**TIGIT: A Key Regulator of the Immune Synapse**

**Antigen Receptor-Induced Functions for Tumour Activity and Improved T cell Stimulation**

- Prevention of CTCs co-stimulation
- TGFβ-induced suppression of FoxP3+ T cells
- Enhanced Treg suppressive activity
- IFNα immunomodulatory effects (Fig 1, TGFβ)

**FcγR Co-Engagement Enhances T cell Responsiveness**

- Co-engagement of FcγR with B7/CTLA-4 or CD28 engagement of TIGIT expands Treg and CTLA-4 Ab with increased binding affinity to activating FcγR receptors (CD16a+ mouse) or FcγRIIB (CD16b human), augment T cell priming by improving the quality of the immune synapse between T cell and an antigen presenting cell (APC).

**FcγR Binding Characteristics of Antibody Fc Variants Used**

**Enhanced FcγR Co-Engagement Enhances T cell Responsiveness**

- Human: Fc-dependent T cell priming (in vitro)
- Mice: Anti-TIGIT (h IgG1) and anti-PD-1 (h IgG1, h IgG4) antibodies together with anti-CD80/CD86 antibodies.

**Enhanced FcγRIIIa Engagement Improves T Cell Responsiveness In Vivo (Human)**

- Antitumor activity: Tumour volume (mm3)
- IL-2 (fold change) **
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**Conclusions**

- Our data suggest a novel FcγR-dependent mechanism of action that enhances the therapeutic activity of anti-TIGIT antibodies in preclinical studies.
- Murine FcγRIIIa and human FcγRIIA are critical mediators of anti-TIGIT antibody activity.
- Tumor control is dependent on enhancing CD8+ T cell and NK cell function but not Treg depletion.
- Enhanced FcγRIIIa co-engagement via FcγRIa engagement further enhances T cell responsiveness.

- This novel mechanism extends to antibodies targeting CTLA-4, IgG4, and IgG1 antibodies (clay 4g) by human PBMCs stimulated with SEB/peptide 10 μg of anti-PD-1 antibody or isotype control.