# Development of a fully human T-cell engaging bispecific antibody for the treatment of multiple myeloma.

**Abstract # 60**

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## Background:

- BCMA (B Cell Maturation Antigen) is a plasma cell specific surface molecule attractive as an antibody target in multiple myeloma.
- T-cell engaging bispecific antibodies are well suited to low density targets like BCMA.
- The Teneobio antibody platform uses fully human VH domains and an NGS-based discovery pipeline (Figure 1A).
  - NGS identifies multiple high affinity leads to any target within 3-4 months.
- We developed a novel BCMA x CD3 antibody (TNB-383B) that selectively activates T-cell subsets with reduced cytokine secretion

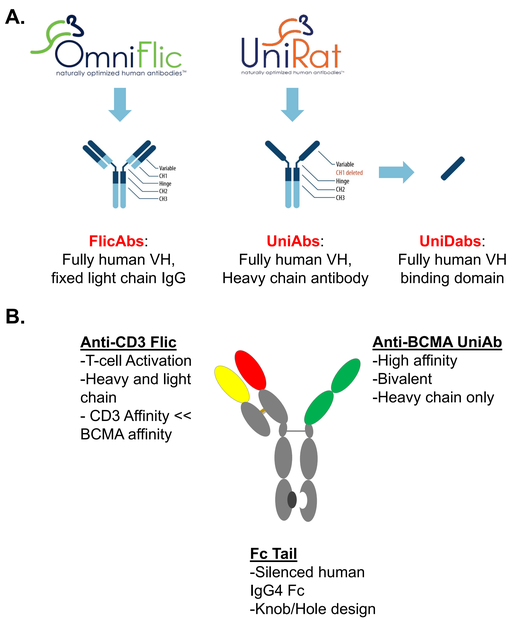


**Figure 1**: BCMA x CD3 development **A.** TNB-383B is a hybrid of fixed light chain (αCD3, FlicAb) and heavy chain only (αBCMA, UniAb) antibody arms. **B.** TNB-383B is composed of two αBCMA moieties in sequence on one arm, a single αCD3 arm, and a silenced IgG4 Fc.

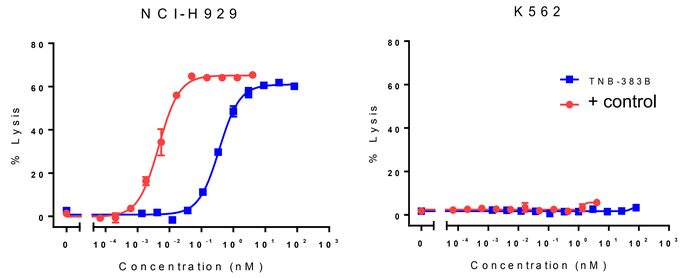


**Figure 2**: TNB-383B Lyses BCMA-positive tumor cells (H929) but not BCMA-negative tumor cells (K562) with an EC50 ~2 logs higher than a pan-T-cell anti-CD3 containing bispecific (+ control); the maximum achievable lysis is identical.

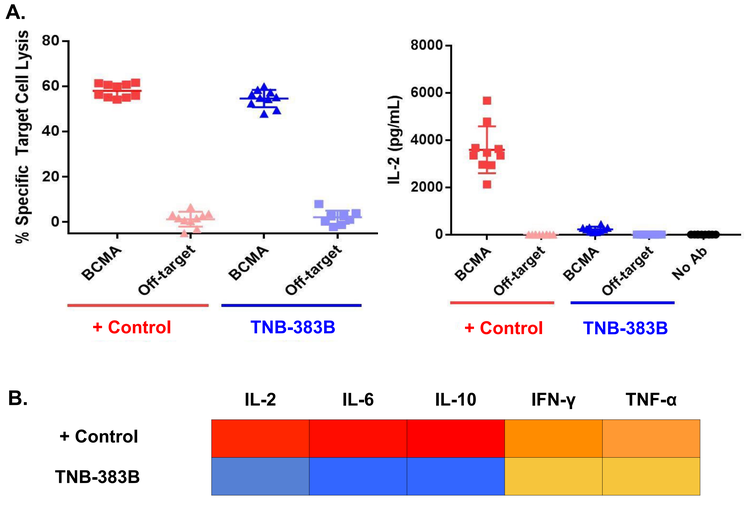


**Figure 3**: TNB-383B tumor lysis and T-cell activation are consistent across multiple donors and multiple cytokines **A.** T-cells from 10 donors lyse myeloma cells (NCIH929, BCMA-positive) in the presence of TNB-383B, but not K562 cells (BCMA-negative). **B.** T-cells exposed to TNB-383B and BCMA-positive cells secrete lower levels of cytokines than those exposed to a pan T-cell activating bispecific.

