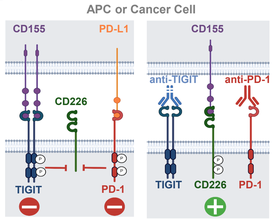
American Association for Cancer Research IO
Annual Meeting
February 18-21st, 2026
Abstract ###

TIGIT Blockade Enhances the Effect of Anti-PD-1 Against CD155^{hi} Expressing Tumors in Mouse and Human Models

Hannah E. Meibers, Casey G. Mitchell, Gabrielle L. Reiner, Dana Piovesan, Jas Singh, Saranya Chandrasekar, Yihong Guan, Ritu Kushwaha, Lauren Rocha, Ferdie Soriano, Ruben Flores, Matthew J. Walters, Patrick G. Schweickert, Kelsey E. Sivick
Arcus Biosciences, Hayward, CA

Background

- TIGIT (T-cell immunoreceptor with Ig and ITIM domains) is an inhibitory receptor expressed on T cells and natural killer (NK) cells.
  - TIGIT competes with CD226 (DNAM-1) for binding to CD155 (PVR), a ligand expressed by cancer and antigen-presenting cells (APCs)[1-4].
  - CD155-CD226 interactions promote cell activation followed by rapid internalization of CD226 as a form of feedback regulation[5].
- PD-1 (programmed cell death 1) is an inhibitory receptor that can suppress cell activation through dephosphorylation of CD226[6,7].
  - High CD155 expression on cancer cells is associated with poor performance of PD-1 blockade in multiple settings[8,9].
- **We elucidate that simultaneous blockade of PD-1 and TIGIT could enhance CD155-CD226 signaling, promoting anti-tumor immunity and exhausted T (T_{EX}) cell effector function.**
  - Fc-silent human and mouse antibodies were used to focus on blocking TIGIT rather than Fc-driven mechanisms.



Results

Exhausted CD8$^+$ T Cell Subsets in Multiple Cancer Indications Exhibit Similar Patterns of PD-1, TIGIT, and CD226 Co-expression

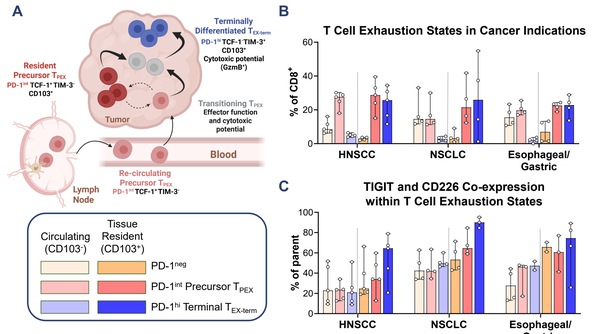


Figure 1. (A) (Top) Illustration of circulating and intratumoral CD8$^+$ T cell exhaustion states. (Bottom) Legend showing six T cell subsets. "Transitioning" cells are likely present in both PD-1^{int} and PD-1^{hi} subsets. **(B)** Frequency of circulating and tissue-resident T_{PEX} and $T_{EX\text{-}term}$ in head and neck squamous cell carcinoma (HNSCC), non-small cell lung cancer (NSCLC), and esophageal/gastric tumor samples. **(C)** Percentage of TIGIT$^+$CD226$^+$ cells within CD8$^+$ T cell populations in the indicated tumor samples.

Results

CD155 and CD226 Show Inverse Staining Patterns in Tumor Biopsies

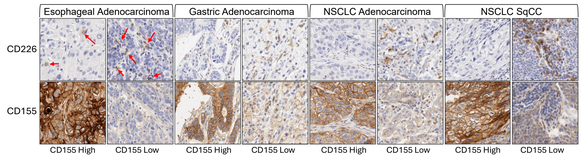
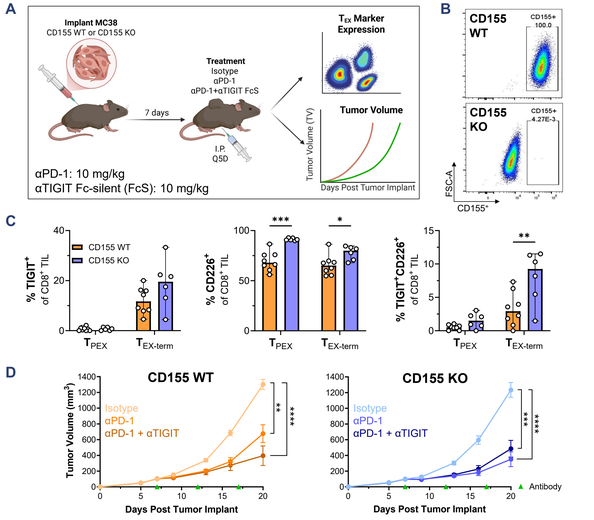


Figure 2. Immunohistochemistry (IHC) images of CD226 and CD155 expression (brown) from esophageal adenocarcinoma, gastric adenocarcinoma, NSCLC adenocarcinoma, and NSCLC squamous cell carcinoma (SqCC) tumor samples at 63x magnification. Red arrows indicate examples of CD226 expression in CD155 high versus CD155 low expressing tumors.

