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Combinatorial assembly and design of enzymes

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PURPOSE OF THE ABSTRACT
The design of structurally diverse enzymes is constrained by long-range interactions that are necessary for accurate folding. We introduce an atomistic and machine learning strategy for the combinatorial assembly and design of enzymes (CADENZ) to design fragments that combine with one another to generate diverse, low-energy structures with stable catalytic constellations. We applied CADENZ to endoxylanases and used activity-based protein profiling to recover thousands of structurally diverse enzymes. Functional designs exhibit high active-site preorganization and more stable and compact packing outside the active site. Implementing these lessons into CADENZ led to a 10-fold improved hit rate and more than 10,000 recovered enzymes. This design-test-learn loop can be applied, in principle, to any modular protein family, yielding huge diversity and general lessons on protein design principles.

FIGURES

FIGURE 1

FIGURE 2

KEYWORDS
enzyme design | xylanase

BIBLIOGRAPHY