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Computational design of functional protein repertoires

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Understanding how protein sequence and structure determine function promises to unlock vast opportunities in basic and applied research. We develop strategies that combine phylogenetic analysis, atomistic calculations, and machine learning to optimise natural proteins. Thousands of protein scientists have used these strategies to generate stable therapeutic enzymes, vaccine immunogens, therapeutic antibodies, and membrane proteins for a range of needs in basic and applied research. A stabilised malaria vaccine immunogen designed in our lab has recently entered phase II clinical trials in West Africa. We now present a machine-learning strategy to design and economically synthesize millions of active-site variants that are likely to be stable, foldable, and active. We applied this strategy to design large libraries of enzymes and fluorescent proteins, and experimental screening revealed more than 10,000 functionally diverse proteins in each set. Our methods can be universally applied to optimise biologics, dramatically accelerating the development of promising proteins into useful pharmaceutical reagents and therapeutics. Furthermore, we demonstrate that these methods can be adapted to design completely new-to-nature enzymes with catalytic rates that are orders of magnitude higher than those seen to date. Thus, a unified and principled framework enables the design and optimisation of protein function.