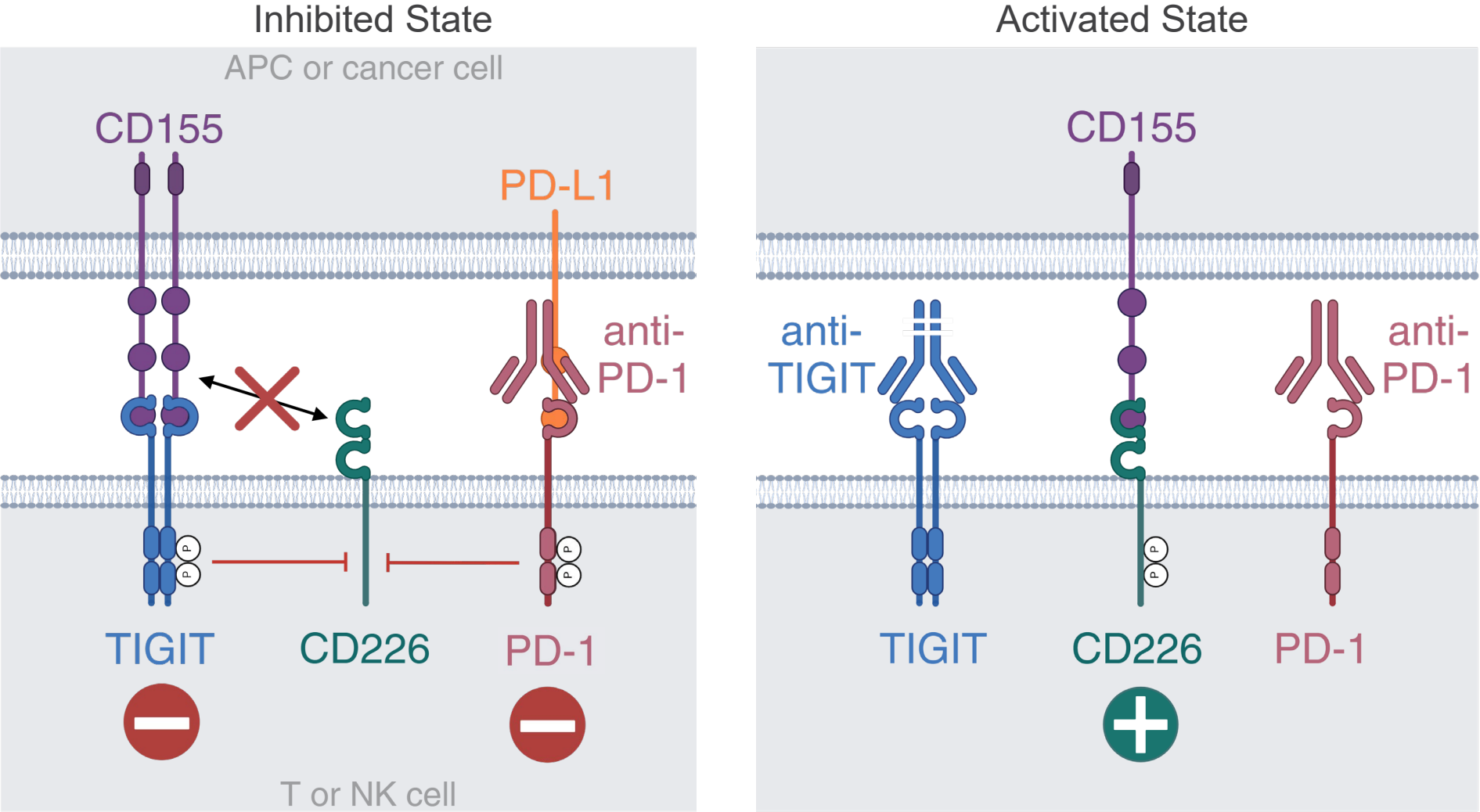


Fc-silent Anti-TIGIT Antibodies Offer Best-in-Class Potential By Potentiating Robust CD8⁺ T Cell-Mediated Anti-tumor Immunity Without Peripheral Regulatory T Cell Depletion

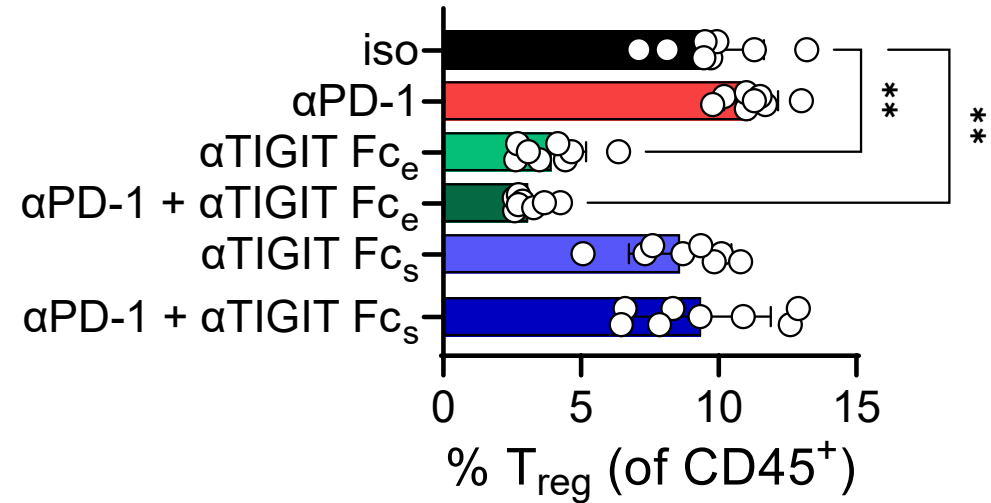
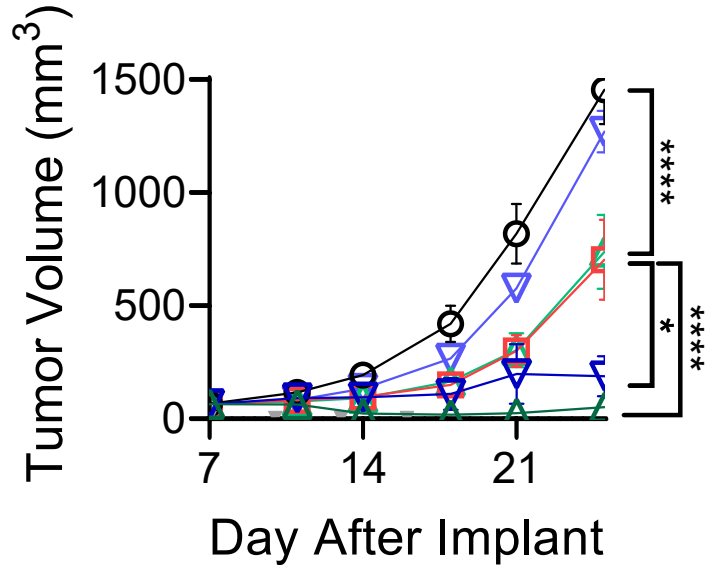
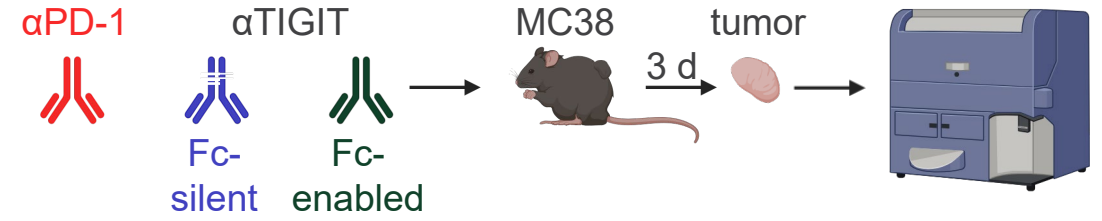
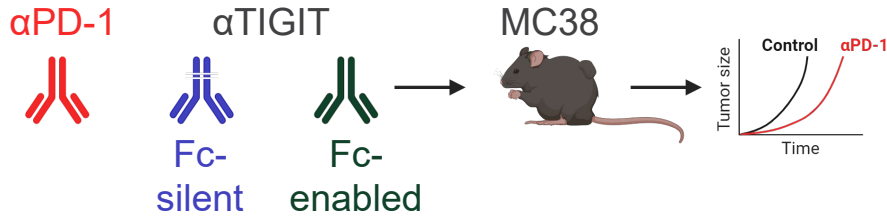
Kelsey E. Sivick Gauthier, PhD
Director, Biology
March 18th, 2024

Co-blockade of TIGIT and PD-1 is Required for Full Activation of the CD226 Axis



Does adding TIGIT blockade enhance tumor control by anti-PD-1?

