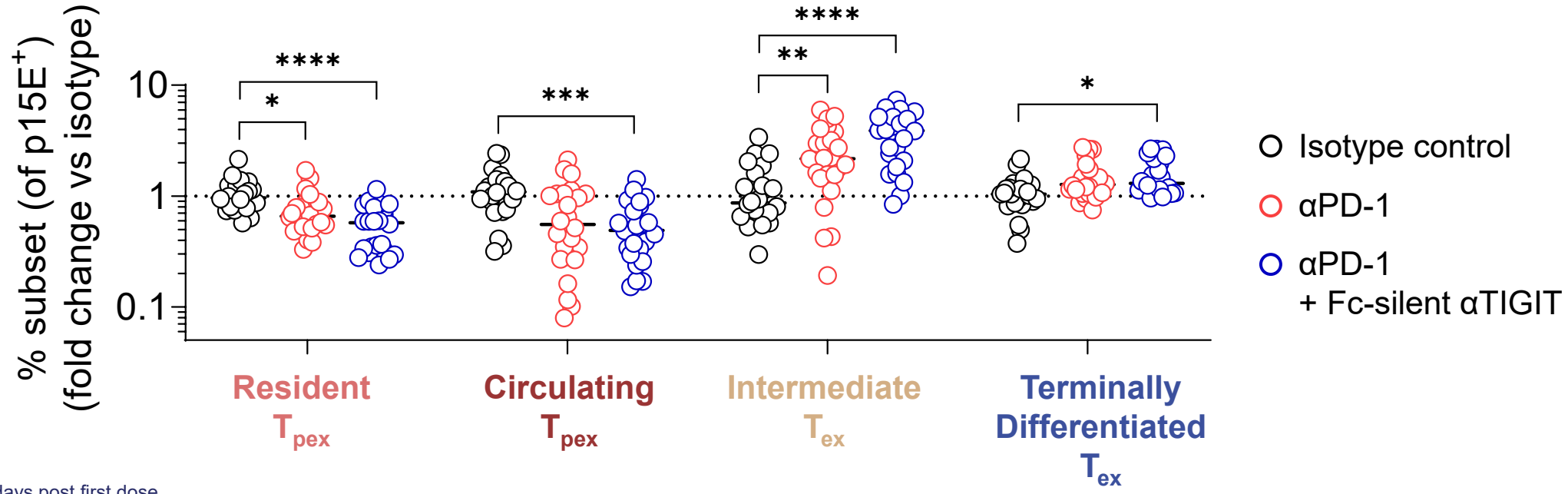




Terminally Differentiated **TCF-1⁻ CD69⁺**

Intermediate **TCF-1⁻ CD69⁻**

Resident & Circulating T_{pex} **TCF-1⁺ CD69⁻/⁺**



 TIL assessment 3 days post first dose

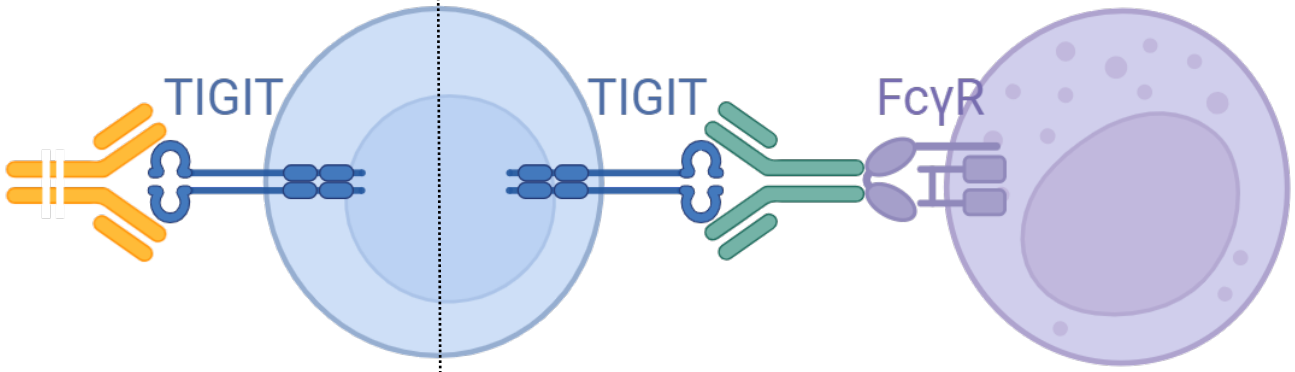
Summary of Human TIL Phenotyping and Mouse Model Investigations

- **Subsets of exhausted T cells from NSCLC and gastroesophageal cancer patients co-express PD-1, TIGIT, and CD226**
- **Fc-silent and Fc-enabled anti-TIGIT both enhance anti-tumor efficacy of anti-PD-1, but by differential mechanisms**
  - Fc-enabled anti-TIGIT depletes tumor T_{reg}, leading to exaggerated efficacy in the MC38 model
- **Anti-PD-1 in combination with Fc-silent anti-TIGIT enhances tumor-specific T cell responses and efficacy**

How do human TIGIT-specific Fc-silent and Fc-enabled anti-TIGIT antibodies compare *in vitro* and in patients?

