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Optimized Second-generation IL-4 α Inhibition: Structural And Molecular Dynamics Properties Of Rademikibart Fab-il-4 α Complex

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Abstract:

RATIONALE: Interleukin (IL)-4 is a key cytokine involved in type 2 inflammation, and anti-IL-4 α biologics have shown efficacy in reducing exacerbations and improving lung function in patients with uncontrolled asthma, and recently COPD, with an eosinophilic phenotype. Dupilumab, an IL-4 α inhibitor, was first approved for the treatment of asthma in 2018. Rademikibart is a next-generation human monoclonal antibody with, compared to dupilumab, higher binding affinity to IL-4 α , better inhibition of STAT6 intracellular signaling *in vitro* and similar potency inhibiting both IL-4 induced TARC release and IL-4¹. The current study was undertaken to determine differences in the atomic-resolution 3D structures of rademikibart and its predecessor, dupilumab, that may potentially lead to differences in efficacy and safety between the two drugs.

METHODS: X-ray crystallography was used to determine the atomic resolution 3D structure of rademikibart fragment antigen binding (Fab) bound to IL-4 α . This structure was analyzed and compared computationally with the 2.82 Å resolution crystal structure of dupilumab Fab bound to IL-4 α (Protein Data Bank Code 6WGL). Molecular dynamics studies on rademikibart and dupilumab bound to IL-4 α examined the stability of the complexes and effects of amino acid mutations on complex formation.

RESULTS: The x-ray crystal structure of rademikibart Fab bound to IL-4 α was determined at 2.71Å and compared to the complex of dupilumab Fab and IL-4 α . The rotation angle between dupilumab and rademikibart bound to IL-4 α is 59.17°. This rotation enables the epitope of rademikibart, but not dupilumab, on IL-4 α to overlap more closely with the conserved binding interface utilized by IL-4 and IL-13 cytokines. Molecular dynamics simulations of rademikibart Fab and dupilumab Fab complexed with IL-4 α showed the third interface loop (residues 148 to 152 in domain 2) of IL-4 α interacts directly with rademikibart, which is absent in dupilumab/IL-4 α complex. This finding is confirmed by analysis of the hydrogen bond interactions at the interface between the antibodies and IL-4 α , demonstrating superior binding energy for rademikibart. Through single amino acid mutation analysis on rademikibart, we identified residue Y50 on rademikibart as the key residue interacting with IL-4 α 's third interface loop.

CONCLUSION: These data provide a molecular and structural rationale for the enhanced IL-4 α inhibition by rademikibart over dupilumab, confirming rademikibart as an optimized second-generation IL-4 α inhibitor.

References:1.Zhang, L., et al., *Preclinical immunological characterization of rademikibart (CBP- 201), a next-generation human monoclonal antibody targeting IL-4 α , for the treatment of Th2 inflammatory diseases.* Sci Rep, 2023. **13**(1): p. 12411.

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