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Structural insights into Crenezumab's mechanism of action

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Crenezumab is a fully humanized immunoglobulin isotype G4 (IgG4) monoclonal antibody that binds to monomeric as well as aggregated Aβ forms (oligomers, fibers and plaques). Notably, crenezumab binds with higher affinity to Aβ oligomers over monomers and *in vitro* studies have demonstrated crenezumab's ability to block Aβ aggregation and promote Aβ disaggregation. To understand the structural basis for this activity and crenezumab's broad binding profile, we determined the crystal structure of crenezumab in complex with Aβ. The structure reveals a sequential epitope and the conformational requirements for epitope recognition, which include a subtle but critical element that is likely the basis for crenezumab's versatile binding profile. We find interactions consistent with high affinity for multiple forms of Aβ, particularly oligomers. Crenezumab also sequesters the hydrophobic core of Aβ and breaks an essential salt-bridge characteristic of the β-hairpin conformation, eliminating features characteristic of the basic organization in Aβ oligomers and fibrils, and explains crenezumab's inhibition of aggregation and promotion of disaggregation. These insights highlight crenezumab's unique mechanism of action, particularly regarding Aβ oligomers and provide a strong rationale for the evaluation of crenezumab as a potential treatment for patients with Alzheimer's disease.

Biography

Weiru Wang has completed his PhD in Biophysics from Cornell University and Post-doctoral studies from University of California, Berkeley. He is currently a Senior Scientist and a Group Leader in the Structural Biology Department at Genentech, a member of the Roche Group. His research focuses on understanding of molecular basis of protein-drug interactions using biophysical methods, primarily macromolecular crystallography.

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