AB154 (Domvanalimab) and AB308 are Potent Anti-TIGIT Antibodies

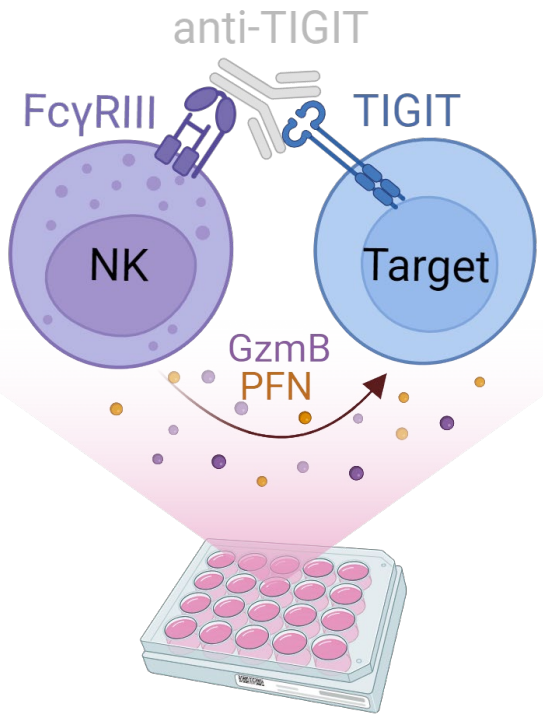
Domvanalimab (dom)	AB308
Blocking	Blocking & Effector Function



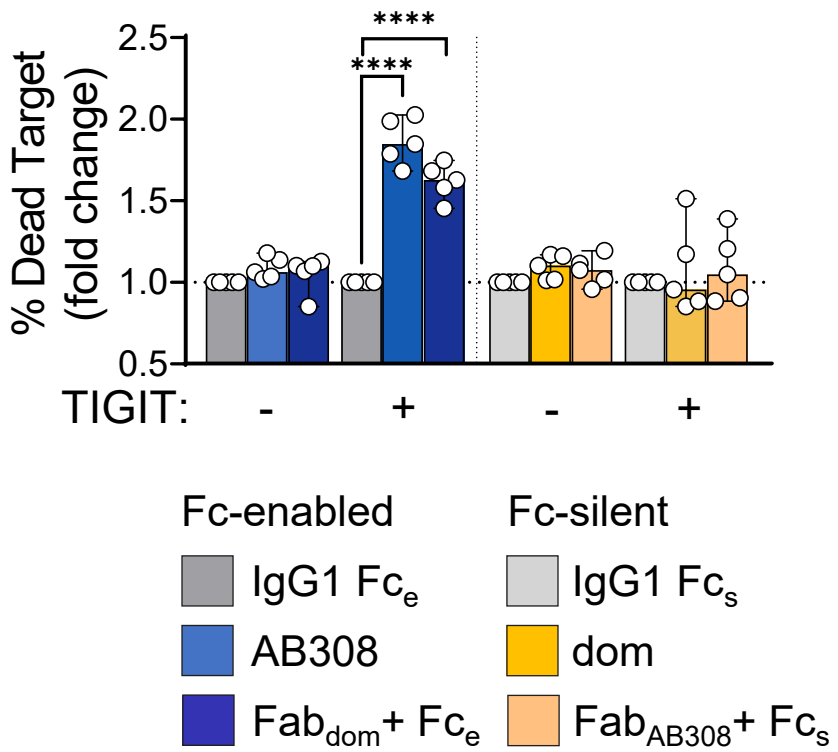
	Silent ('LALA' mutated hIgG1)	Enabled (wild type hIgG1)
Binding EC_{50}	0.42 nM	0.36 nM
Blocking IC_{50}	0.69 nM	0.68 nM

In Contrast to Fc-enabled Anti-TIGIT, Dom Does Not Promote ADCC Against TIGIT Expressing Cell Lines

