Protein-Binding Proteins Designed from Target Structural Information

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Designing proteins that recognize a specific site on a target protein surface using only the three-dimensional structure is an ongoing challenge. A new approach to this challenge has been proposed, leading to the de novo design of highly stable protein-binding proteins with 65 or fewer amino acids for twelve unique targets. First, a broad search begins as a selected region of the target protein surface is sampled to identify favorable hydrogen and non-polar interactions. This is initiated by docking disembodied amino acids referenced against the "Rotamer Interaction Field" (RIF) to identify and rank possible binding modes. Protein backbones are then selected that can support these sidechains without clashing with the target. This search is intensified by determining recurrent backbone motifs that are then leveraged to place scaffolds that contain these interacting motifs against the target. These synthetic proteins were found by biophysical characterization to bind with affinities in the nM-pM range after further sequence optimization. Crystal structures were solved for five of twelve target-binder complexes. Comparison of the experimentally and computationally derived structures shows strong agreement, demonstrating the viability of this technique to design novel protein binders. This computational approach enables the design of protein binders for a wide array of targets that can be applied to diagnostic and therapeutic applications.