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

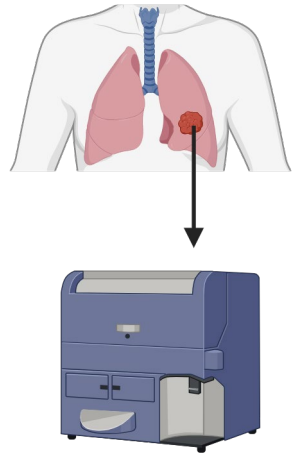


- isotype
- αPD-1
- Fc_e = Fc-enabled
- △ αTIGIT Fc_e
- ▽ αPD-1 + αTIGIT Fc_e
- Fc_s = Fc-silent
- ▽ αTIGIT Fc_s
- ▽ αPD-1 + αTIGIT Fc_s

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

T_{reg} and Exhausted CD8⁺ T Cell Subsets in Human NSCLC Tumors Co-express PD-1, TIGIT, and CD226

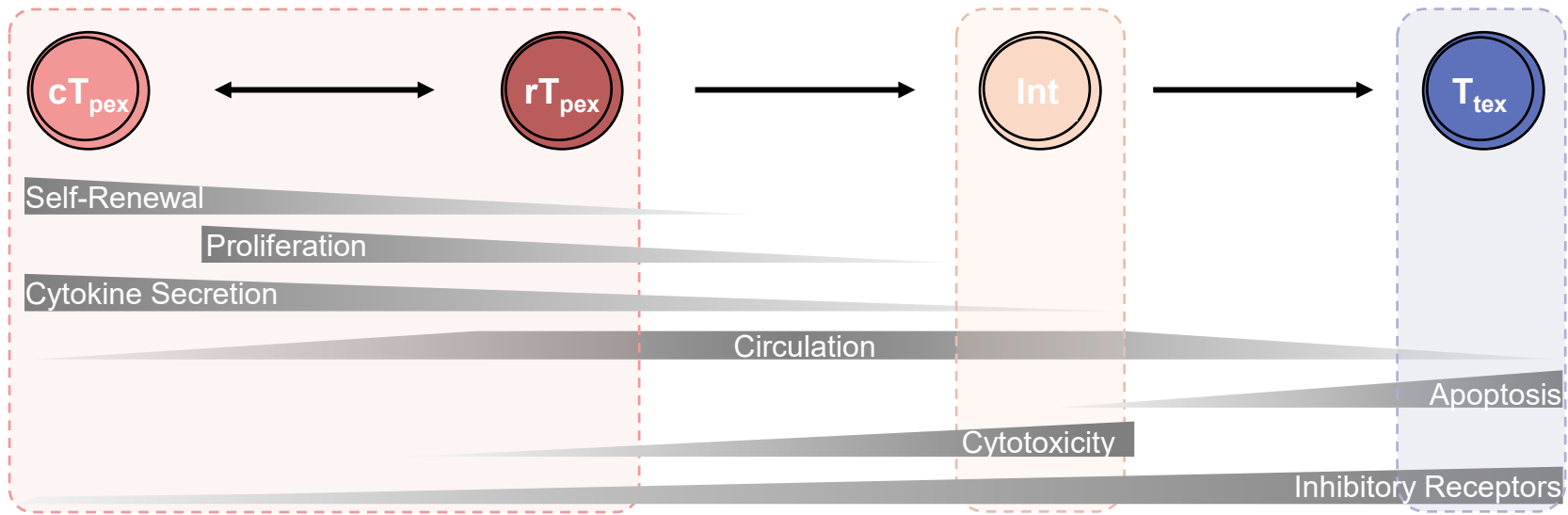
Exhausted T Cell Differentiation



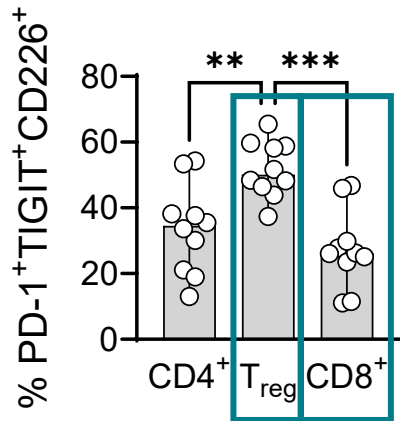
Circulating and Resident precursor exhausted (T_{pex})

Intermediate (T_{ex})

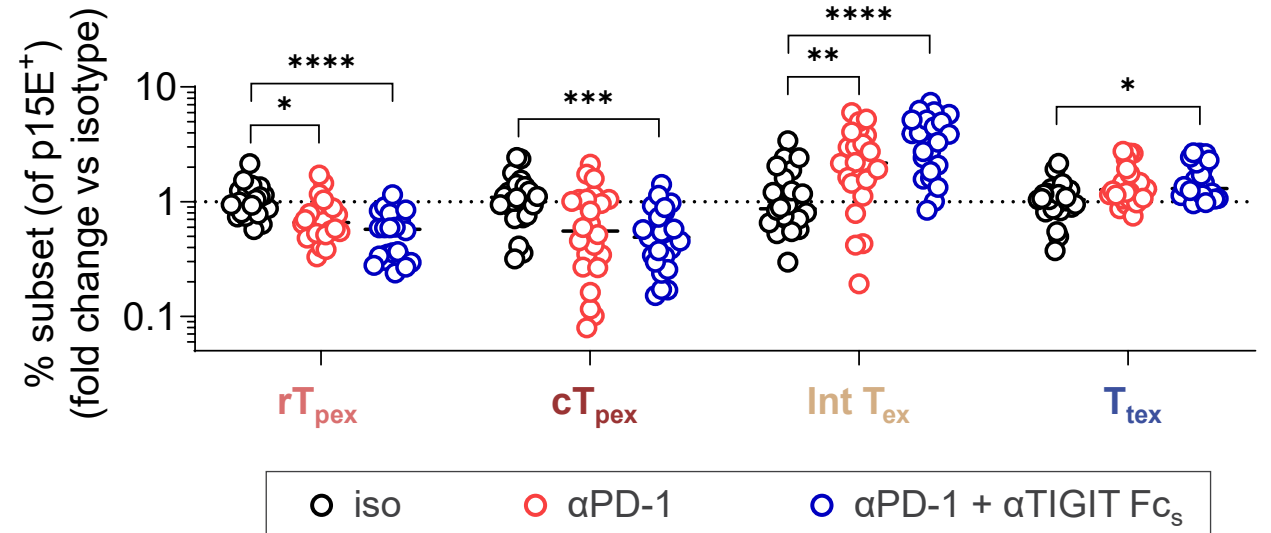
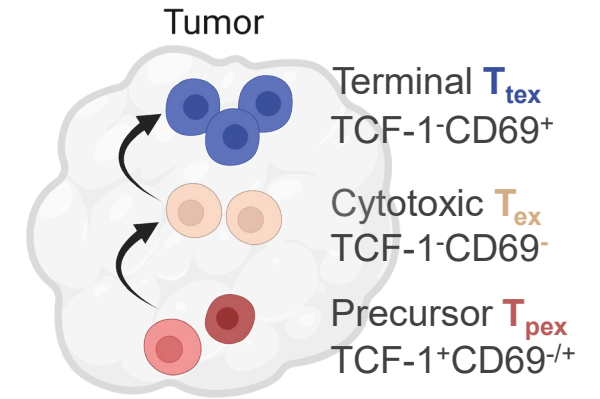
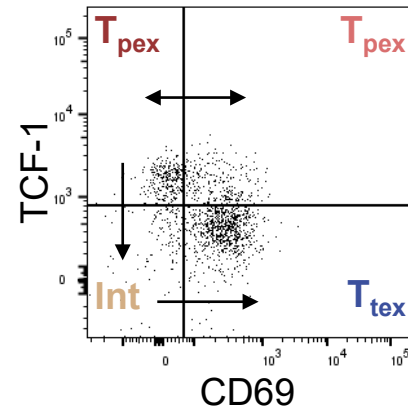
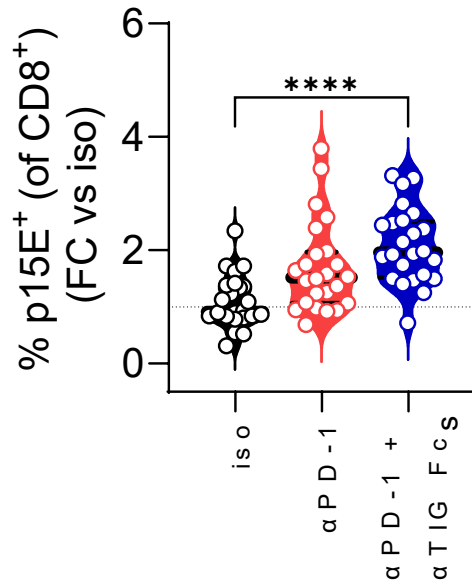
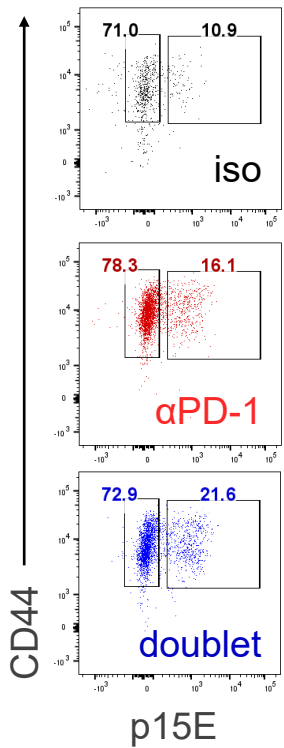
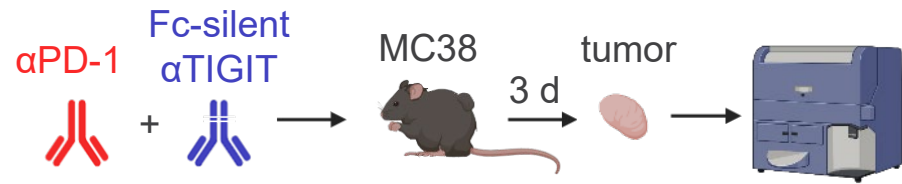
Terminally Differentiated (T_{tex})