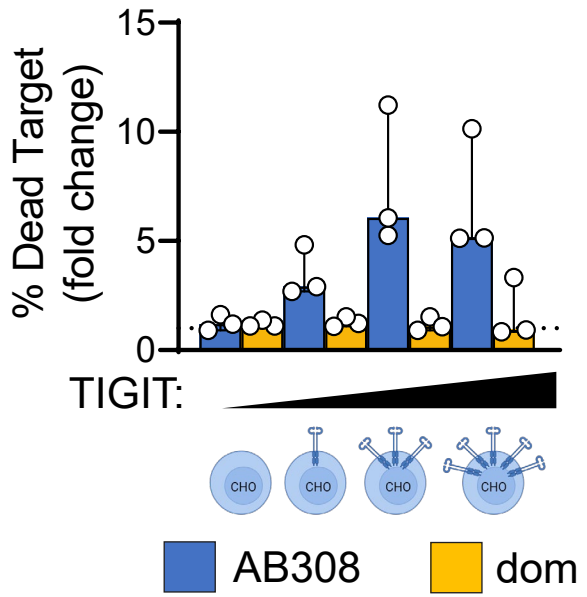
Target: CHO ± TIGIT



Killing is Fc Dependent

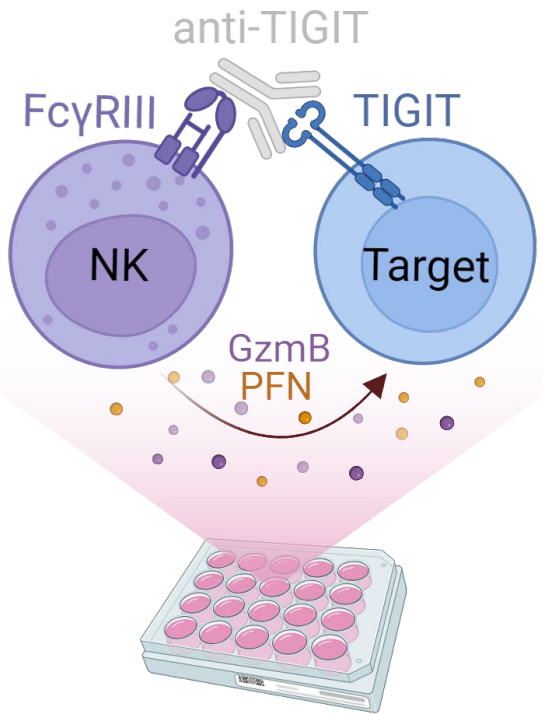


Killing Correlates with TIGIT Expression

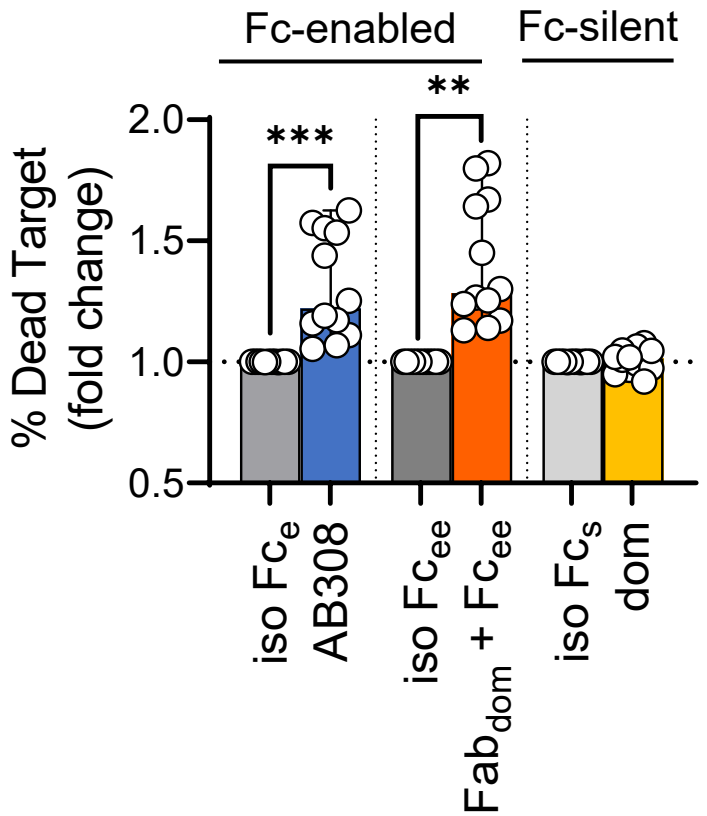


In Contrast to Fc-enabled Anti-TIGIT, Dom Does Not Promote ADCC Against Human T_{reg}

