13f Computational Prediction of the Mab 806-Egfr Complex Structure by Combining Protein Docking with Computational and Experimental Mutagenesis

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We predict the structure of the complex formed by monoclonal antibody 806 (mAb 806) and the extracellular domain of the Epidermal Growth Factor Receptor (EGFR) using the protein docking program RosettaDock. MAb 806, an anti-tumor antibody, is thought to bind a transitional form of the EGFR as it undergoes a conformational change. Since the structure of the transitional form is unavailable, we dock mAb 806 to the experimentally determined 16-residue peptide epitope that contains the EGFR residues known to be important for 806 binding. We use crystal structure conformations for the peptide backbone and an antibody structure modeled by the WAM server. We use computational mutagenesis results to filter the docking decoys and identified three unique 806-peptide orientations that are consistent with published experimental mutagenesis data available for the 806-EGFR system. We propose further aromatic substitutions at peptide locations 293-297 and 300 to discriminate between the three 806-peptide orientations. We determine that E293 and D297 substitutions lead to complete binding loss, while the remaining aromatic substitutions are neutral. This is in agreement with computational mutagenesis predictions for one of the three models, which we propose is the correct orientation of mAb 806 and the peptide epitope in the complex formed by 806 and the full length EGFR. In the final model, mAb 806 binds to the untethered form of the receptor which is consistent with the hypothesis that untethering of the receptor is a prerequisite to 806 binding. We also find that a subtle backbone twist in the peptide backbone orients the E293 side chain, important for mAb 806 binding, differently in different EGFR crystal structures and this is critical to the binding. Our novel approach combines docking with computational mutagenesis and integrates experimental data for the prediction of therapeutic antibody-antigen complex structures.