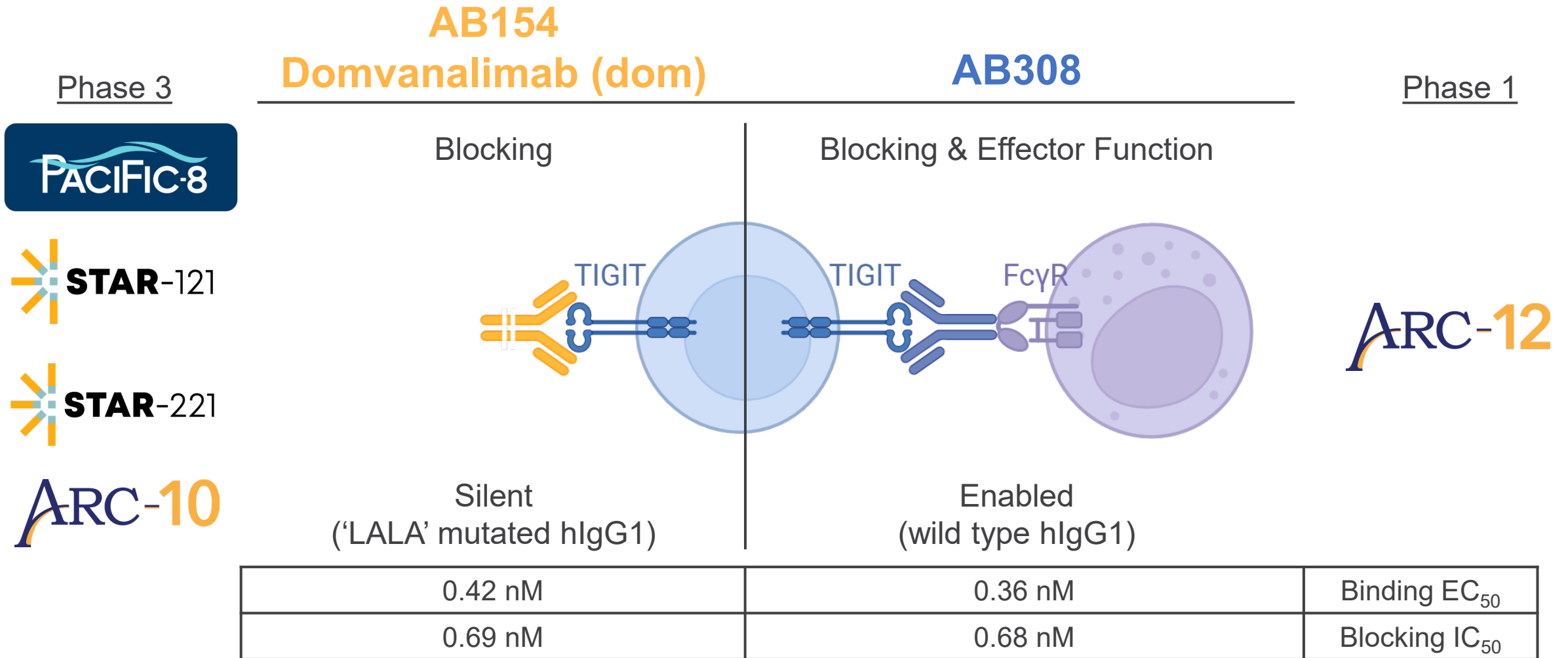
Targets of PD-1 & TIGIT dual blockade



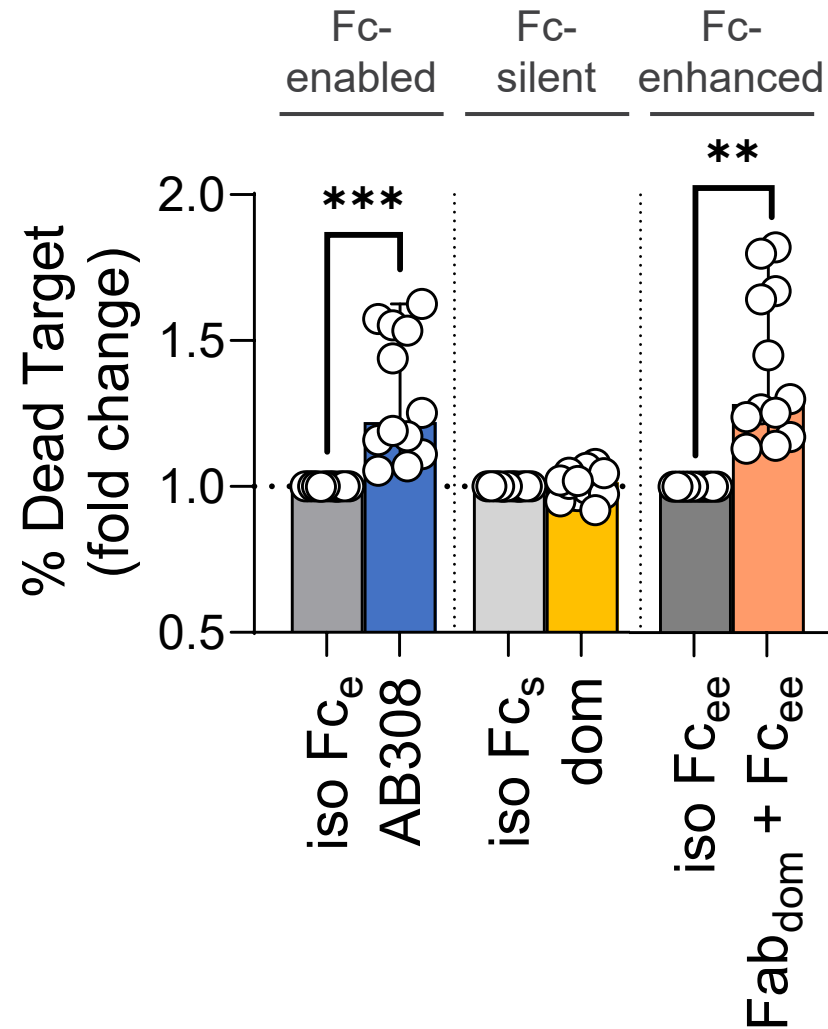
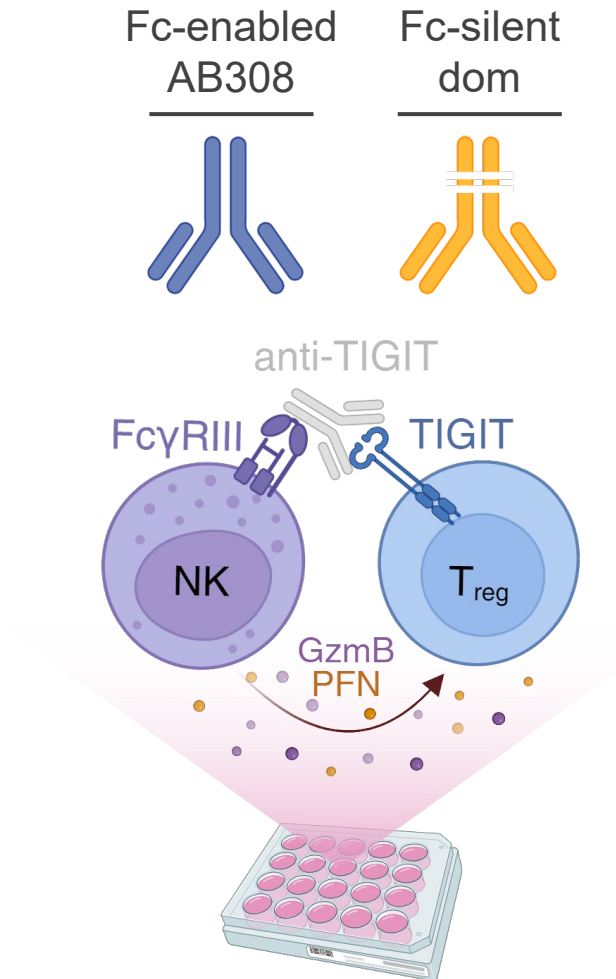
Fc-silent Anti-TIGIT Potentiates Precursor Exhausted Tumor-specific T Cell Activation and Differentiation



AB154 (or dom) and AB308 are Potent Anti-TIGIT Antibodies in Clinical Development

