Discovery of a Novel CD123 x Gamma Delta T Cell Engager for the Treatment of Acute Myeloid Leukemia

Poster # 820

Kevin Dang, Zahra Bahrami-Dizicheh, Harish Medlari, James Allison, Brandon Yuen, Kirthana Prabhakar, Jennifer Lu, Ismael Oumzil, Yvonne Liu, Andrew Boudreau, Duy Pham, Wim van Schooten, Suhasini Iyer, Ben Buelow, Antara Banerjee, Patrick Koenig, Pranjali Dalvi

1190 Zephyr Ave Suite A, Hayward CA 94544

Background

- Gamma delta (γδ) T cells are a distinct subset of T cells with features of innate and adaptive immunity that recognize diverse antigens in an MHC-independent manner.
- Intratumoral γδ T cells are the cell type most highly correlated with favorable prognosis in multiple cancers, underscoring their critical role in tumor control [1].
- CD123 is a prognostic marker and therapeutic target in AML. Prior CD123 therapies have been limited by off-tumor toxicity due to its widespread hematopoietic expression and the immunosuppressive microenvironment. Leveraging the cytotoxic and innate discriminatory capacity of γδ T cells, we developed a bispecific anti-pan δ x CD123 antibody that activates major γδ T cell subsets (Vδ1, Vδ2, Vδ3) to selectively kill CD123+ tumors for treatment of AML.

Screening of Pan-δ x CD123 Bispecific Antibodies

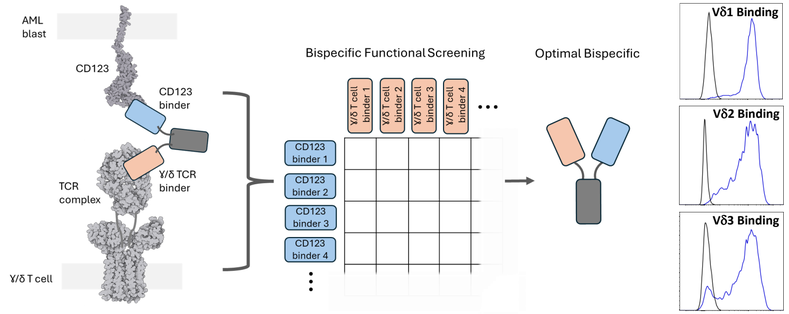

Figure 1. Pan-δ and CD123 binders were paired in all-by-all combinations and evaluated in various functional assays. Vδ1 and Vδ2 benchmark molecules were generated using binders described in literature. The negative control is a pan-δ binder paired with an irrelevant targeting arm. Representative data from one pan-δ x CD123 bispecific is shown.

Pan-δ x CD123 Demonstrates Superior Anti-Tumor Activity Compared to Vδ1 and Vδ2 Engagers

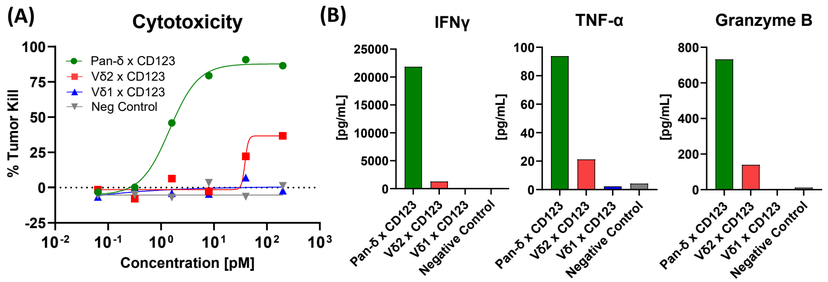

Figure 2. MV4-11-Luc cells were co-cultured with PBMCs and antibody for 72 hours at 37°C. Following incubation, tumor cell killing was measured using a luciferase readout (A). Supernatants were harvested and cytokines were measured by MSD (B)

Pan-δ x CD123 Exhibits Comparable Tumor Killing With Lower Cytokine Release Compared to CD3 x CD123

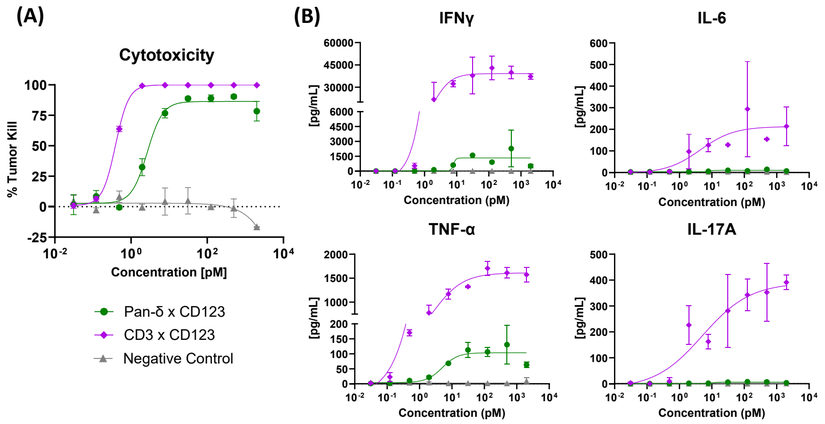

Figure 3. Cytotoxicity and cytokine release were evaluated comparing pan-δ x CD123 and CD3 x CD123. MV4-11-Luc cells were co-cultured with PBMCs (15:1 E:T) and antibody for 72 hours at 37°C. Following incubation, tumor cell killing was measured using a luciferase readout (A). Supernatants were harvested and cytokines were measured by MSD (B).