Target: T_{reg}



Target: T_{reg}

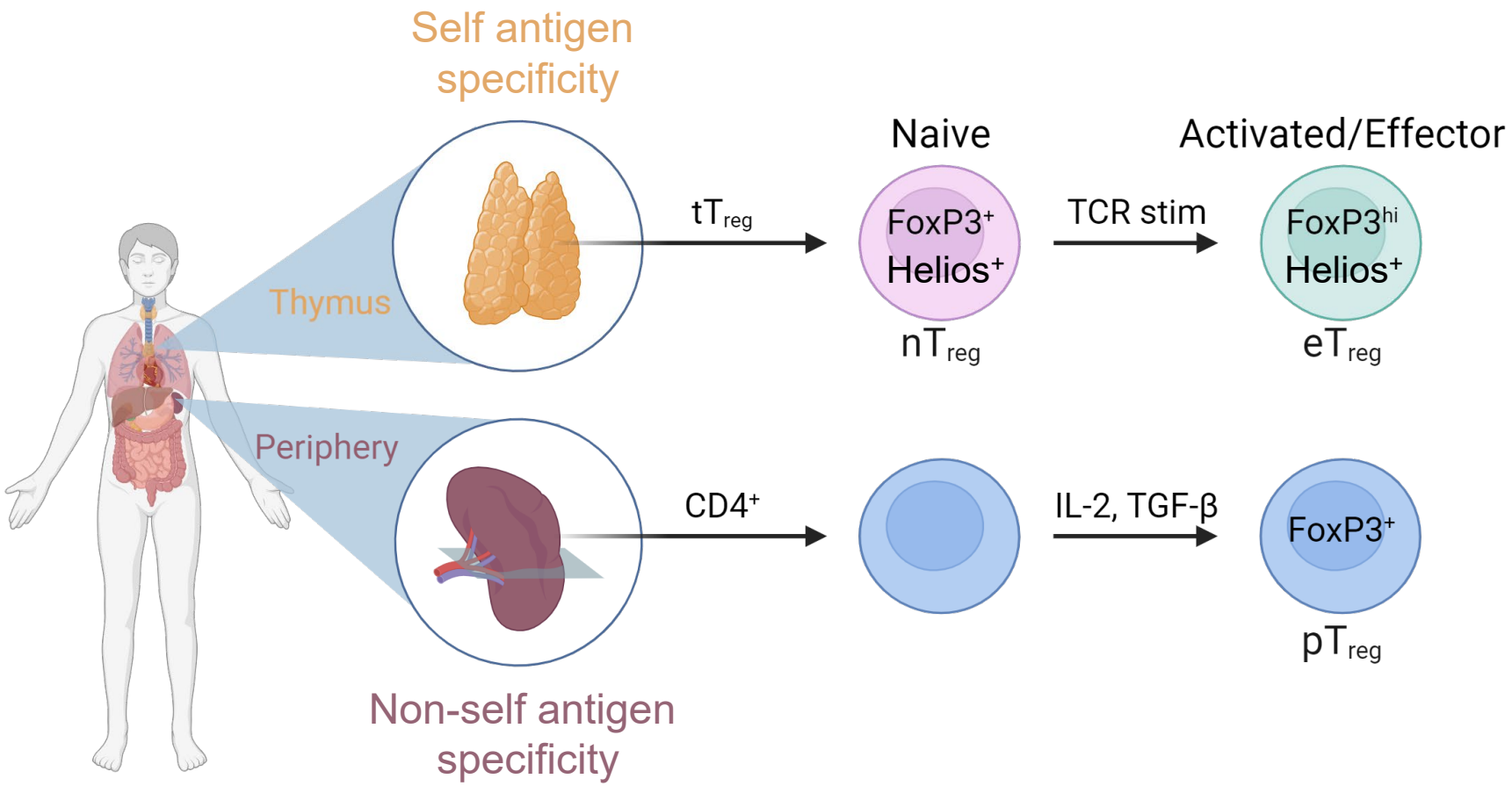


Are different subsets of T_{reg} targeting similarly by anti-TIGIT-mediated ADCC?

Fc_{ee} = Fc-effector enhanced (DLE mutated hIgG1)