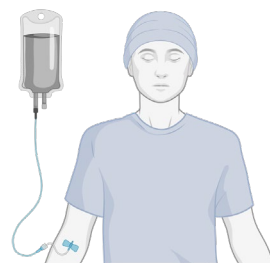
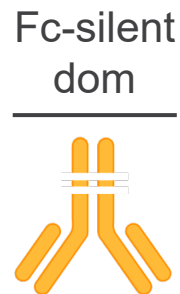


In Contrast to Fc-enabled AB308, Dom Does Not Promote ADCC Against Peripheral Human T_{reg} *in vitro*

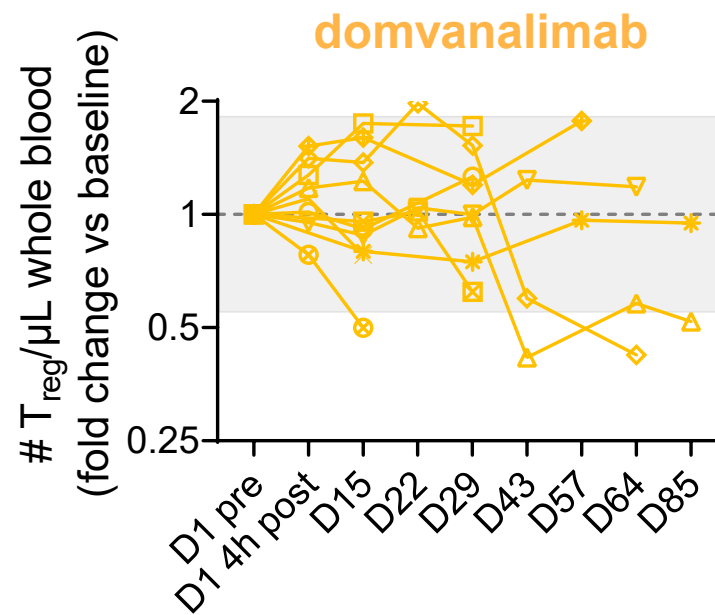
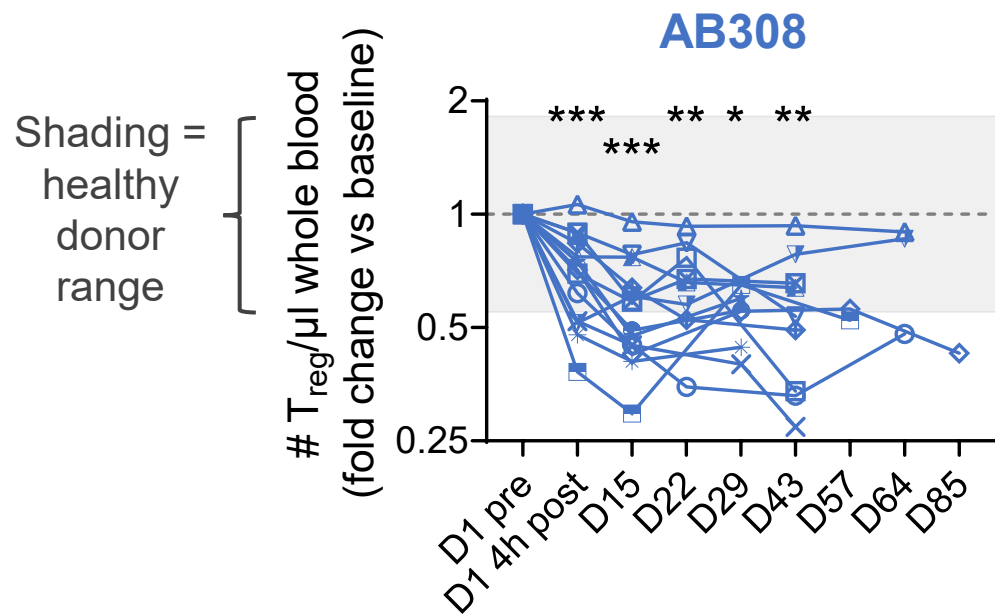


Can Fc-enabled anti-TIGIT deplete peripheral T_{reg} in humans?

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

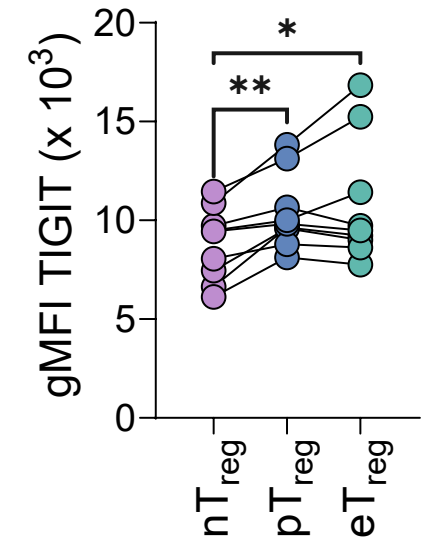
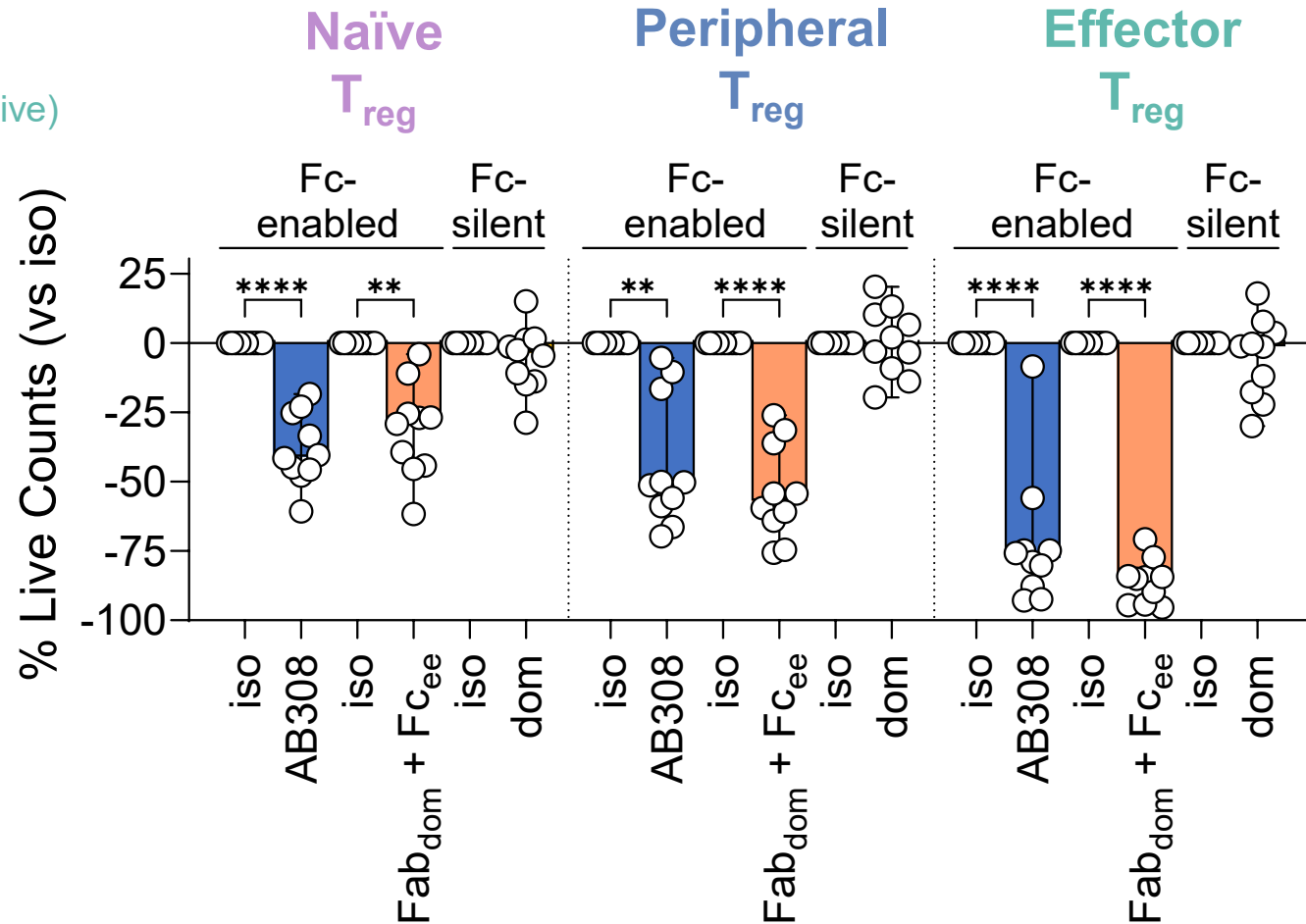
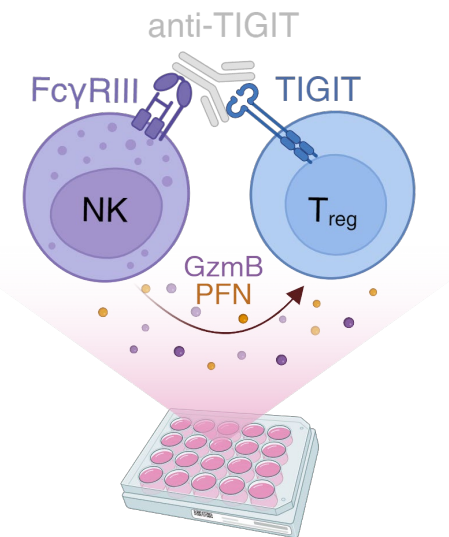
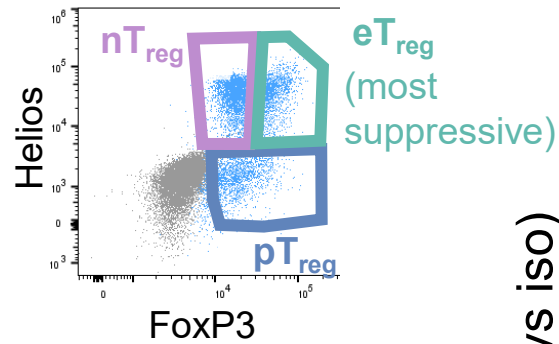


