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

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Background:

- BCMA 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 is based on fully human VH domains and an NGS-based discovery pipeline (Figure 1A).
  - NGS antibody discovery identifies multiple high affinity leads to any target within 3-4 months.
- We developed 2 BCMA x CD3 antibodies (TNB-381M and TNB-382M, Figure 1B).

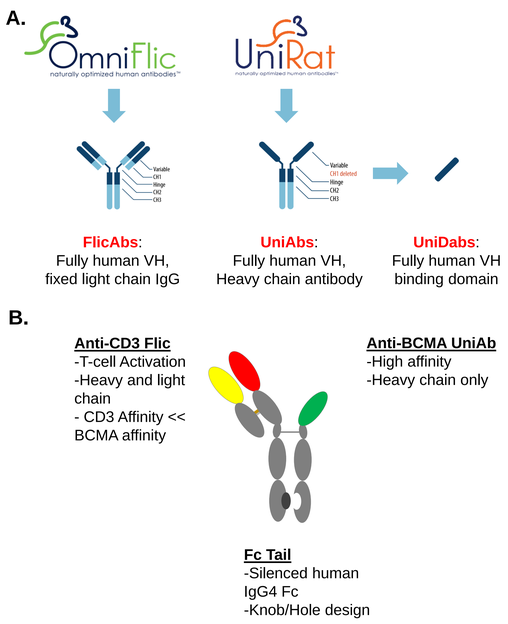

Figure 1: BCMA x CD3 development **A.** The BCMA x CD3 antibody is a hybrid of fixed light chain (anti-CD3, FlicAb) and heavy chain (anti-BCMA, UniAb) antibody arms. **B.** TNB-382M has greater affinity for CD3 than TNB-381M.

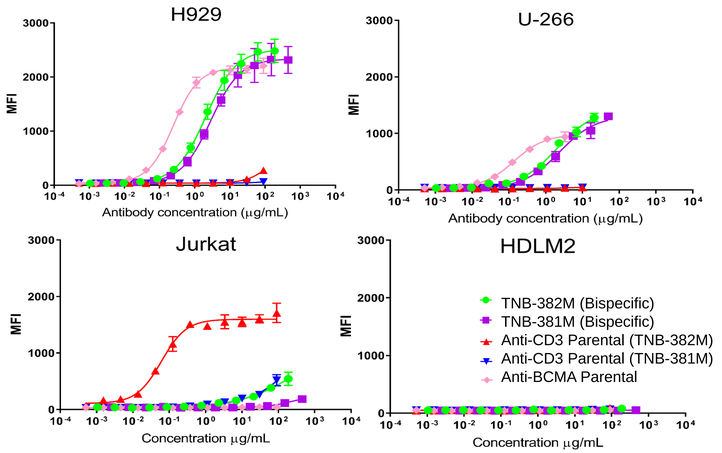

Figure 2: Binding of Anti-BCMA and –CD3 Arms is BCMA and CD3 dependent, respectively. H929 and U266 express BCMA. Jurkat T cells express CD3. HDLM2 are negative for BCMA and CD3.

Figure 3: TNB-381M and TNB-382M lyse tumor cells and activate T cells in a BCMA-dependent manner. **A.** T-cells lyse myeloma cells (NCIH929, U266, RPMI-8226, BCMA-positive) in the presence of TNB-381/2M, but not K562 cells (BCMA-negative). **B.** T-cells exposed to TNB-382M and BCMA-positive cells secrete more cytokines than those exposed to TNB-381M (Top row: IL-2, Bottom row: IFNɣ).

