A207 · Ensemble convergence identifies recurrent structural solutions for pH-responsive CXCL8 antibody design

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Abstract

CXCL8 is an ELR+ CXC chemokine involved in inflammation, immune-cell recruitment and tumour-associated signalling. Its receptor-binding surface is highly polar and dynamic, making it challenging to target with antibodies using conventional hydrophobic interface assumptions. We asked whether repeated complex prediction could distinguish recurrent structural solutions within a GH2-constrained generative antibody design space and prioritise candidates with putative pH-responsive interface features.

RFantibody was used to generate GH2-constrained antibody backbones, followed by ProteinMPNN- and AbMPNN-based sequence design. From approximately 510,000 designed sequences, 1,360 candidates passed initial filtering. For each candidate, we generated 50 independent Protenix predictions of the antibody–CXCL8 complex and quantified ensemble convergence from the dispersion of predicted interface confidence and structural RMSD across predictions.

Two hundred sixty-five candidates formed GH2-convergent groups, characterised by low-RMSD, relatively high-confidence basins repeatedly recovered across the prediction ensemble. In contrast, GH2-divergent candidates displayed broader distributions and extended RMSD tails. Sequence-landscape analysis identified recurrent position-specific residue preferences, particularly in CDR H2 and H3, that distinguished convergent from divergent candidates.

PROPKA analysis prioritised candidates with interfacial histidines predicted to have pKa values of 5.5–7.5, or with multiple perturbed Asp/Glu residues. Representative complexes suggested alternative protonation-sensitive interface hypotheses, including His–Phe packing, His–Pro metastable packing and acid-induced His+–Arg+ repulsion. Molecular-dynamics simulations further differentiated stable and metastable behaviours in representatives D31 and D66.

Together, ensemble convergence provides a reproducibility-oriented criterion for prioritising generated CXCL8 antibody designs, linking recurrent binding-mode hypotheses to CDR sequence features and putative protonation-sensitive interfaces for future experimental evaluation.