T_{reg} are Critical for Maintaining Immune Homeostasis

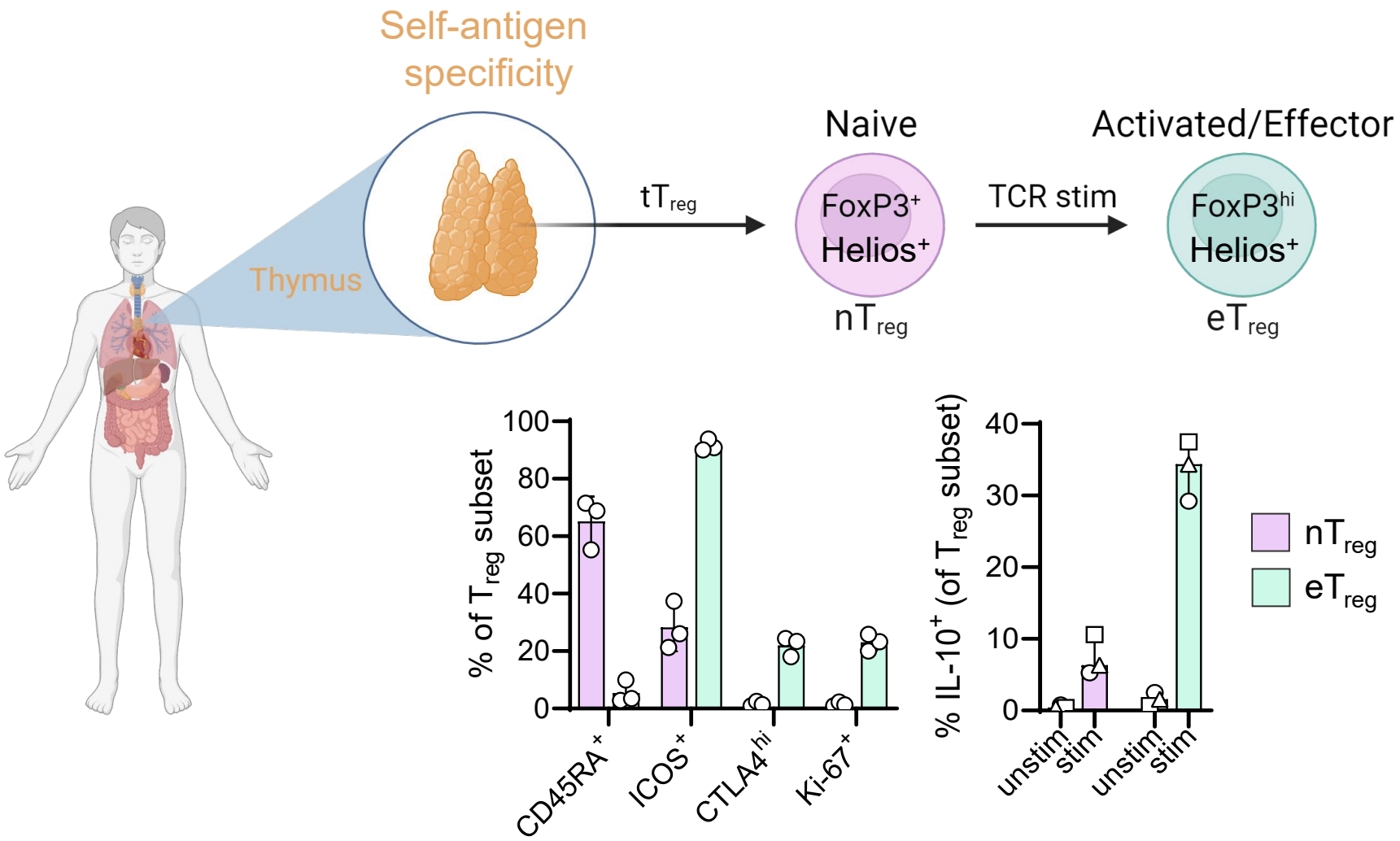
- **Lack of T_{reg} causes severe autoimmune disease (*e.g.*, type 1 diabetes, eczema, enteropathy)**



