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Computational design of protein interactions: designing proteins that neutralize influenza by inhibiting its hemagglutinin surface protein

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Molecular recognition underlies all life processes. Design of interactions not seen in nature is a test of our understanding of molecular recognition and could unlock the vast potential of subtle control over molecular interaction networks, allowing the design of novel diagnostics and therapeutics for basic and applied research. We developed the first general method for designing protein interactions. The method starts by computing a region of high affinity interactions between dismembered amino acid residues and the target surface and then identifying proteins that can harbor these residues. Designs are tested experimentally for binding the target surface and successful ones are affinity matured using yeast cell surface display. Applied to the conserved stem region of influenza hemagglutinin we designed two unrelated proteins that, following affinity maturation, bound hemagglutinin at subnanomolar dissociation constants. Co-crystal structures of hemagglutinin bound to the two designed binders were within 1Angstrom RMSd of their models, validating the accuracy of the design strategy. One of the designed proteins inhibits the conformational changes that underlie hemagglutinin's cell-invasion functions and blocks virus infectivity in cell culture, suggesting that such proteins may in future serve as diagnostics and antivirals against a wide range of pathogenic influenza strains. We have used this method to obtain experimentally validated binders of several other target proteins, demonstrating the generality of the approach. We discuss the combination of modeling and high-throughput characterization of design variants which has been key to the success of this approach, as well as how we have used the data obtained in this project to enhance our understanding of molecular recognition. References: Science 332:816 JMB, in press Protein Sci 20:753