CD155 Expressing Tumors Downregulate CD226 and TIGIT on T_{EX} Populations and are More Susceptible to Dual PD-1 and TIGIT Blockade



% TGI Day 20		
CD155 WT	αPD-1	47.6
	αPD-1 + αTIGIT	70.2
CD155 KO	αPD-1	70.9
	αPD-1 + αTIGIT	60.4

%TGI = $(1-(T_{20}/T_7)/(C_{20}/C_7))*100$
T = mean treated TV, C = mean control TV,
20 = Day 20, 7 = Day 7, TV = tumor volume

Figure 3. (A) MC38 syngeneic mouse model schematic. CD155 WT or CD155 KO MC38 tumor cells were injected in the flank of C57BL/6N mice. Intraperitoneal (I.P.) isotype, αPD-1, or αPD1 + αTIGIT FcS treatment every 5 days (Q5D) began on day 7. Mice were euthanized on day 20. **(B)** CD155 expression on engineered MC38 adenocarcinoma cell lines. **(C)** T_{EX} cell marker expression on CD8$^+$ tumor infiltrating lymphocytes (TIL) on day 20. T_{PEX}: TCF1$^+$TIM3$^-$. $T_{EX\text{-}term}$: TCF1$^-$TIM3$^+$. Two-way ANOVA with Šídák's multiple comparisons test. **(D, E)** Tumor volume (TV) and tumor growth inhibition (TGI) of CD155 WT and CD155 KO MC38 tumors treated with the indicated antibodies. (D) Two-way ANOVA with Geisser-Greenhouse correction and Tukey's multiple comparisons test. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

Results

CD155 Expressing Cancer Cells are Resistant to CD8$^+$ T Cell Mediated Killing which can be Overcome by Dual PD-1 and TIGIT Blockade

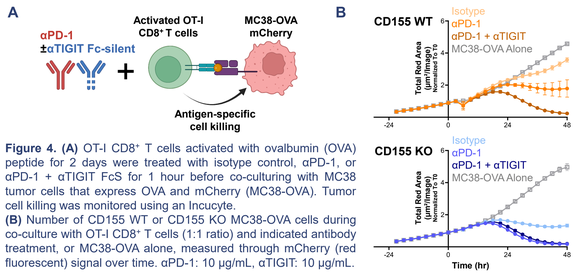


Figure 4. (A) OT-I CD8$^+$ T cells activated with ovalbumin (OVA) peptide for 2 days were treated with isotype control, αPD-1, or αPD-1 + αTIGIT FcS for 1 hour before co-culturing with MC38 tumor cells that express OVA and mCherry (MC38-OVA). Tumor cell killing was monitored using an Incucyte.
(B) Number of CD155 WT or CD155 KO MC38-OVA cells during co-culture with OT-I CD8$^+$ T cells (1:1 ratio) and indicated antibody treatment, or MC38-OVA alone, measured through mCherry (red fluorescent) signal over time. αPD-1: 10 µg/mL, αTIGIT: 10 µg/mL.

Development of a Humanized Mouse Model Using the CD155 Expressing A549 Lung Adenocarcinoma Cell Line