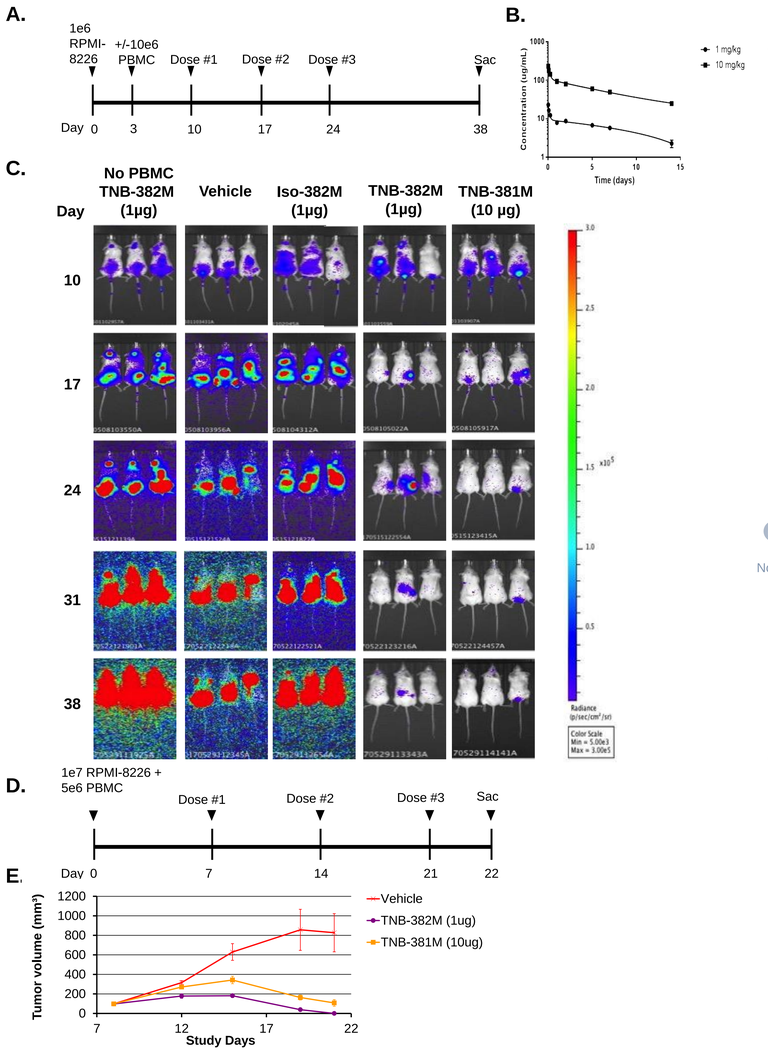

Figure 4: TNB-381/2M mediate clearance of BCMA-expressing tumor cells by T-cells in NSG mice. **A.** Luc-expressing tumor cells were administered on day 0, human PBMCs on day 3, and drug on day 10 (Qweek x3) **B.** TNB-381/2M have a beta phase half life of ~5.5 days in mice. **C.** Representative BLI images from *A.* **D.** Tumor cells were injected subcutaneously on day 0 together with human PBMCs, and drug starting on day 7 (Qweek x3). **E.** Tumor size from *D.*

Conclusions:

- TNB-381M and TNB-382M bind to tumor cells in a BCMA-dependent manner.
- TNB-381M and TNB-382M mediate T-cell dependent tumor cell lysis and T cell activation *in vitro*.
- TNB-381M and TNB-382M have the half-life of a conventional IgG4.
- TNB-381M and TNB-382M clear tumor cells in a BCMA- and T-cell dependent manner *in vivo.*
- TNB-381M induces less cytokine secretion than TNB-382M *in vitro*, without reduction of tumor cell kill *in vivo* (Figures 3-5).

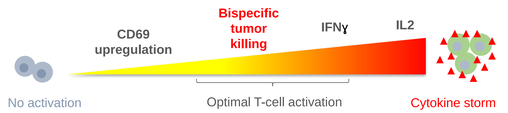

Figure 5: Proposed model of anti-tumor T-cell activation and cytotoxicity by TNB-381/2M.

Future Directions:

- Additional *in vivo* efficacy studies with RPMI-8226 and other myeloma lines are ongoing.
  - We are testing constructs with bivalent anti-BCMA binding moieties.
- Preliminary PK/PD and toxicology studies are ongoing in *Cynomolgus* non-human primates.
- *Ex vivo* efficacy studies utilizing primary patient myeloma samples have been initiated.