# Characterization of AB154, a Humanized α-TIGIT Antibody for the Treatment of Cancer

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## Introduction

TIGIT (T-cell immunoreceptor with Ig and ITIM domains) is an inhibitory receptor expressed on NK and $CD8^+$ T cells, as well as immunosuppressive Tregs. TIGIT binds to CD155 and CD112, both of which are expressed by tumors and antigen-presenting cells, resulting in immune suppression. These ligands also bind the costimulatory receptor CD226 resulting in NK and T cell activation. Shifting the balance within the tumor from one that favors binding of CD155 / CD112 to TIGIT towards the more productive CD226 interaction induces a strong anti-tumor immune response. Thus, TIGIT blockade represents an attractive approach to the treatment of cancer.

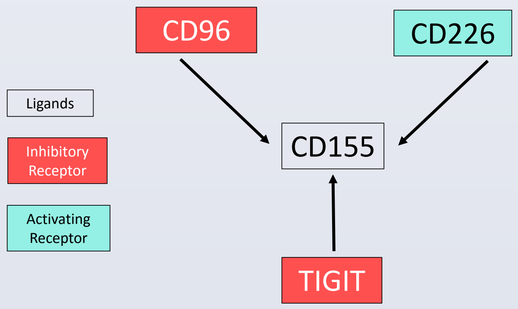


Figure 1. TIGIT, expressed on the surface of immune cells, binds to CD155 resulting in decreased anti-tumor activity of the TIGIT expressing cells.

## TIGIT Expression on Tumor Infiltrating Immune Cells

| Cancer | Cell type | Cell Surface Markers | TIGIT |
|---|---|---|---|
| SKCM | T cells | $TCR\beta^+ CD4^+ CD25^-$ | +/- |
| | | $TCR\beta^+ CD4^+ CD25^+$ | ++++ |
| | | $TCR\beta^+ CD8^+$ | ++++ |
| | Antigen Presenting Cells | $CD11b^+ CD14^+ HLA\text{-}DR^+$ | - |
| | | $CD11b^- CD14^- HLA\text{-}DR^+$ | - |
| CRC | T cells | $TCR\beta^+ CD4^+ CD25^-$ | +/- |
| | | $TCR\beta^+ CD4^+ CD25^+$ | ++++ |
| | | $TCR\beta^+ CD8^+$ | ++++ |
| | Antigen Presenting Cells | $CD11b^+ CD14^+ HLA\text{-}DR^+$ | - |
| | | $CD11b^- CD14^- HLA\text{-}DR^+$ | - |
| NSCLC | T cells | $TCR\beta^+ CD4^+ CD25^-$ | +/- |
| | | $TCR\beta^+ CD4^+ CD25^+$ | ++++ |
| | | $TCR\beta^+ CD8^+$ | ++++ |
| | Antigen Presenting Cells | $CD11b^+ CD14^+ HLA\text{-}DR^+$ | - |
| | | $CD11b^- CD14^- HLA\text{-}DR^+$ | - |

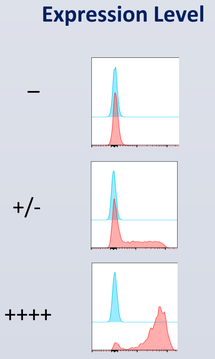


Table 1. TIGIT is highly expressed on $CD8^+$ & $CD4^+$ $CD25^+$ tumor infiltrating T cells in different cancers. Right panel shows example TIGIT expression levels.

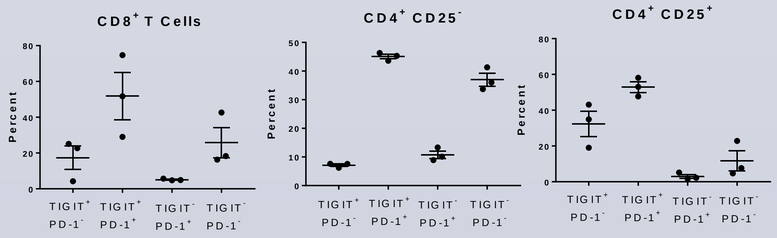


Figure 2. Immunophenotyping of tumor infiltrating T cells highlights significant TIGIT and PD-1 double positive cells. Example data from NSCLC shown.

