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1170 DEVELOPMENT OF A NOVEL ECONOMICAL ANTI-BCMA ANTIBODY FOR TARGETED THERAPEUTIC INTERVENTION IN MULTIPLE MYELOMA

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Background Multiple myeloma (MM) is a hematologic malignancy characterized by the clonal proliferation of malignant plasma cells within the bone marrow, leading to the overproduction of monoclonal immunoglobulins. While monoclonal antibody (MoAb)-based therapies have significantly improved patient outcomes, MM remains largely incurable, primarily due to disease relapse and the emergence of drug-resistant clones. B-cell maturation antigen (BCMA), a transmembrane glycoprotein predominantly expressed on malignant plasma cells, has emerged as a promising therapeutic target for antibody-based and cellular immunotherapies.

Methods BCMA expression was assessed in 20 MM patients using real-time quantitative PCR (RQ-PCR) and ELISA, revealing elevated mRNA and soluble BCMA levels. The extracellular domain (ECD) of BCMA was cloned, sequence-verified, and expressed in Expi293 cells. The recombinant protein was purified and characterized using SDS-PAGE. BALB/c mice were immunized with purified BCMA-ECD to generate hybridomas. These were screened via immunoassays, including western blotting, to identify high-affinity clones. The lead candidate, clone 9C4, was purified using Protein A affinity chromatography. To map epitope-paratope interactions, molecular docking and dynamics simulations were conducted, identifying four novel epitope residues (S, Q, N, E) in BCMA interacting with 23 amino acids, surpassing binding profiles of existing antibodies. The single-chain variable fragment (scFv) of 9C4 was incorporated into a second-generation chimeric antigen receptor (CAR) and expressed in engineered T cells to create novel anti-BCMA CAR-T cells.

Results The study confirmed increased BCMA expression in MM samples, supporting its relevance as a therapeutic target. The successful expression and purification of BCMA-ECD enabled effective mouse immunization and hybridoma generation. Among 20 clones, 9C4 demonstrated the highest binding affinity to BCMA-ECD. In silico analysis showed 9C4 engages more BCMA residues than known antibodies, suggesting enhanced targeting potential. Incorporation of 9C4's scFv into a CAR construct led to successful expression in modified T cells, producing a novel candidate for BCMA-directed CAR-T therapy

Conclusions Analysis confirmed significantly elevated BCMA expression in MM patient samples, supporting its utility as a therapeutic target. Recombinant BCMA-ECD expression enabled successful immunization and hybridoma generation. Of the 20 clones screened, 9C4 exhibited the highest binding affinity to BCMA-ECD. In silico analyses identified four novel epitope residues (S, Q, N, E) involved in interaction with 23 residues on BCMA—surpassing known antibody interactions. The single-chain variable fragment (scFv) of 9C4 was subsequently incorporated into a second-generation chimeric antigen receptor (CAR) construct and successfully expressed in genetically modified T cells, yielding a novel anti-BCMA CAR-T cell candidate.

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