Sakaguchi *et al* (2020) Ann Rev Immunol

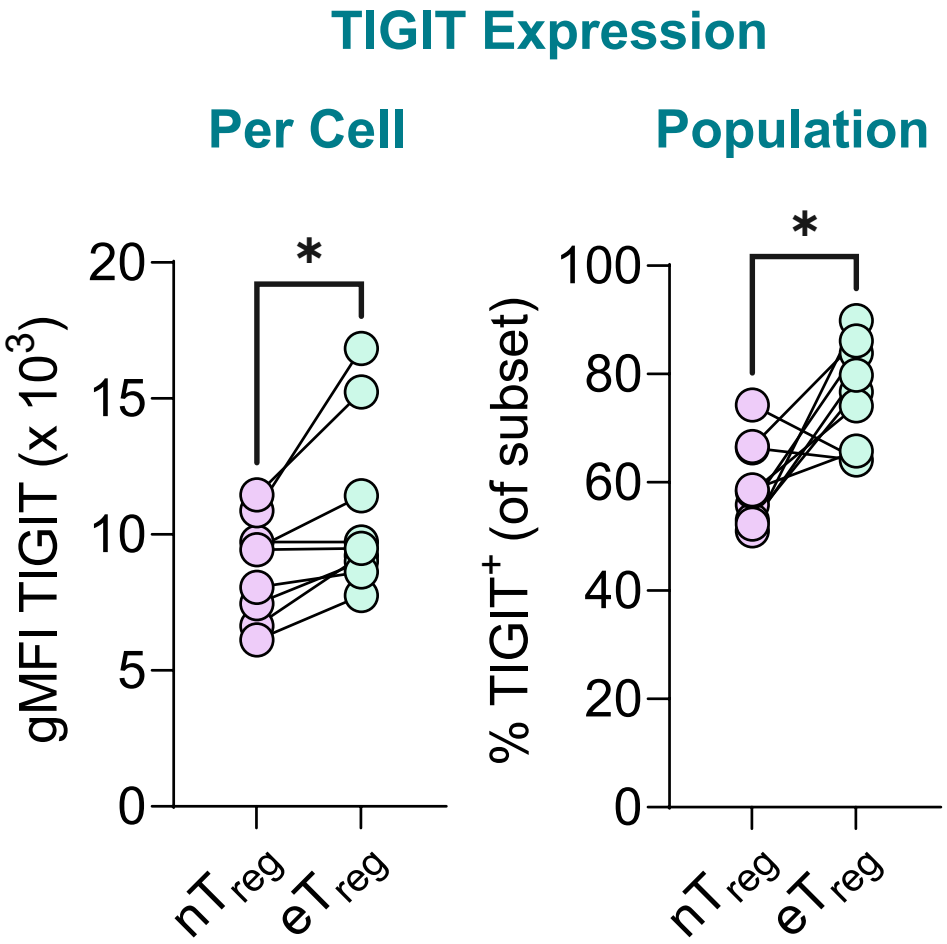
T_{reg} are Critical for Maintaining Immune Homeostasis

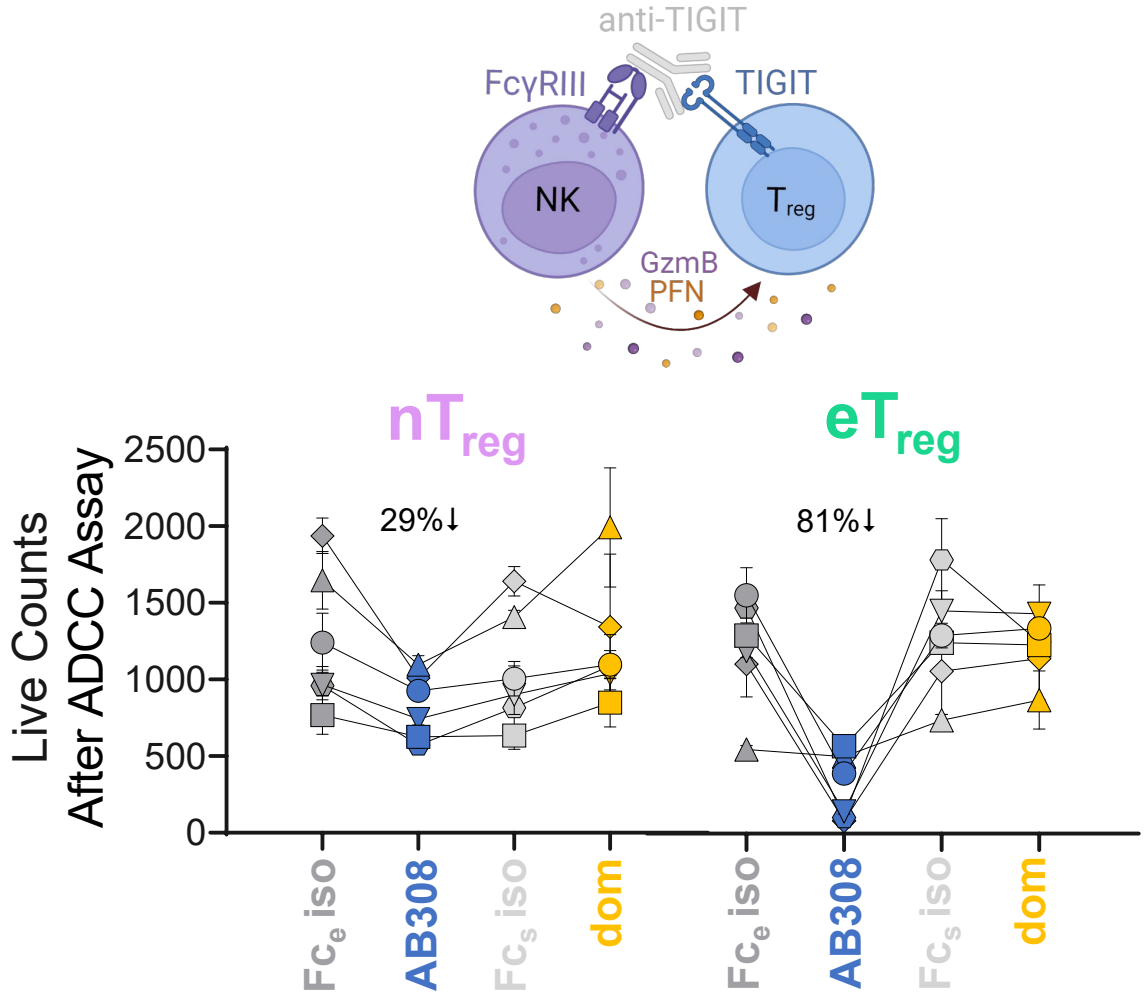
- Lack of T_{reg} causes severe autoimmune disease (*e.g.*, type 1 diabetes, eczema, enteropathy)
- eT_{reg} are more suppressive, more proliferative, and express higher levels of activation and inhibitory receptors