AB308: NCT04772989, n = 14
dom: NCT03628677, n = 10



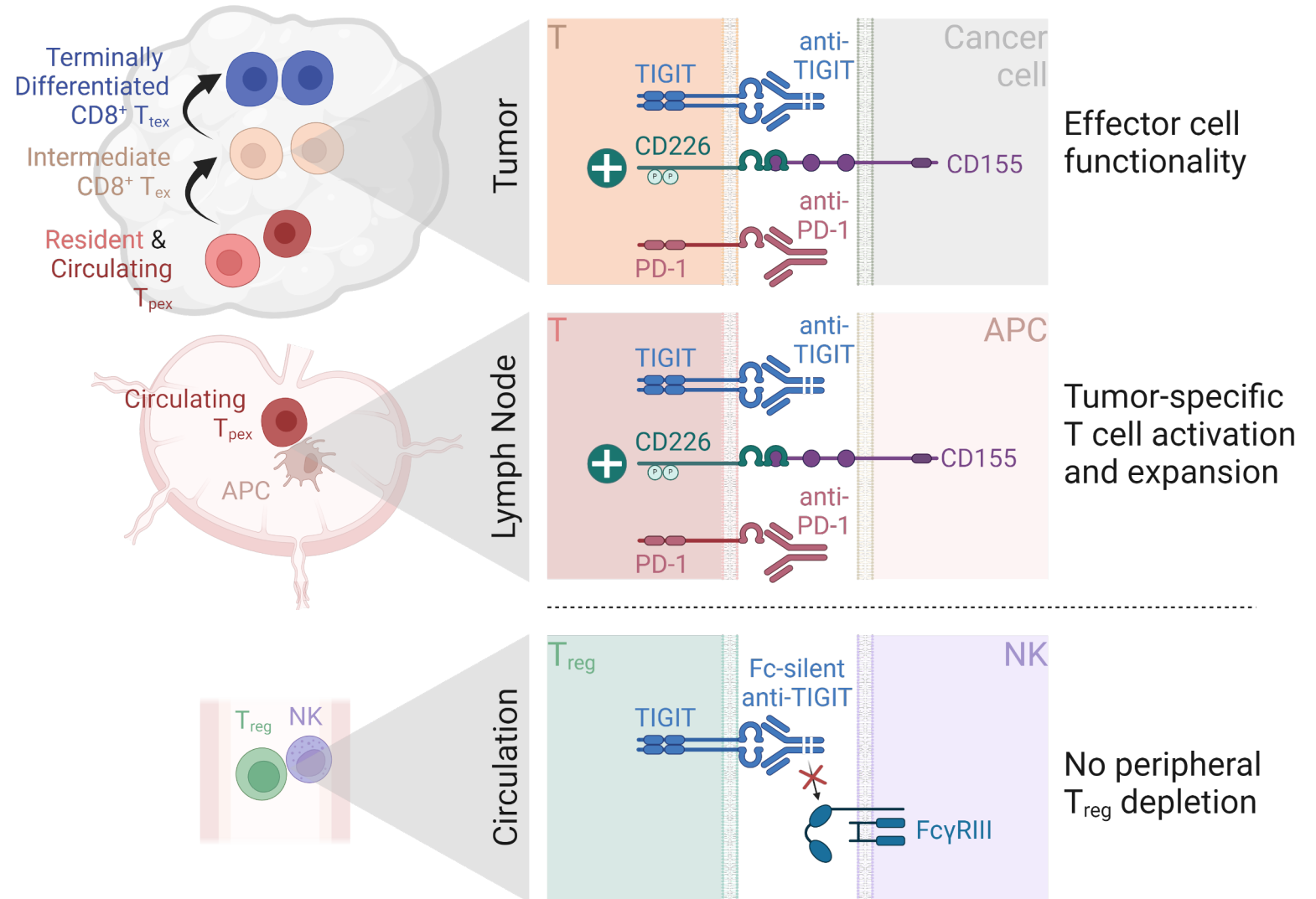
Are certain peripheral T_{reg} subsets more prone to Fc-enabled anti-TIGIT-mediated depletion?

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



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**

The Team at Arcus Biosciences



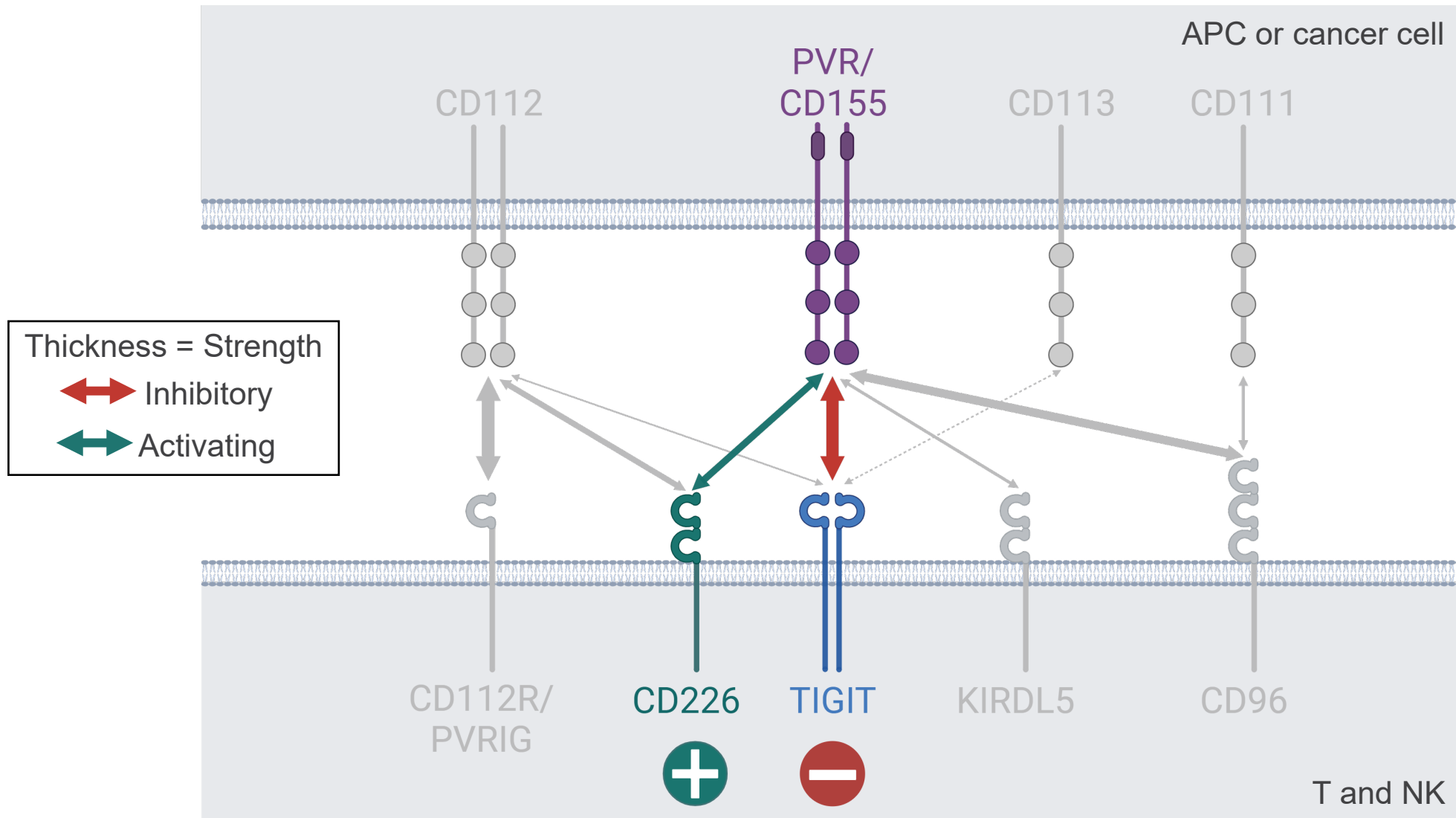
2023 Research and Non-clinical Development Retreat