## Inhibition of CD155 Binding to Human TIGIT by AB154

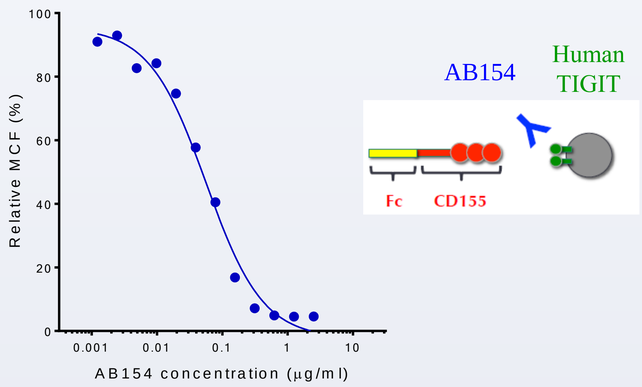


Figure 3. AB154 potently inhibits binding of CD155 to TIGIT with an $IC_{50}$ of 0.4 nM.

## Inhibition of TIGIT Augments Antigen Specific T Cell Responses

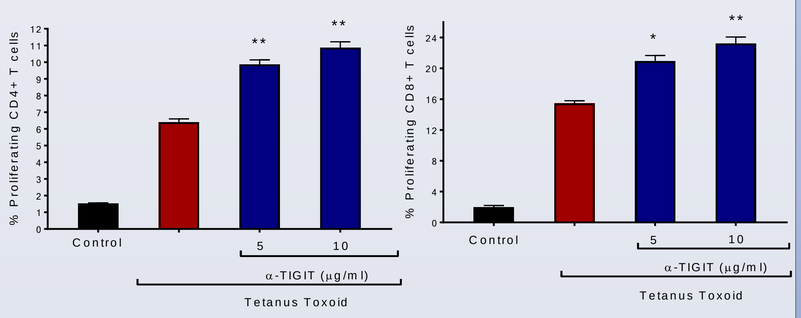


Figure 4. Inhibition of TIGIT significantly increases $CD4^+$ & $CD8^+$ T cell proliferation in an antigen specific recall response. *p<0.05 vs. tetanus toxoid alone; **p<0.01 vs. tetanus toxoid alone; Representative data shown from two separate donors.

## Inhibition of TIGIT Augments Antigen Specific Cytokine Release

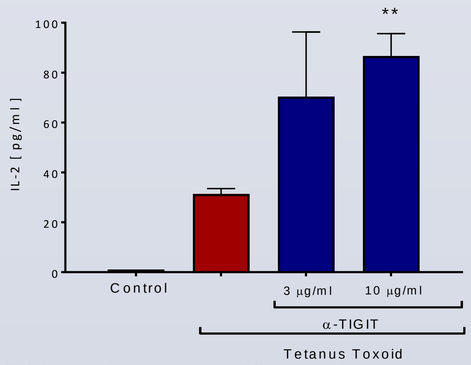


Figure 5. Inhibition of TIGIT significantly increases IL-2 levels In response to tetanus toxoid challenge **p<0.01 vs. tetanus toxoid alone.

## AB154 Increases Human NK Cell-Mediated Cell Lysis

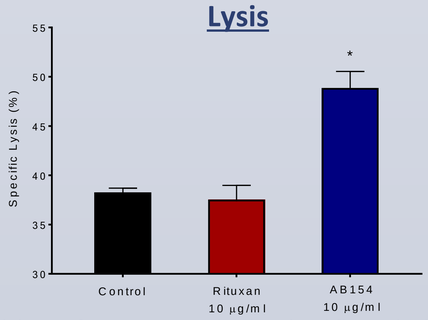


Figure 6. Inhibition of TIGIT results in significantly increased K562 target cell lysis. *p<0.05 vs. control Ab.

