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

Kevin Dang1, Pranjali Dalvi2, Yu-Ping Li1, Chiara Rancan1, Preethi Sankaran2, Duy Pham1, Katherine Harris1, Laura Davison1, Aarti Balasubramani2, Starlynn Clarke, Lawrence Fong2, Suhasini Iyer1, and Ben Buelow3

Corresponding Authors: Pranjali Dalvi: pdlav@teneobio.com
Ben Buelow: bbuelow@teneobio.com

Background

- PSMA (Prostate Specific Membrane Antigen) is highly expressed on the surface of prostate tumor cells and expression increases with disease progression, making PSMA an attractive target for new therapeutic agents to treat metastatic CRPC
- Traditional T cell-engaging bispecific antibodies can lead to cytokine release syndrome due to over-stimulation of effector cells
- We developed novel CD3 x PSMA bispecific antibodies for efficient T cell-mediated lysis of prostate tumors with reduced cytokine secretion (Figure 1).

Figure 1: TNB-585 Development

TNB-585 is a fully human T-BsAb combining fixed-light-chain (FLC) and heavy-chain-only (HCO) arms pairs using knobs-in-holes. The FLC arm weakly activates CD3. The HCO arm has a high-affinity anti-PSMA moiety. TNB-585 has a silenced human IgG4 Fc to limit non-specific activation and confer long half-life.

Figure 2: TNB-585 lysed PSMA-positive tumor cells

PSMA-positive prostate tumor cells were incubated with resting human T cells at an E:T of 5:1 (A) or 1.25:1 (B) in the presence of 125 nM negative control antibody, TNB-585, or a positive control antibody containing a high affinity anti-CD3 domain (PC). Images of individual wells after 4 days of incubation are shown on the right; dead cells were identified by annexin V staining.

In Vitro Pharmacology

Figure 3: CD3xPSMA antibodies have good developability and specificity

Off-target toxicity was assessed using the PSMA-negative prostate tumor cell line DU145 under identical conditions as in Fig 4A (A). No toxicity was observed with TNB-585, the positive control, or the negative control antibodies. (B) CD3xPSMA bispecific antibodies were stable at 37°C for 1 month. Changes in high and low molecular weight species as well as diameter and polydispersity were analyzed.

Figure 5: CD3xPSMA antibodies induce T cell expansion in the presence of PSMA+ tumor cells

T-cell expansion was measured by CFSE-dilution following incubation with either PSMA-positive 22Rv1 (A) or PSMA-negative DU145 (B) tumor cells and CD3xPSMA bispecific antibodies.

Figure 4: Efficient prostate tumor cell lysis with limited cytokine response

(A) Cell death was measured using the reagent WST-1 after incubation of LNCaP tumor cells for 48 hrs at an E:T ratio of 10:1. Supernatant from the assay wells was collected and using ELISA for production of IL-2 (B) and IFNγ (C). Despite complete tumor cell lysis, TNB-585 stimulated low levels of IL-2 and IFNγ release compared to a positive control antibody comprised of the same anti-PSMA VH used in TNB-585 paired with a high affinity anti-CD3 domain.

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Figure 6: TNB-585 Slows PSMA-positive tumor growth in Vivo

NOD mice were implanted on day 0 with 5x6 22Rv1 tumor cells. On day 1 106x human PBMCs were adoptively transferred into the mice i.v., and beginning on day 2 they were treated every 4 days with 100ug of TNB-585. All mice were sacrificed on day 30.

Conclusions

- TNB-585 is a PSMA x CD3 bispecific antibody that mediates tumor cell lysis with minimal cytokine secretion.
- TNB-585 shows excellent manufacturability.
- No off-target activity was observed.
- TNB-585 is anticipated to enter phase 1 clinical studies in Q1 2021.

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1 Teneobio Inc. Menlo Park, CA
2 University of California San Francisco
3 Teneobio Inc. Menlo Park, CA

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