Sakaguchi *et al* (2020) Ann Rev Immunol

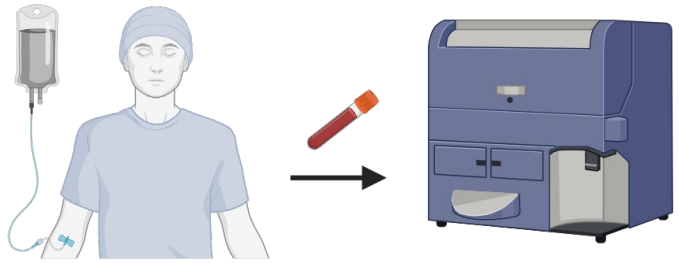
eT_{reg} Have Higher Levels of TIGIT and are Preferentially Targeted by NK Cell-mediated ADCC

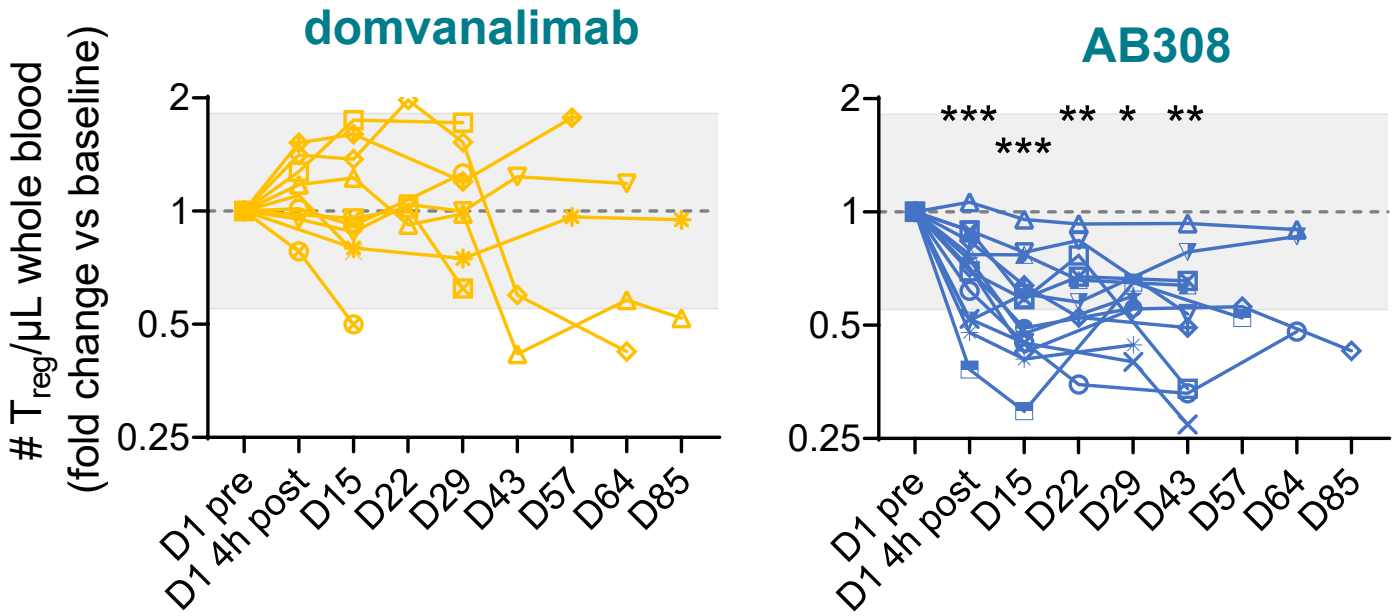




In Contrast to AB308, Dom Does Not Deplete Peripheral T_{reg} in Phase 1 Patients with Advanced Solid Cancer

