TIGIT pathway phenotyping sheds light on promising strategies to restore anti-tumor immunity.

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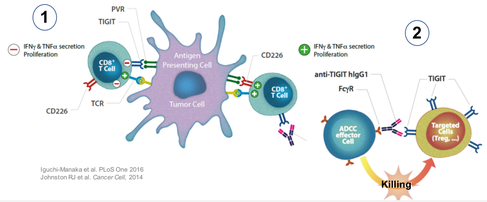
BACKGROUND

- T cell Immunoreceptor with Ig and ITIM domains (TIGIT) is a negative costimulatory receptor that inhibits effector T cell and NK cell function and marks a highly suppressive regulatory T cell (Treg) subset.
- TIGIT ligands belong to the PVR/nectin family, among which PVR (CD155) shows the highest affinity and is commonly expressed on antigen presenting cells (APC) and tumor cells.
- TIGIT expression is increased on T and NK(T) cells from cancer patients and is correlated to poor outcome and response to aPD1 therapy in some indications.
- EOS884448 properties and functionality make it an attractive Immuno-Oncology therapy candidate (See poster #3240)
  - ✓ Strong binding to primary human and cyno T cells (sub-nM Kd)
  - ✓ Competition with natural ligands with IC_{50} in sub-nM range
  - ✓ Increase of primary T cell functions in healthy donors and cancer patients
  - ✓ Depletion through ADCC of highly suppressive TIGIT$^+$ Tregs.
  - ✓ Antitumor efficacy in animal model
  - ✓ Excellent developability profile
  - ✓ Excellent safety profile

TIGIT-DRIVEN IMMUNOSUPPRESSION



1 drug = multiple anti-tumor mechanisms of action

1. Reactivation of immune response by
   - Suppressing TIGIT-mediated inhibitory signaling
   - Increasing ligand availability for CD226 co-stimulatory receptor
2. Depletion of TIGIT+ highly suppressive Treg subpopulation and TIGIT+ tumor cells with ADCC-triggering isotype (FcγR dependent)

HIGH TIGIT EXPRESSION ON IMMUNE CELLS, FURTHER INCREASED IN CANCER PATIENTS

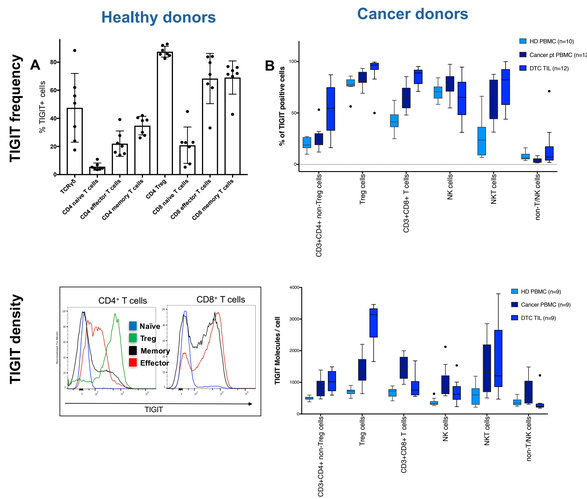


Fig. 1. Flow cytometry analysis of TIGIT expression, gating on different lymphocyte subsets in healthy donor (A) PBMCs (n=7). Frequency of TIGIT expressing cells is highest on CD4$^+$ Tregs and effector and memory T cells and (B) further increases in cancer patient PBMCs or tumor infiltrated lymphocytes (TILs) (n=12). Infiltrated Tregs display both the highest frequency and density of TIGIT receptor.

INFILTRATED TIGIT$^+$ CD4$^+$ AND CD8$^+$ T CELLS ARE DYSFUNCTIONAL

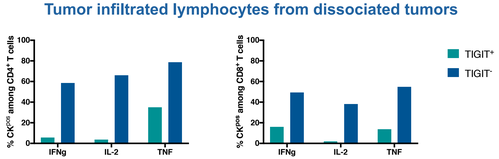


Fig. 2. Tumor infiltrated T cells positive for TIGIT are dysfunctional. Lymphocytes from dissociated tumor cells were activated for 3h ex-vivo with PMA/Ionomycin before detection of intracellular cytokines by intracellular staining (flow cytometry). Representative example showing a strong immunosuppression of infiltrated T cells that express TIGIT (n=5).

