

TNB-585: A Novel CD3xPSMA Bispecific Antibody for Efficient T Cell Mediated Killing of Prostate Tumor Cells with Minimal Cytokine Release

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BACKGROUND

Castration resistant prostate cancer (CRPC) is an incurable disease with limited therapeutic options and novel therapies are urgently needed. Prostate specific membrane antigen (PSMA) is a protein highly expressed on the surface of prostate cancer cells; expression increases with disease progression. Therapies targeted to PSMA, such as anti-PSMA radioligand conjugates, have shown promise in clinical trials, validating this target for CRPC. T-cell recruiting bispecific antibodies (T-BsAbs) have demonstrated potent tumor killing activity, but immune-mediated toxicity, especially cytokine release syndrome, have hampered T-cell redirecting therapies to date. Using Teneobio's unique antibody discovery platform, we have developed a fully human CD3xPSMA bispecific antibody (TNB-585) that retains the potent cytotoxicity but with significantly reduced cytokine release.

METHODS

Antibodies targeting CD3 and PSMA were generated via immunization of our proprietary transgenic animals (UniRat™, OmniFlic™) that are engineered to produce fully human antibodies. Candidate antibodies were selected by repertoire deep sequencing of B-cells from draining lymph nodes, followed by high-throughput gene assembly and recombinant expression. Bispecific antibodies targeting CD3 and PSMA were assembled and evaluated for their ability to selectively activate primary human T-cells and eliminate PSMA+ tumor cells *in vitro* and *in vivo*. T-cell activation surface markers, cytokine production and tumor cell cytotoxicity were measured.

RESULTS

Primary human T-cells were activated only in the presence of both TNB-585 and PSMA (either recombinant or cell-surface protein). Potent and selective cytotoxicity against PSMA-positive tumor cells was observed in co-cultures of primary human T-cells and tumor cells treated with TNB-585. Strikingly, TNB-585 mediated comparable tumor cell cytotoxicity to CD3xPSMA T-BsAbs containing a high affinity anti-CD3 domain, but with significantly reduced cytokine production. Preliminary *In vivo* xenograft experiments showed tumor growth inhibition in NOG mice.

CONCLUSIONS

We have created a novel CD3xPSMA T-BsAb that mediates T-cell killing of PSMA+ tumor cells with minimal production of cytokines. This molecule may improve safety, efficacy, and offer opportunities for combination therapy to treat CRPC.

CONFLICT OF INTEREST

The authors except Lawrence Fong and Chiara Rancan are employees of Teneobio, Inc. Lawrence Fong is a consultant to Teneobio, Inc.

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