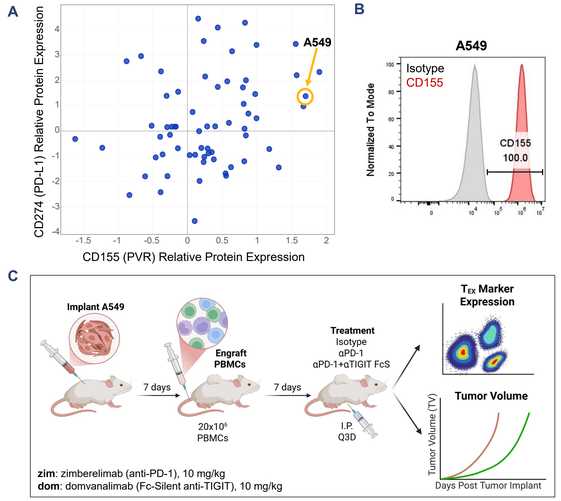


Figure 5. (A) Cancer Cell Line Encyclopedia (CCLE) DepMap Data Explorer 2.0 analysis of PD-L1 versus CD155 protein expression on lung cancer cell lines. **(B)** A549 cells highly express CD155 protein.
(C) Schematic of the A549 humanized mouse model. CD155 expressing A549 tumor cells were injected in the flank of NSG MHCI/II double knockout mice (Jax # 025216). Seven days later, 2x10^7 PBMCs were engrafted via tail vein injection. Fourteen days post-tumor implant, I.P. treatment with human-specific isotype control, αPD-1, or αPD1 + αTIGIT Fc-silent (FcS) occurred every 3 days (10 mg/kg, Q3D). Animals were euthanized on day 63.

Results

TIGIT Blockade Enhances the Effect of Anti-PD-1 Against CD155 Expressing Tumors in a Humanized Mouse Model

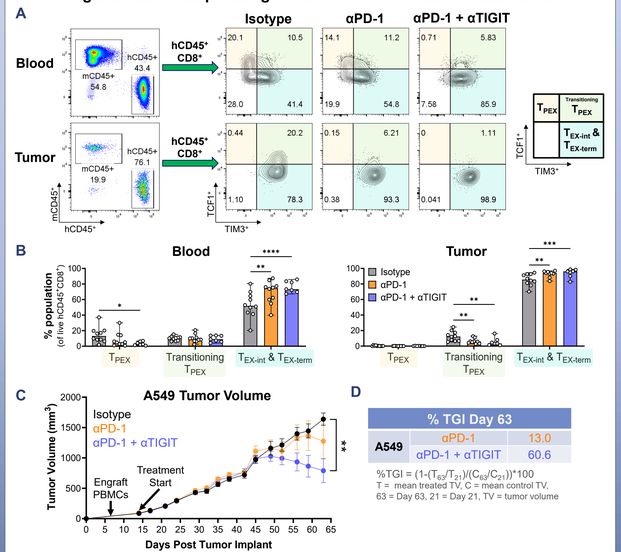


Figure 6. (A) Human T_{EX} cell populations in blood and A549 tumors 63 days post-tumor implant (see Figure 5C for additional humanized mouse model information). mCD45$^+$: mouse CD45$^+$, hCD45$^+$: human CD45$^+$, T_{PEX}: precursor exhausted T cells (TCF1$^+$TIM3$^-$), Transitioning T_{PEX}: TCF1$^+$TIM3$^+$, $T_{EX\text{-}int}$ & $T_{EX\text{-}term}$: intermediate and terminally exhausted T cells (TCF1$^-$TIM3$^+$). **(B)** Quantification of T_{EX} populations observed in (A). Two-way ANOVA with Dunnett's multiple comparisons test. **(C, D)** Tumor volume and % TGI of animals treated with the indicated antibodies. (C) Mixed-effects analysis with Geisser-Greenhouse correction and Dunnett's multiple comparisons test. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

Summary

- Multiple solid tumor types contain TIGIT, CD226, and PD-1 co-expressing CD8$^+$ T_{EX} cells that can be targeted with dual PD-1 and TIGIT blockade (Figure 1).
- Downregulation of CD226 in the presence of CD155, as seen in human samples and mouse models, is indicative of negative regulation upon receptor engagement (Figures 2, 3).
- Fc-silent anti-TIGIT can enhance antigen-specific killing of tumor cells by PD-1 blockade *in vitro*, particularly in CD155^{hi} settings (Figure 4).
- *In vivo* TIGIT blockade increased tumor control by anti-PD-1 specifically in the CD155^{hi} setting in both a syngeneic and humanized mouse model (Figures 3, 5, 6).
- Dual blockade of TIGIT and PD-1 can tune the immune system toward an activated state, particularly in settings when CD155 is highly expressed, promoting optimal anti-tumor immunity.

Some images made with BioRender. [1]Jin HS et al. (2020) *Cancer Immuno Res;* [2]Worbys JD et al. (2023) *Nat Comm;* [3]Joller N et al. (2011) *J Immunol;* [4]Yu X et al. (2008) *Nat Immunol;* [5]Weulersse M et al. (2020) *Immunity;* [6]Banta KL et al. (2022) *Immunity;* [7]Wang B et al. (2018) *Science Immunol;* [8]Jiang C et al. (2022) *Clin Exp Immunol;* [9]Oyama R et al. (2022) *Oncol Lett*