- **Gilead colleagues**

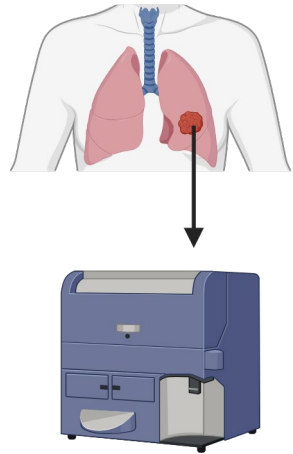
APPENDIX

TIGIT is an Inhibitory Receptor that Outcompetes the CD226 Activating Receptor for Shared Ligand CD155



T_{reg} and Exhausted CD8⁺ T Cell Subsets in Human NSCLC Tumors Co-express PD-1, TIGIT, and CD226

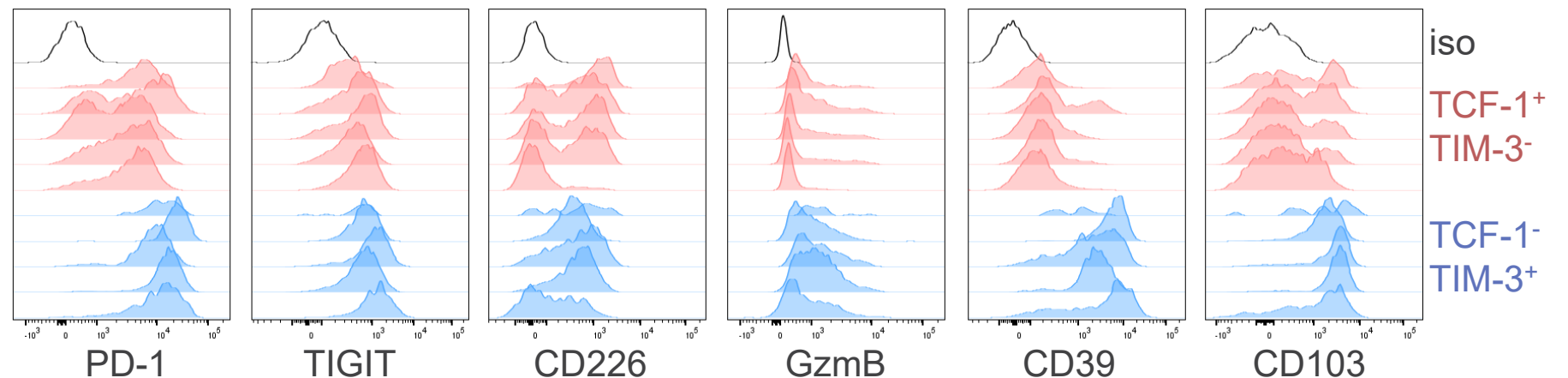
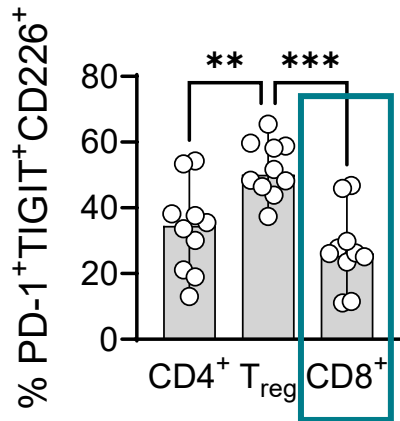
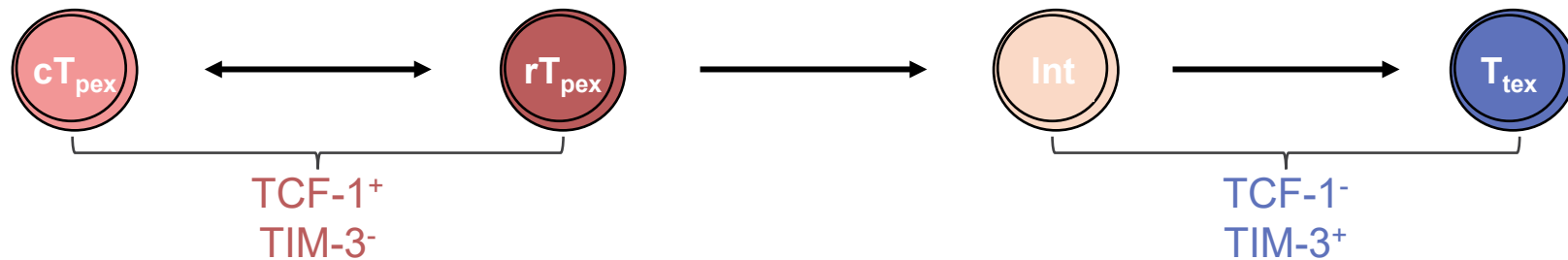
Exhausted T Cell Phenotyping



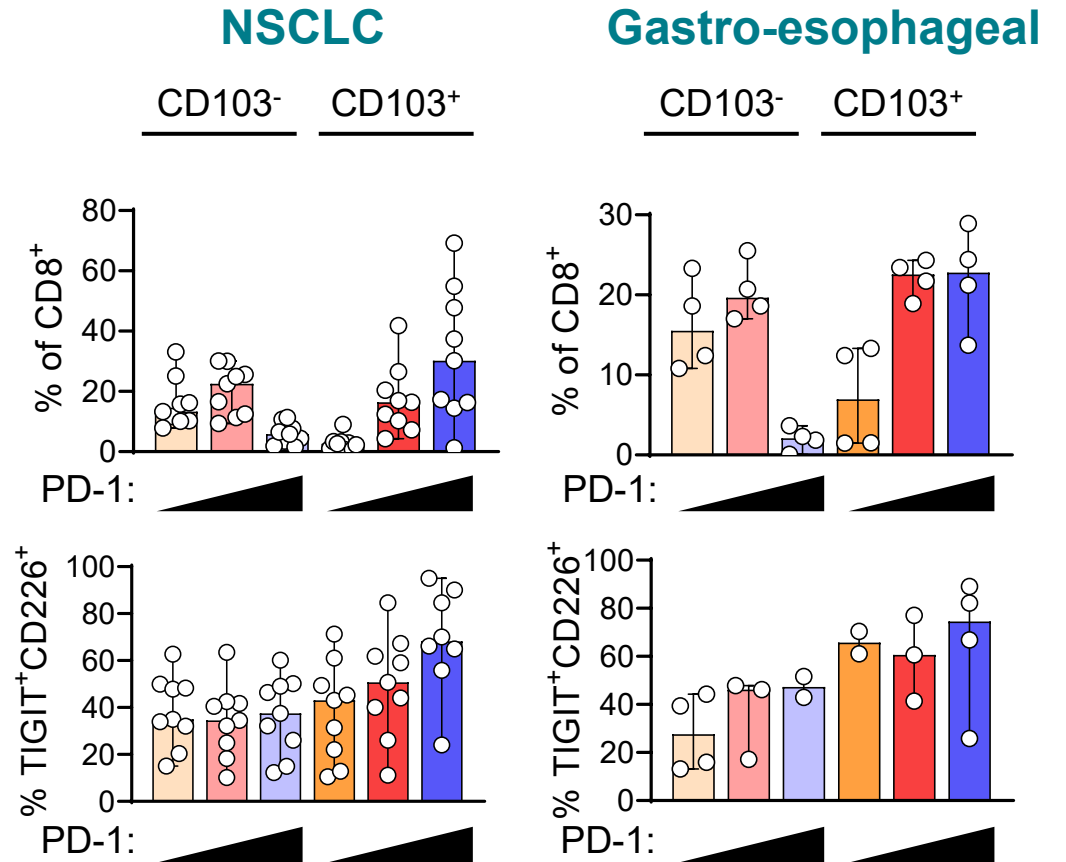
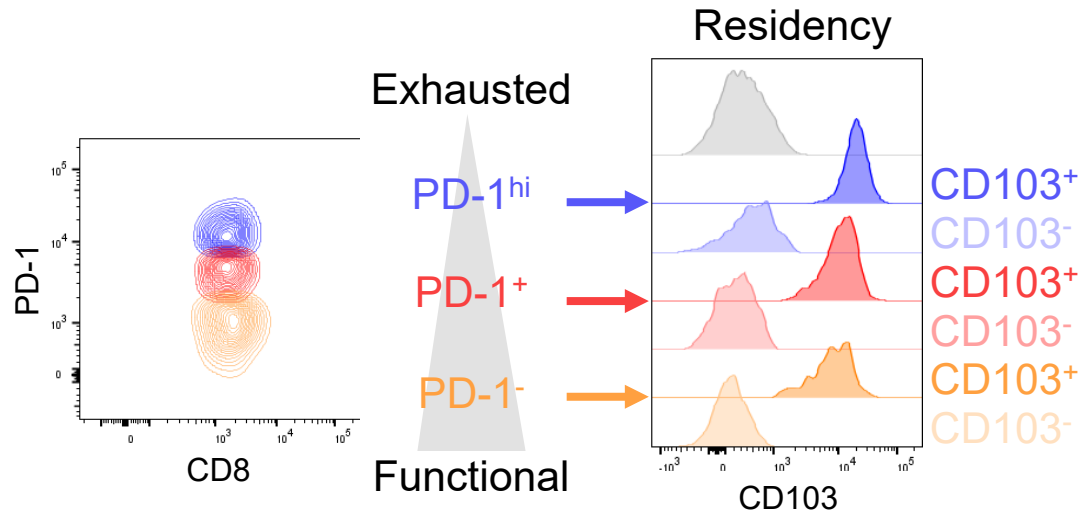
Circulating pre-exhausted (T_{pex})
and Resident T_{pex}

