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Characterization of AB154, a Humanized Anti-TIGIT Antibody, For Use in Combination Therapies

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Introduction

AB154 is a humanized antibody that blocks human TIGIT (T-cell immunoreceptor with Ig and ITIM domains), an inhibitory receptor expressed on natural killer (NK) cells, $CD8^+$ T cells, $CD4^+$ T cells and regulatory T cells (T_{reg}). CD226 (or DNAX Accessory Molecule-1, DNAM-1) is an activating receptor that competes with TIGIT for shared ligands CD155 (*PVR*) and CD112 (*Nectin-2*), expressed by cancer and antigen-presenting cells. TIGIT blockade by AB154 prevents binding to its ligands and shifts the immune balance towards a more favorable CD226 interaction. AB154 has the potential to promote sustained immune activation and tumor clearance, particularly in combination with other immunotherapies such as AB122 (anti-PD1).

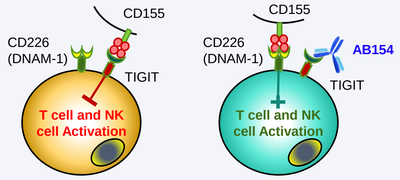

Figure 1. TIGIT binds to CD155 and results in decreased activation of the TIGIT-expressing immune cells. AB154 blockade of TIGIT allows CD155 to bind CD226, favoring T cell and NK cell activation.

Materials and Methods

In Vitro Assays: AB154 binding affinity was determined in CHO cells over-expressing human TIGIT. Inhibition of CD155 interaction was quantified using a TIGIT-expressing reporter gene cell line.

Gene Expression: Expression of TIGIT, PD-1 (*PDCD1*), CD226, PD-L1 (*CD274*), and CD155 (*PVR*) on select tumor types were derived from RNASeq in The Cancer Genome Atlas (TCGA) database and displayed as log2 transformed expression of counts per million.

Flow Cytometry on Human Head & Neck Tumors: Dissociated tumor samples were purchased from Discovery Life Sciences (n = 5). Cells were stained with LIVE/DEAD Fixable Aqua (ThermoFisher), then stained for surface markers or isotype controls related to T cell lineage, exhaustion, and activation. Cells were fixed and permeabilized, washed and stained for intracellular markers prior to data collection.

Immunohistochemistry (IHC): Anti-CD155 antibody (Cell Signaling Technology, D8A5G) was used to stain FFPE human tissues. Samples were deparaffinized according to standard methods and heat-induced epitope retrieval was performed using sodium citrate. Anti-rabbit HRP and DAB chromogen were used for detection.

Clinical / PD: A Phase 1 dose-escalation study is underway to evaluate AB154 as a monotherapy and in combination with AB122 (anti-PD1) in participants with advanced solid malignancies. Whole blood was obtained from patients at the first dose level (n = 3) and receptor occupancy (RO) was determined by flow cytometry using saturating levels of a competing anti-TIGIT antibody.

Results

AB154 Binding to Human TIGIT Blocks Interaction with CD155

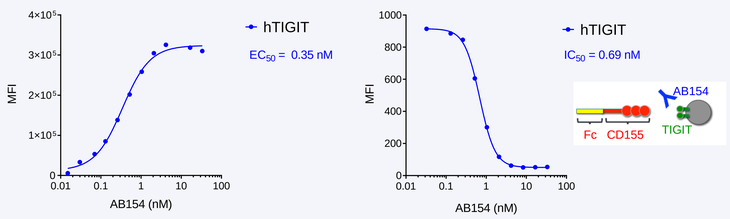

Figure 2. In a CHO cell line expressing human TIGIT, AB154 binds with sub-nanomolar affinity (0.35 nM). Binding of soluble CD155-Fc to TIGIT was abrogated in the presence of AB154 with an IC_{50} of 0.69 nM.

TIGIT, PD-1, and CD226 Are Co-Expressed on Human Tumors

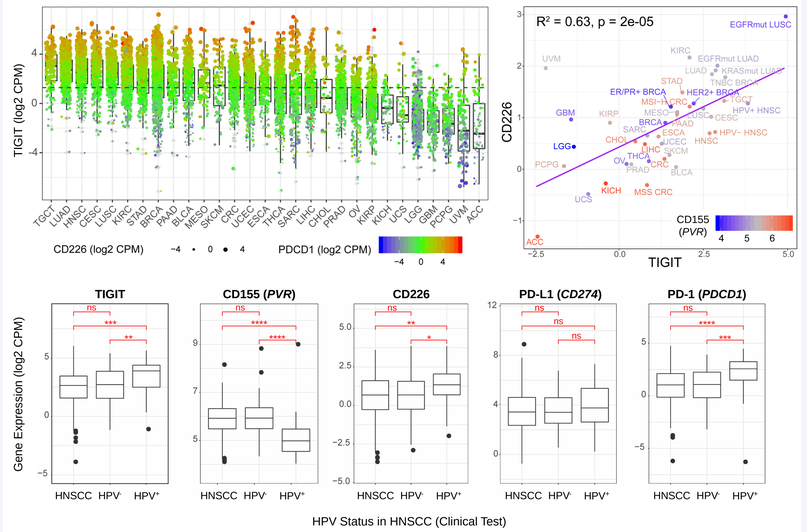

Figure 3. RNASeq data from TCGA reveals high levels of TIGIT and PD-1 (*PDCD1*) co-expression across many tumor types. CD226 is often expressed in $TIGIT^{hi}$ $PD\text{-}1^{hi}$ tumor types; however, CD155 (*PVR*) is not strongly correlated with these immune markers. Positive viral status in HNSCC is associated with higher levels of TIGIT, CD226, and PD-1. CD155 is negatively correlated with viral status, while PD-L1 (*CD274*) has no significant correlation with HPV status. *p ≤ 0.05. **p ≤ 0.01. ***p ≤ 0.001. ****p ≤ 0.0001.