Pan-δ x CD123 Promotes Substantial Expansion of γδ T Cells

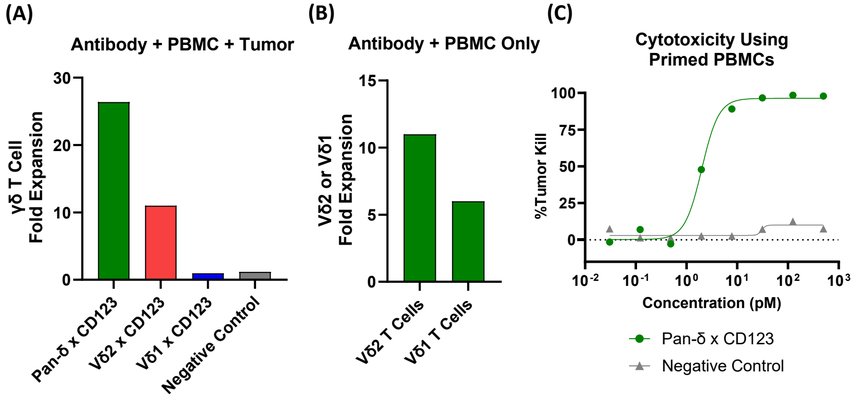

Figure 4. PBMCs were cultured with antibody in the presence (A) or absence (B) of tumor cells for 6-7 days at 37°C followed by measurement γδ T cell expansion by flow cytometry. (C) Post expansion, "primed" PBMCs were assessed for their ability to induce antibody-mediated killing of MV4-11 tumor cells.

Pan-δ x CD123 Enhances Innate Killing of CD123-Negative Tumor Cells

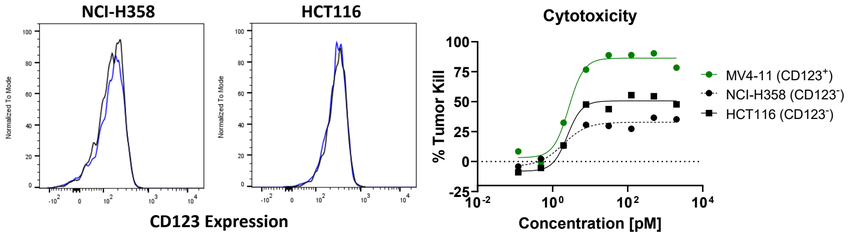

Figure 5. CD123-negative NCI-H358-Luc and HCT116-Luc cells were co-cultured with PBMCs and antibody for 72 hours at 37°C. Following incubation, tumor cell killing was measured using a luciferase readout and normalized to untreated control.

Pan-δ x CD123 Induces Minimal Killing of CD123-Positive Healthy Cells

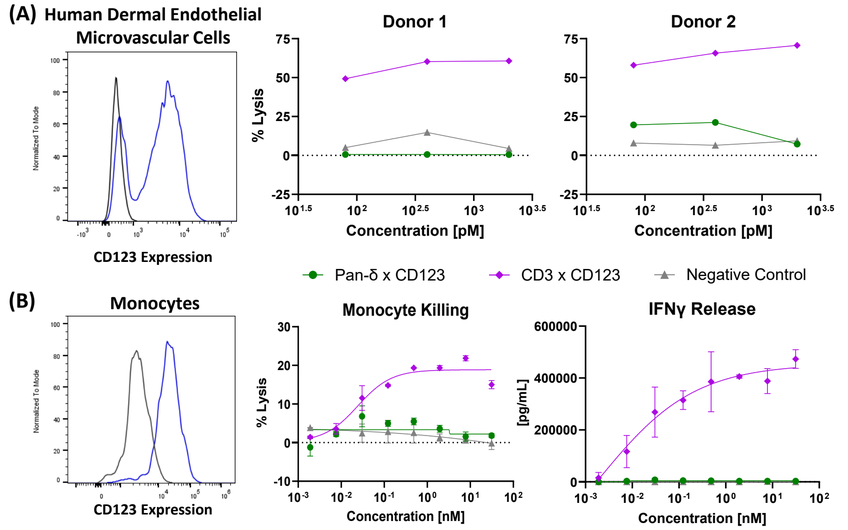

Figure 6. PBMCs were co-cultured with target cells and antibody for 72 hours at 37°C. Following incubation, cytotoxicity and/or cytokine release was measured.

Conclusions

Anti-pan δ x CD123 engages all γδ T cell subsets to induce killing of CD123+ tumor cells while sparing CD123+ healthy cells and may provide an effective, safer treatment option for AML compared to traditional T cell engagers.

References

Gentles AJ, et al. The prognostic landscape of genes and infiltrating immune cells across human cancers. Nat Med. 2015;21:938–945

Disclosures

All authors are employees of 92Bio, Inc., Hayward, CA

Presented at Society for Immunotherapy of Cancer (SITC), National Harbor, MD USA. November 7-9, 2025. For questions or comments, please contact: Antara Banerjee (abanerjee@92biotech.com)