Intermediate T_{ex}

Terminally
Differentiated (T_{tex})

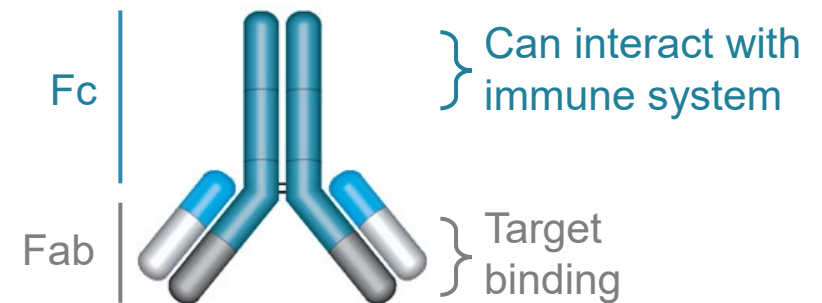
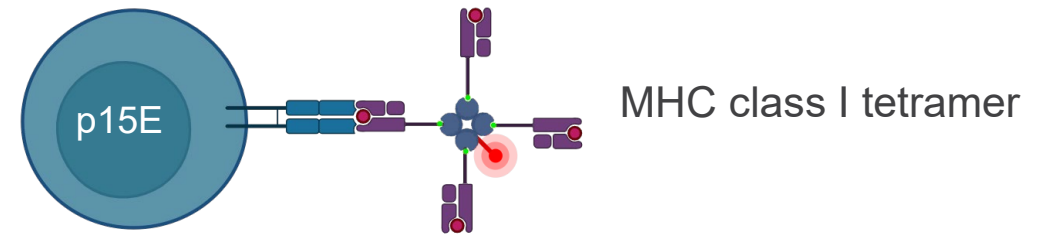
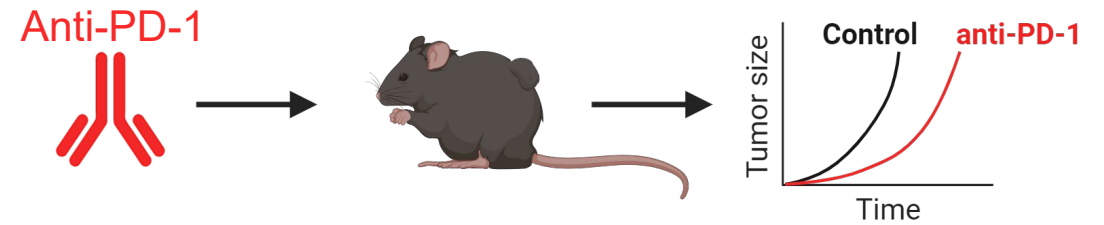


Exhausted T Cell Subsets in Human NSCLC Tumors Express PD-1, TIGIT, and CD226

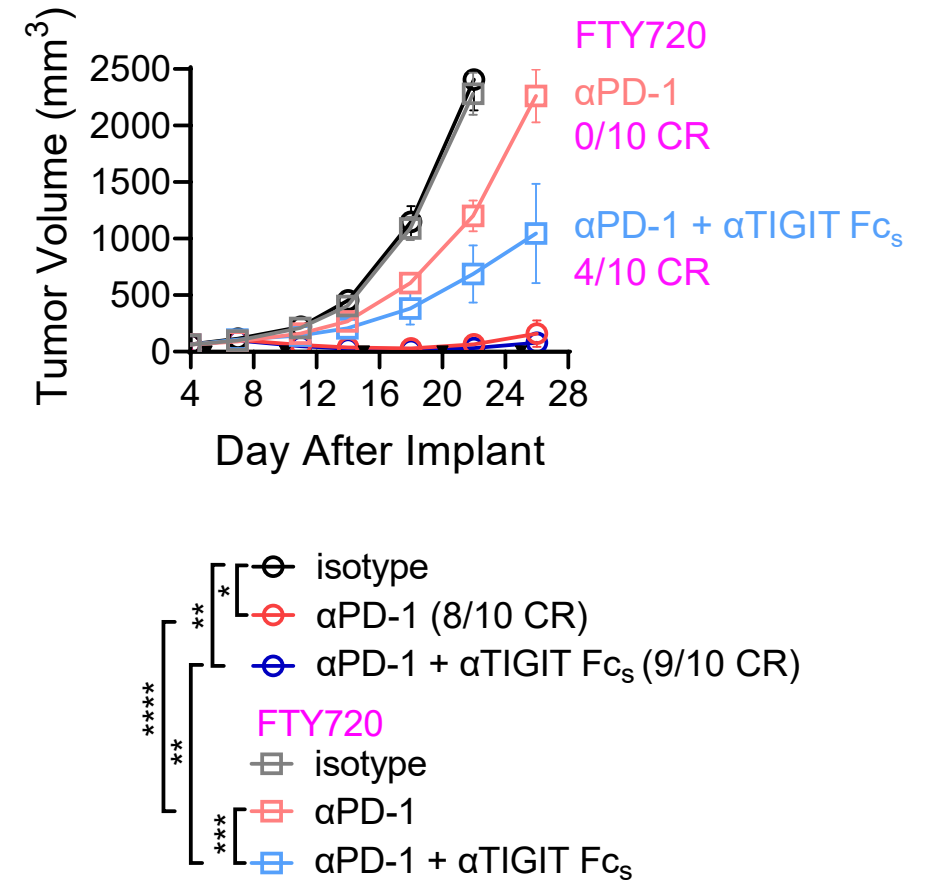
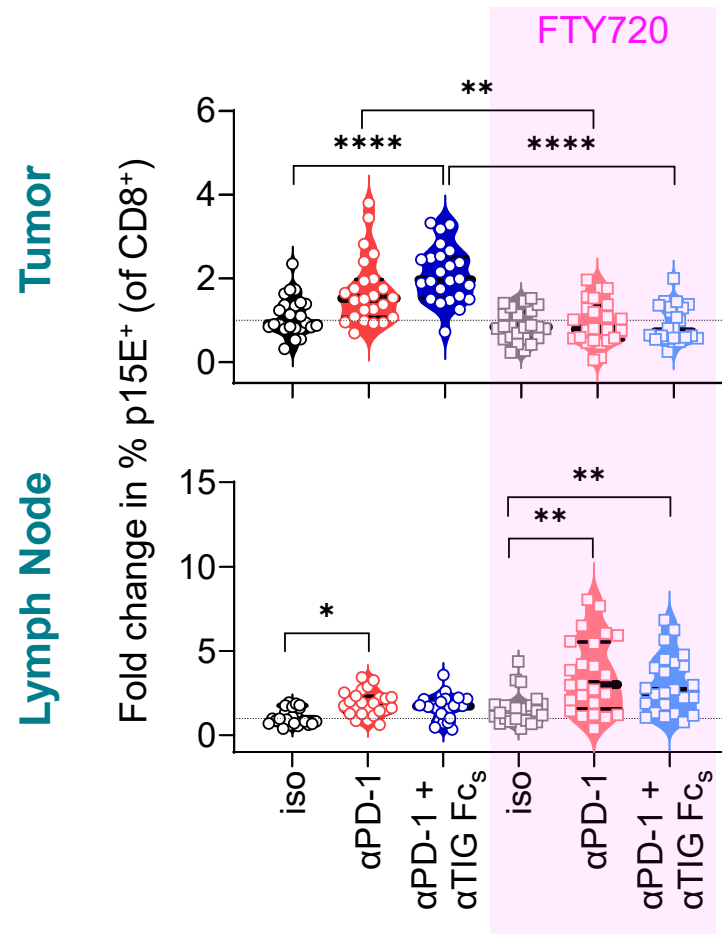
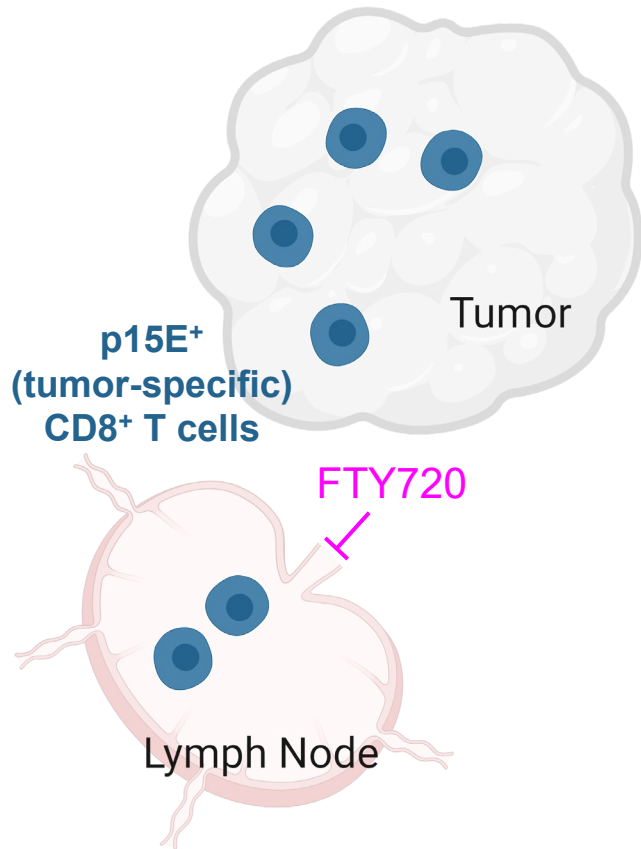