Antigen Experienced $CD8^+$ T Cells Isolated from Advanced Head and Neck Tumors Express Higher TIGIT and PD-1

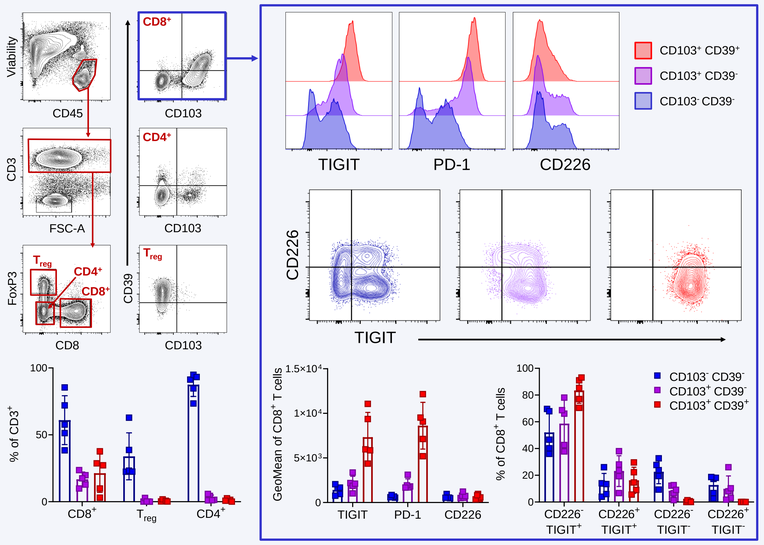

Figure 4. In T cells isolated from advanced head and neck tumors (n = 5), markers of antigen experience are predominantly found on the $CD8^+$ subset. The $CD8^+$ antigen-experienced T cells ($CD103^+CD39^+$) express higher levels of PD-1 and TIGIT that are consistent with an "exhausted" phenotype. Expression of CD226 is progressively lost from the inexperienced $CD103^-CD39^-$ CD8 T cell population to the experienced $CD103^+CD39^+$ CD8 T cell population.

CD155 Stains Strongly in Cancer Types of Interest

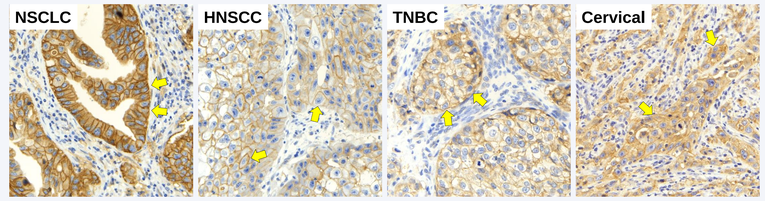

Figure 5. CD155 immunohistochemistry (IHC) shows membrane and cytoplasmic localization on cancerous cells in non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), triple negative breast cancer (TNBC), and cervical carcinoma. Arrows indicate areas of positive staining on tumor cells.

Total Receptor Coverage Achieved in AB154 Monotherapy Cohort

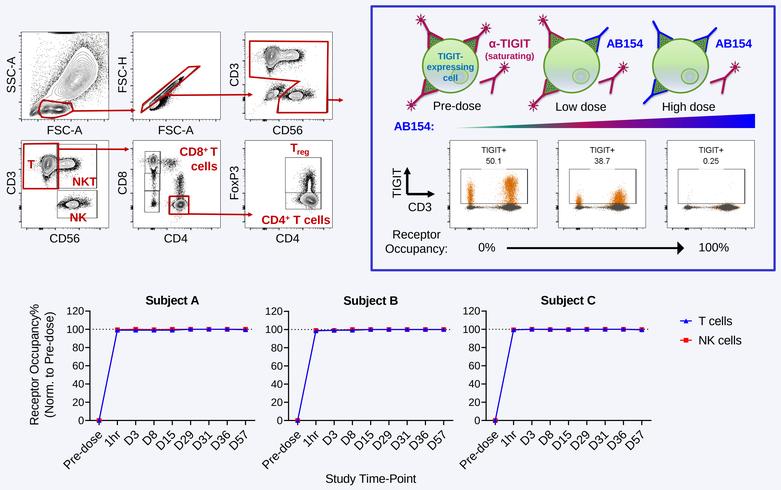

Figure 6. Complete receptor coverage was observed in all three AB154-dosed patients in the first cohort of a monotherapy dose escalation study (Dose Level 1). With dosing every two weeks, AB154 achieved complete inhibition at trough drug levels on all TIGIT-expressing leukocytes in peripheral blood.

Conclusions

- AB154 is a humanized monoclonal antibody that potently inhibits the interaction of TIGIT and CD155 with sub-nanomolar affinity.
- TIGIT, PD-1, and CD226 expression are correlated in many tumor types and are often co-expressed on tumor infiltrating lymphocytes (TILs). CD155 is also presented by cancer types of interest.
- Positive viral status is associated with higher levels of TIGIT, PD-1, and CD226 in head and neck tumors. CD155 expression is negatively correlated with HPV^+ status.
- $CD8^+$ T cells make up the majority of antigen-experienced T cells in advanced head and neck tumors. Antigen experience occurs alongside markers of immune exhaustion and loss of CD226 expression.
- AB154-dosed patients had complete receptor coverage on all TIGIT-expressing peripheral leukocytes in the first cohort of a Phase 1 trial (NCT03628677).

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