## Inhibition of TIGIT and PD-L1 Results in Significantly Increased IFN-γ in DC-MLR

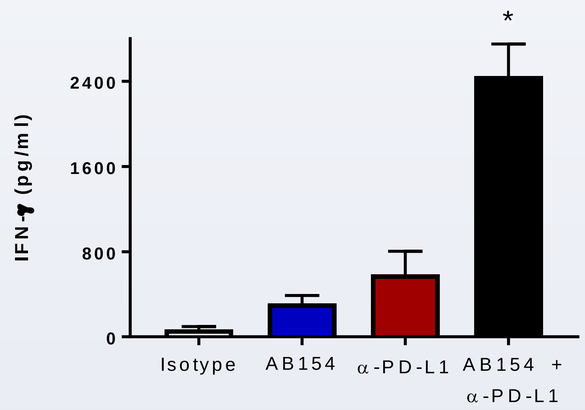


Figure 7. Inhibition of TIGIT in combination with PD-L1 results in increased IFN-γ production relative to monotherapy. *p<0.05.

## Functional Inhibition of TIGIT by AB154 *in vivo*

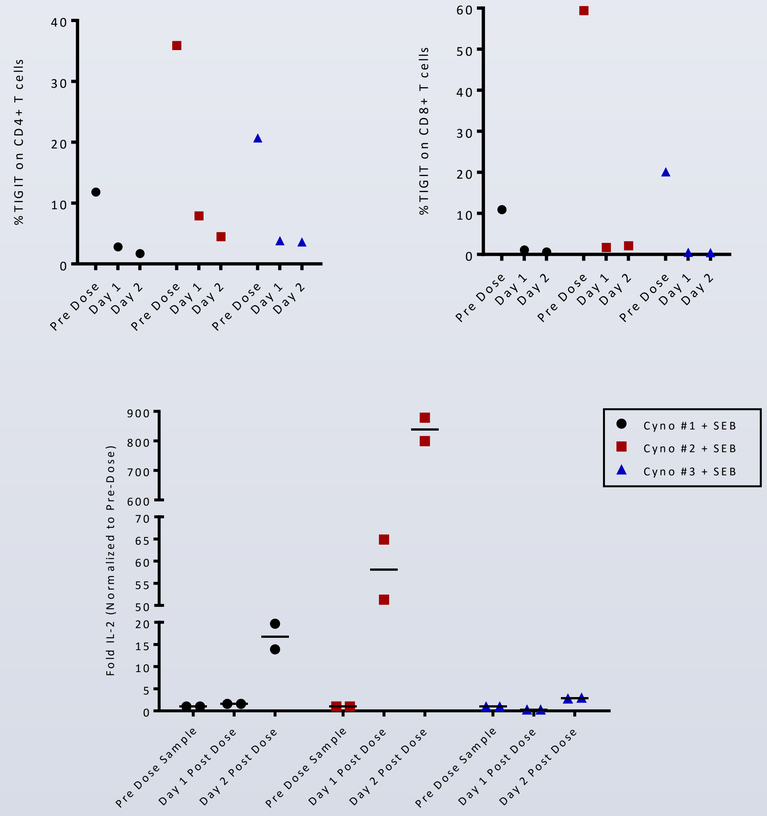


Figure 8. AB154 binds to TIGIT on $CD4^+$ (left panel) and $CD8^+$ (right panel) T cells in cynomolgus monkeys (no reduction in $CD4^+$ or $CD8^+$ cells was observed, data not shown). Functional inhibition of TIGIT was confirmed with an *ex vivo* SEB super antigen stimulation (lower panel).

## Summary

- **AB154 is a fully humanized monoclonal antibody that potently inhibits TIGIT from binding to CD155.**
- **AB154 is expected to advance into clinical trials in the near future.**