(PF1208) A NEXT-GENERATION FCRL5/BCMA TRISPECIFIC ANTIBODY DEMONSTRATES SUPERIOR ACTIVITY OVER BISPECIFIC CONSTRUCTS AND SUPPORTS CLINICAL DEVELOPMENT IN B-CELL MALIGNANCIES

Topic: 25. Gene therapy, cellular immunotherapy and vaccination - Biology & translational research

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Background

BCMA-directed CAR T cell therapy has improved outcomes in multiple myeloma (MM), but their impact is limited by manufacturing challenges and relapses driven by antigen escape. In this context, trispecific T cell engagers (TriTE) represent an attractive alternative approach, enabling simultaneous targeting of multiple tumor antigens designed to broaden tumor coverage, reduce antigen escape, and potentially enhance depth of response. As an off-the-shelf therapy with simplified logistics and manageable toxicity profile, TriTEs represent a promising next-generation immunotherapeutic approach.
FcRL5 is a B-lineage-restricted surface antigen that supports malignant plasma cell differentiation. FcRL5 is universally expressed in MM cell lines and in primary samples from newly diagnosed and relapsed/refractory MM. It is also uniquely expressed in Waldenström macroglobulinemia (WM), where a protein-coding RNA isoform is absent in healthy B cells. Unlike GPRC5D, FcRL5 is not expressed in other healthy tissues, highlighting its potential as a selective therapeutic target. Based on these findings, we developed a TriTE targeting BCMA and FcRL5.

Aims

The goal is to assess the preclinical efficacy of the next-generation BCMA/FcRL5 TriTE in models of MM and WM, and to establish the rationale that dual-antigen trispecific targeting can outperform BCMA-directed bispecific therapies.

Methods

FcRL5 and BCMA expression in MM and WM cells was evaluated by flow cytometry, western blot, and RNA-seq. High-throughput TriTE generation and screening were performed. In vitro cytotoxicity and T-cell activation were evaluated using flow-based assays. In vivo efficacy was tested in humanized mouse models bearing subcutaneous NCI-H929 or intravenous U266B1 tumors, followed by PBMC infusion and Q7D×4 dosing, and benchmarked against commercial BCMA and FcRL5 bispecific antibodies.

Results

We utilized a novel antibody discovery platform combining high-throughput functional screening with generative AI to select and optimize antibodies with the strongest immune response, independent of affinity. We generated BCMA/FcRL5 TriTEs that markedly enhanced tumor cell killing and T-cell response both against MM cell lines and primary patient MM cells compared with the other benchmark clinical BCMA or FcRL5 TCE. The activity extended to WM, where the TriTEs also mediated potent killing in WM cell lines and primary cells. TriTE demonstrated synergistic activity even when both antigens were expressed at low levels and remained effective in myeloma cells with BCMA knockout. In vivo, BCMA/FcRL5 TriTEs produced robust antitumor efficacy in humanized mice bearing subcutaneous NCI-H929 tumors, yielding tumor volume reduction in all treated animals. In the disseminated U266B1 MM model, dose-escalation studies showed that TriTE achieved superior antitumor activity at a 10-fold lower dose than Teclistamab and prolonged survival; median survival: 62 days for control, 82 days for Teclistamab while all TriTE-treated mice remained alive beyond 130 days, consistent with durable responses in this model.

Summary/Conclusion

Leveraging a high-throughput discovery platform, we have generated BCMA/FcRL5 TriTE antibodies with superior antitumor activity and increased in vivo potency, outperforming BCMA-directed therapy even at lower doses in vivo. These results support dual-antigen targeting as a strategy to overcome the limitations of BCMA-only approaches and provide a strong rationale for clinical translation of our BCMA/FcRL5 TriTE in MM and WM.