MC38 is an Ideal Experimental Model to Evaluate Anti-PD-1 Combination Partners

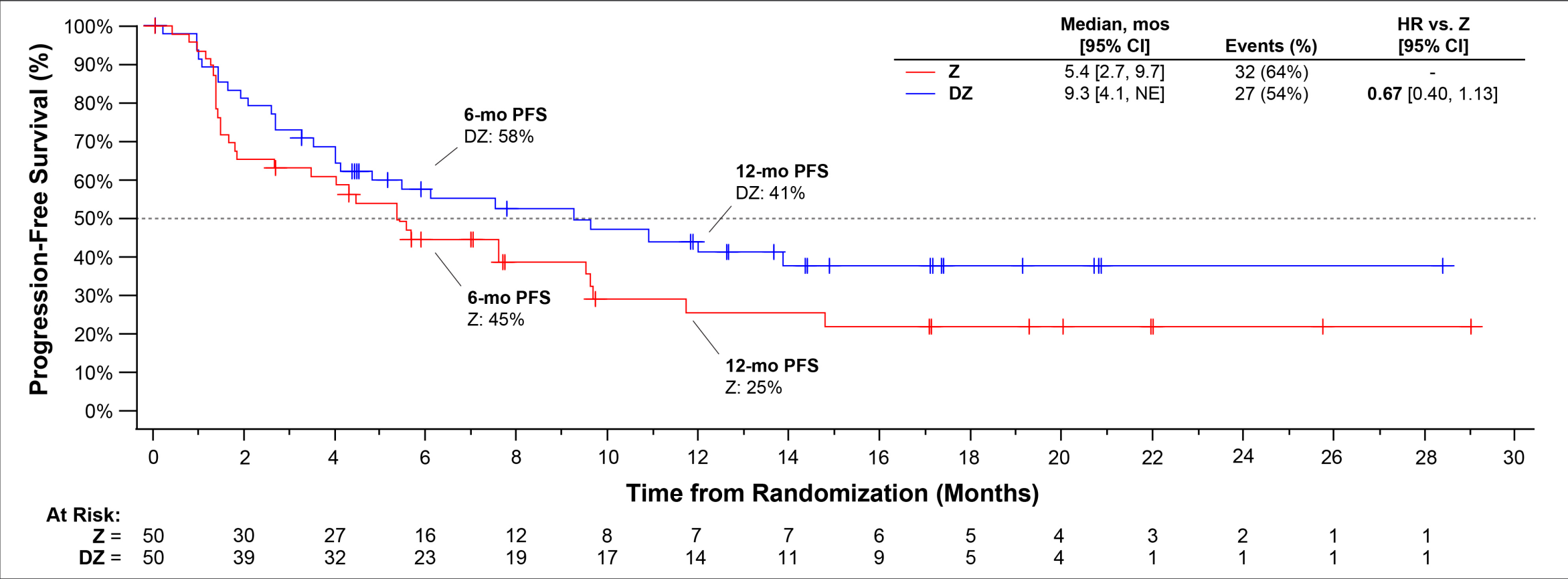
- **Model:** The MC38 colon carcinoma model is T cell infiltrated and anti-PD-1 responsive
- **Readouts:** Tools exist to monitor endogenous MC38 cancer cell-specific CD8⁺ T cell responses
- **Surrogate antibody design: Fc-silent domain for a pure blocking antibody**
 - Avoid tumor-specific effector T and NK cell killing
 - Avoid toxicities associated with peripheral T_{reg} depletion



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



Addition of Dom to Anti-PD-1 Zimberelimab (Zim) Resulted in a 33% Reduction in Risk of Progression or Death as Compared to Zim Alone in PD-L1 High Metastatic NSCLC



CI: confidence interval; HR: hazard ratio; Mos: months; NE: not evaluable

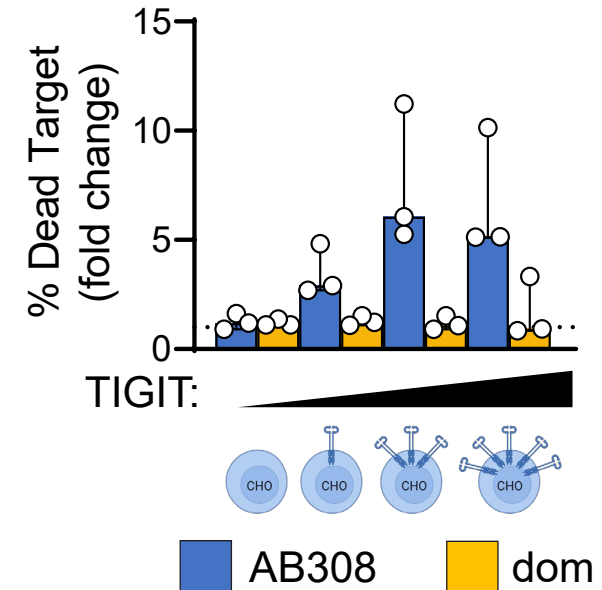
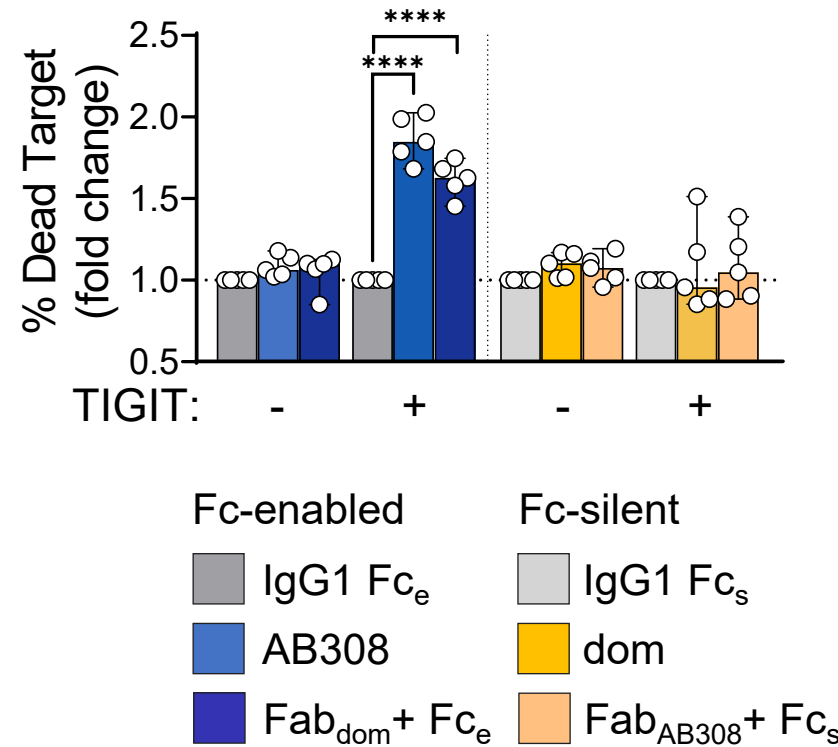
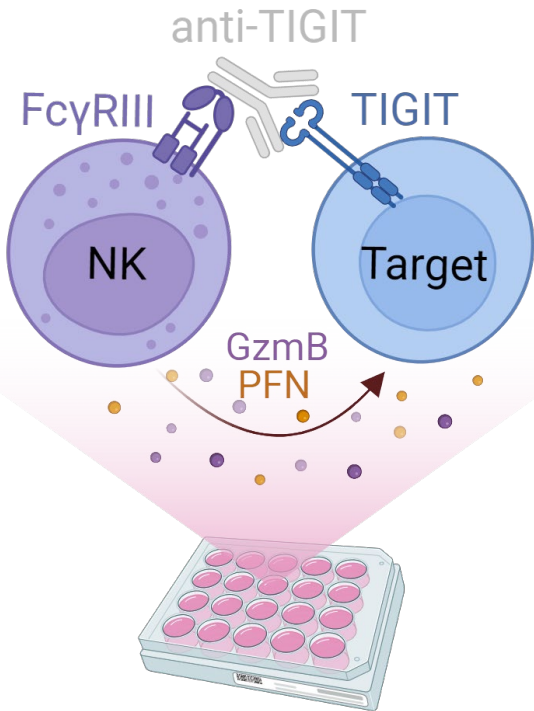
- Addition of dom to zim does not appear to add any meaningful toxicity

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



Based on FoxP3 and Helios Expression, Three Subsets of T_{reg} Can Be Identified in Human Peripheral Blood