Tregs SHOW THE HIGHEST TIGIT EXPRESSION AMONG IMMUNE CELLS WITHIN THE TME

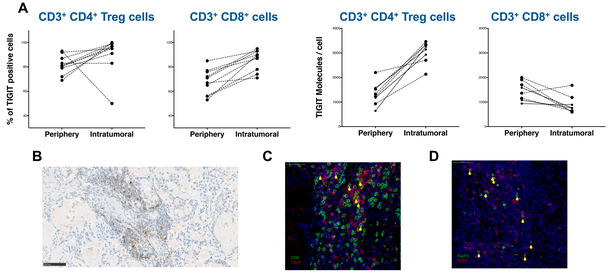


Fig. 3. TIGIT expression in human lung cancer tissues analyzed by IHC and immunofluorescence (IF).
(A) Specific increase of TIGIT expression on tumor infiltrated Tregs by flow cytometry (B). Representative picture of TIGIT chromogenic staining in lung cancer. TIGIT expression was observed in 10 out of the 11 lung tumor tissues analyzed. A visual analysis of IF costaining of TIGIT and CD8 (C) or Foxp3 (D) showed that a higher proportion of cells are TIGIT positive among FoxP3$^+$ T cells compared to CD8$^+$ T cells (yellow arrows).

STRONG CD155 EXPRESSION ON TUMOR CELLS FROM MULTIPLE SOLID TUMOR TYPES

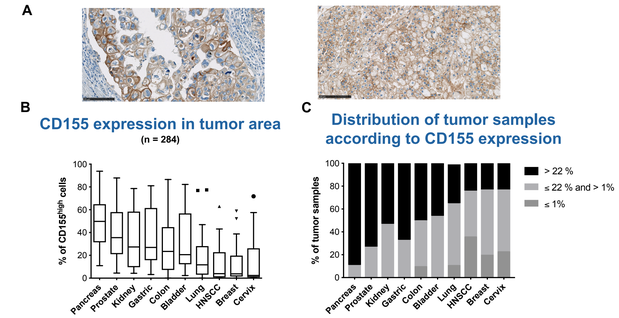


Fig. 4. CD155 expression is highly expressed by tumor cells from numerous human solid cancers.
(A) Representative IHC pictures of CD155 expression by tumor cells in bladder and kidney cancers are shown. CD155 is mainly expressed by tumor cells. (B) Percentages of cells expressing high levels of CD155 was analyzed in tumor area (i.e. pancytokeratin$^+$ area) by automated quantification (Visiopharm® software) of IHC-stained tissue microarrays (TMAs; n=284). (C) Percentages of samples with proportion of CD155^{high} cells above or below the cut-off values of 1% (arbitrary cut-off of positive samples) and 22% (median overall value of % of CD155^{high} cells) are shown.

DIRECT EXPRESSION OF TIGIT ON TUMOR CELLS FROM SPECIFIC BLOOD CANCER INDICATIONS

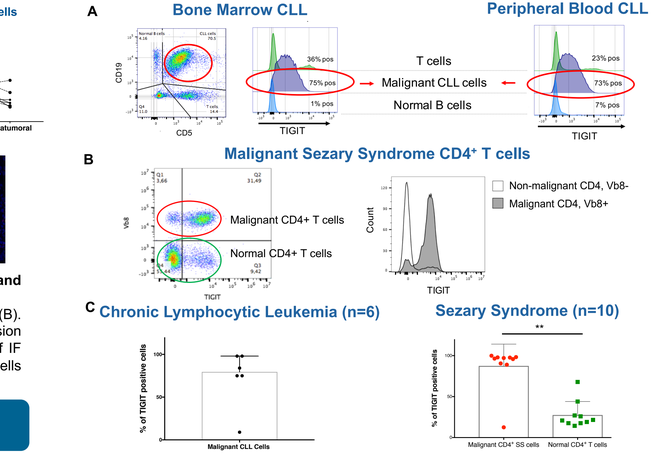


Fig. 5. TIGIT is directly expressed on the malignant cells from specific blood cancer indications. (A) Flow cytometry analysis of TIGIT expression on Chronic Lymphocytic Leukemia malignant cells gated as CD19$^+$CD5$^+$ CLL cells (B) Identification of Sezary malignant clone TCRVβ rearrangement using a TCRVβ repertoire kit before assessment of TIGIT expression on tumor cells compared to normal CD4$^+$ T cells.
(C) Summary of all patient samples analysed. For Sezary Syndrome cohort, p=0.0015 (Mann-Withney u test).

CONCLUSIONS

- TIGIT is strongly expressed on infiltrated T cells from patients with solid tumors. Infiltrated TIGIT$^+$ CD4$^+$ T cells and CD8$^+$ T cells show impaired pro-inflammatory cytokine secretion. The highest TIGIT expression is observed on infiltrated Tregs that are known to be highly immunosuppressive compared to TIGIT$^-$ Tregs.
- CD155 is widely expressed by tumor cells in all the solid cancers analyzed.
- Direct expression on tumor cells in dedicated blood cancers opens the possibility of a direct tumor effect of ADCC fully enabled a-TIGIT antibodies.

⇒ TIGIT is a promising target in both solid tumors and blood cancers with a strong rationale to be targeted with an antibody fully equipped with effector functions.

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