
Ben Buelow1, Duy Pham2, Priya Choudhry2, Shelley Force Aldred2, Andrew Boudreau2, Starlyn Clarke1, Laura Davison1, Kevin Dang1, Katherine Harris1, Suhaisini Iyer1, Brett Jorgensen2, Heather Ogana2, Payal Pratap1, Udaya Rangaswamy1, Ute Schellenberger1, Nathan Trinklein1, Harshad Ugamraj1, Arun Witta2, Nina Shah2, and Wim van Schooten1

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

Contact: bbuelow@tenebio.com

Background:

- BCMA (B Cell Maturation Antigen) is a low-density surface molecule highly specific for plasma cells well suited to T-cell engagement based treatment of myeloma.
- The Tenebio antibody platform uses fully human VH domains and an NGS-based discovery pipeline.
- NGS identifies multiple high affinity leads to any target within 3-4 months.
- Heavy-chain-only chemistry simplifies construction of multivalent Abs.
- Simple protein chemistry improves yields (>4g/L), stability, and purification.

We developed a novel BCMA x CD3 antibody (TNB-383B) that selectively activates T-cell subsets with reduced cytokine secretion (Figure 1).

Figure 1: TNB-383B Development

TNB-383B is a fully human T-8sAb combining fixed-light-chain (FLC) and heavy-chain-only (HCO) arms paired using knob-in-hole. The FLC arm weakly activates CD3. The HCO arm has two high-affinity anti-BCMA moieties. TNB-383B has a silenced human IgG4 Fc to limit non-specific activation and confer long half life.

Table 1: TNB-383B mediates lysis of primary myeloma cells ex vivo. After characterizing plasma cell % and E:T ratio by flow, bone marrow from MM patients was incubated ~18h. With TNB-383B and max -lysis determined. *At time 0, prior to treatment.

<table>
<thead>
<tr>
<th>Donor #</th>
<th>Plasma Cell %</th>
<th>E:T Ratio</th>
<th>TNB-383B Max Lysis (16h)</th>
<th>ABC</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>3.1%</td>
<td>3:1</td>
<td>14.1%</td>
<td>45%</td>
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<tr>
<td>2</td>
<td>0.0%</td>
<td>1:1</td>
<td>16.1%</td>
<td>35%</td>
</tr>
<tr>
<td>3</td>
<td>0.2%</td>
<td>2:1</td>
<td>102.1%</td>
<td>35%</td>
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<tr>
<td>4</td>
<td>0.2%</td>
<td>2:1</td>
<td>58.1%</td>
<td>91%</td>
</tr>
<tr>
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<td>1.0%</td>
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<td>24.1%</td>
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</tr>
<tr>
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<td>1:1</td>
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<td>0.1%</td>
<td>1:1</td>
<td>346.1%</td>
<td>61%</td>
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<tr>
<td>8</td>
<td>75.9%</td>
<td>1:1</td>
<td>361.2%</td>
<td>2085</td>
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</tbody>
</table>

*E:T = Effector:Target

Figure 2: TNB-383B lysed BCMA(+)+ NCI-H929 & RPMI-8226 cells in a dose-dependent manner but not BCMA(-) K562 cells. While the EC50 for lysis by TNB-383B is ~2 logs greater than the Positive Control (PC) antibody, it achieves the same max. lysis as the PC that has a strong pan-T-cell activating gCD3 moiety.

Figure 3: TNB-383B shows max. lysis similar to pos. control (PC) with minimal cytokine secretion. T-cells from 10 donors were incubated with TNB-383B, PC, or isotype and NCI-H929 cells at lysis saturating doses for 18 hours, and tumor lysis measured by flow (left panel). IL-2 and IFN-γ were measured by ELISA (middle and right panels). Other cytokines were tested, with levels similar to IL-2 (heat map, bottom panel; blue = low, red = high).

Figure 4: TNB-383B mediates clearance of BCMA(+) tumor cells in mice and has a long half life in vivo. A. Luc-expressing RPMI-8226 tumor cells were administered on day 0, human PBMCs on day 7, and drug on day 10 (weekly x3) B. TNB-383B showed similar efficacy in a subcutaneous H929 model as in A. Both treated arms in (blue) received 10µg TNB-383B/Animal C. TNB-383B’s half-life is ~5.5 days in mice (bottom) and ~13-16 days in Cynomolgus (top)

Conclusions:

- TNB-383B clears tumor cells in a BCMA- and T-cell dependent manner in vitro and in vivo.
- TNB-383B lysed primary patient myeloma cells ex vivo without exogenous T-cell supplementation.
- 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).
- TNB-383B has the half-life of a conventional IgG4 in mice and Cynomolgus.
- TNB-383B is BCMA-specific in Tissue Cross Reactivity studies (data not shown).

Phase 1 FIH Trial to begin Q4 2018/Q1 2019

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.

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