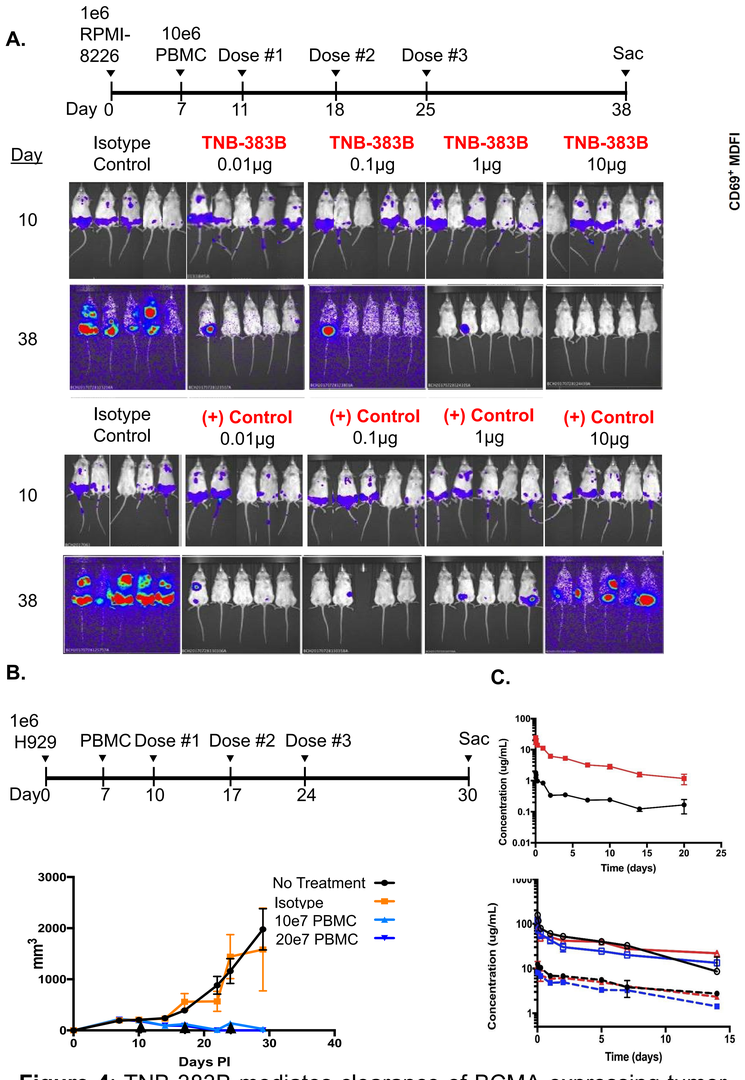


**Figure 4**: TNB-383B mediates clearance of BCMA-expressing tumor cells by T-cells in NSG mice and has a long half life *in vivo*. **A.** Luc-expressing tumor cells were administered on day 0, human PBMCs on day 3, and drug on day 10 (Qweek x3) **B.** TNB-383B showed similar efficacy in a subcutaneous model as in *A*. Both treated arms (in blue) received 10µg TNB-383B/Animal **C.** TNB-383B has a ~10 day half life in *Cynomolgus* (top) and a ~5.5 day half life in mice (bottom).

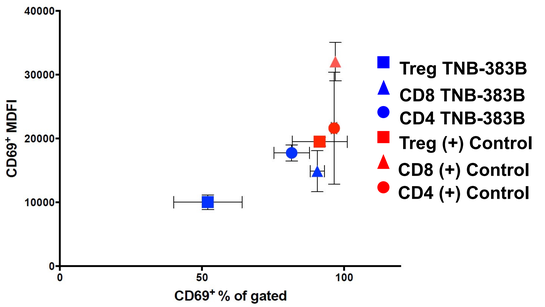


**Figure 5:** TNB-383B preferentially activates effector T-cells (CD4/CD8) over Tregs. Human T-cells from healthy donors were incubated either fresh or after high-density culture (48h) together with drug and plate-bound BCMA for 24h. CD69 was measured by flow cytometry.

## Conclusions:

- TNB-383B binds to tumor cells in a BCMA-dependent manner.
- TNB-383B mediates T-cell dependent tumor cell lysis and T cell activation *in vitro*.
- TNB-383B has the half-life of a conventional IgG4.
- TNB-383B clears tumor cells in a BCMA- and T-cell dependent manner *in vivo*.
- TNB-383B induces less cytokine secretion than a conventional T-cell engaging bispecific *in vitro*, without reduction of tumor cell kill *in vivo* (Figures 3-5).

## Future Directions:

- Preliminary tissue cross reactivity studies show absence of nonspecific staining by TNB-383B in human tissues.
- TNB-383B is well tolerated in preliminary *Cynomolgus* tolerability studies.
- IND Filing is anticipated in Late 2018.