dom: NCT03628677, n = 10
AB308: NCT04772989, n = 14

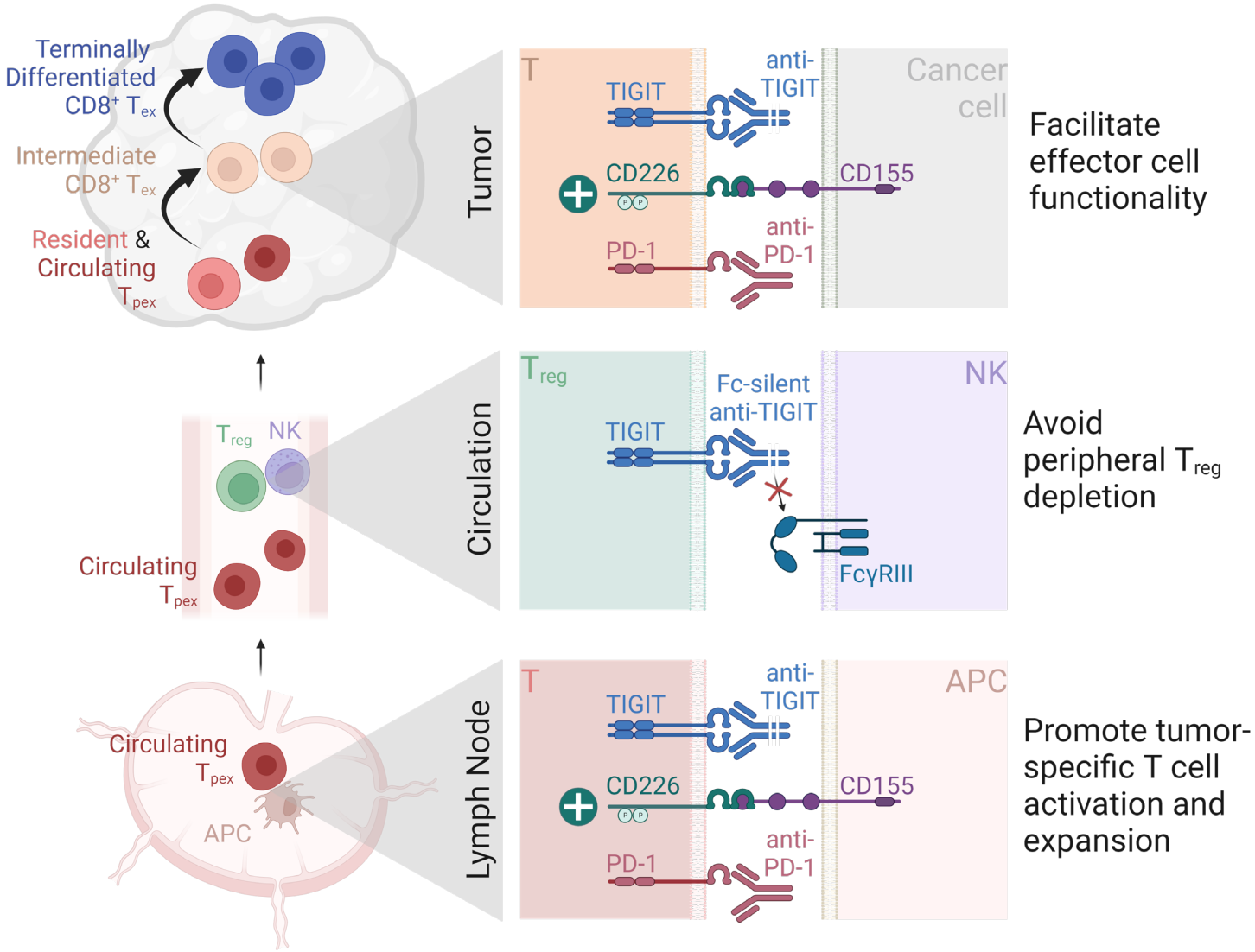




Shading = healthy donor range

Fc-silent Anti-TIGIT Potentiates Anti-tumor Immunity While Avoiding Depletion of Peripheral T_{reg}

- **TIGIT blockade potentiates activation, differentiation, and effector function of tumor-specific CD8⁺ T cells**
- **Silencing the Fc domain of anti-TIGIT prevents depletion of peripheral T_{reg}, potentially critical for an optimal safety-efficacy profile**



Thank You to the Teams at Arcus Biosciences

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Translational: Amber de Groot

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Protein Therapeutics: Nigel P. Walker

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Napa, CA
(Circa 2019)

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