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IJBLS 2023; 2(1):49-49

International Journal of BioLife Sciences

Abstract

Generation of Clinical Diagnostic Antibodies against Common Lymphatic Endothelial and Vascular Endothelial Receptor 1

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***Received**: 24 May 2023* ***Revised**: 30 May 2023* ***Accepted**: 24 June 2023*

Abstract

Background and Aim: Common lymphatic endothelial and vascular endothelial receptor 1 (CLEVER-1) is a scavenger glycoprotein receptor expressed on the surface of a subset of immunosuppressive macrophages. CLEVER-1 promotes tumor growth and spread in cancer. Immunotherapeutic blockade of CLEVER-1 delays tumor growth by activating cytotoxic CD8+ T-cells. Bexmarilimab, a novel anti-Clever-1 antibody, has shown promising efficacy and safety in phase II clinical trials. This study aims to optimize bexmarilimab dosing by developing a companion diagnostic quantitative time-resolved fluorescence immunoassay (TRFIA) for CLEVER1 using novel antibody fragments.

Method: The University of Turku Fab phage display libraries were panned against recombinant CLEVER-1 protein. The epitopes of the newly discovered Fabs were mapped to CLEVER-1 using TRFIA. The best antibody fragments were sequenced and affinity-measured with bio-layer interferometry. They were then used in a TRFIA to measure the concentration and drug occupancy of CLEVER-1 protein in human plasma.

Results: After three rounds of Fab phage library panning, considerable enrichment of the libraries was observed with a specific CLEVER1 binding to background ratio of 85. Followed by screening for the best Fabs, six clones demonstrated over 150 signal to background ratio in specific binding to CLEVER1. After sequencing, the fragments were identified as having different CDR regions. Bexmarilimab epitope blocking did not significantly affect binding of the Fabs to CLEVER1, with an average Fab binding decrease of 9% (P=0.2267) The K_D value of the Fabs ranged from 2.1 nM to 16.5 nM. The results from the final validation TRFIA on healthy serum samples were in line with the CLEVER-1 normal range in serum.

Conclusion: Six unique Fab antibody fragments were selected against CLEVER1. Using the fragments, a TRFIA was developed to measure the CLEVER1 concentration in plasma.

Keywords: *Bexmarilimab, Cancer, CLEVER1, Phage display, TRFIA*

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