Design and evolution of artificial enzymes

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Enzyme design represents a formidable challenge. Extensive mechanistic and structural studies have provided a solid qualitative understanding of enzyme action. Nevertheless, our knowledge of structure-function relationships in these macromolecules remains incomplete and a quantitative accounting of the incredible efficiency achieved by enzymes still eludes us. Diverse strategies have therefore been explored to engineer enzymes for novel applications, ranging from repurposing existing active sites to generation of antibodies with tailored catalytic properties. Among these approaches, computational design has emerged as particularly promising. Computational enzyme design has afforded made-to-order catalysts for a variety of reactions lacking biological counterparts, including simple proton transfer reactions, multi-step retroaldol transformations, Diels-Alder cycloadditions, and several metal-dependent processes. Although the starting activities of these artificial enzymes are typically low, they can be significantly increased by directed evolution. In favorable cases, activities approaching those of natural enzymes have been achieved. Analysis of the (sometimes surprising) evolutionary trajectories provides valuable feedback for the design process as well as insights into natural protein evolution. Recent progress on the computational design and evolutionary optimization of artificial enzymes will be surveyed in this lecture, highlighting both the opportunities and challenges facing this emerging field.