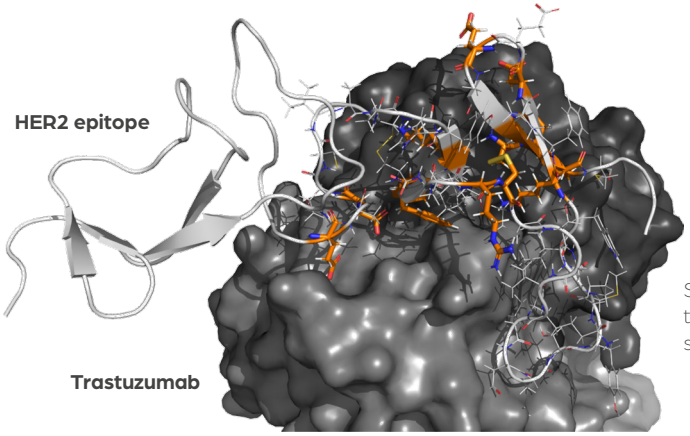
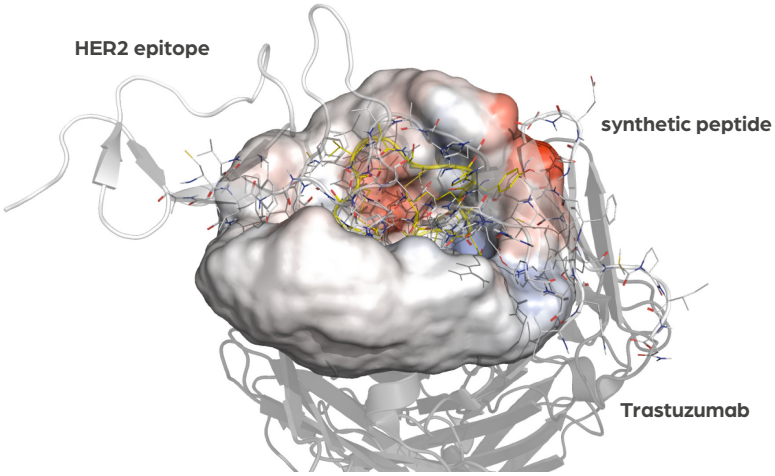


Structure of human HER2 complexed with Trastuzumab Fab. Key binding residues (orange) served as scaffold for the peptide design.

CASE STUDY | STRUCTURE-BASED LIGAND DESIGN

Synthetic **Peptides**

Synthetic peptides mimic the binding behavior of a protein to its interaction partner. The interaction between human epidermal growth factor receptor 2 (HER2) and Trastuzumab (Herceptin®), a therapeutic antibody for breast cancer treatment, was the subject of our structure-based design of mimetic peptides. Computational alanine scanning enables us to identify critical HER2 residues for binding to Trastuzumab. We focused on these positions and rationally designed synthetic peptides representing different binding regions in the discontinuous epitope, adding stabilizing mutations where appropriate. Critical binding residues served as scaffolds for the Rosetta peptide design steps and optimization by a genetic algorithm. Finally, the peptide candidates were ranked using force-field-based energy contributions, Catalophore™ Halo-based structural comparisons, and MD simulation-based stability analyses. The binding of several proposed candidates to Trastuzumab has been confirmed through a series of in vitro peptide microarray analyses.



Halo difference point clouds (surface representation) allow comparison of the surface environment of the native HER2 epitope to the synthetic peptide in extreme detail.

Unpublished Results