DESIGNING DE NOVO RETRO-ALDOLASE CATALYSTS

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Evolutionary history of native proteins, shaping observed sequences by complex interplay between mutational drift, maintaining stability and developing functionality, often complicates rationalization of protein engineering experiments making it hard to learn even from large datasets available with advent of high throughput screening and deep-sequencing technologies.

Use of de novo protein scaffolds for gain of function design projects should, arguably, allow better understanding of fundamental principles underlying implementation of this function in nature and application of these principles to new protein engineering problems.

Computational design of enzymatic activity in the de novo built idealized protein scaffolds instead of natural proteins from PDB has a promising advantages of avoiding limitations associated with evolutionary history and virtually unlimited number of geometric variants that can be generated for given scaffold to accommodate catalytic machinery.

I am going to present computational strategy used to design de novo proteins with enzymatic activity and experimental data collected using recently identified de novo designed beta-barrels catalyzing retro-aldolase reaction. This information helps to narrow down range of catalytic mechanisms compatible with the structural model, which in turn help to highlight features and interactions potentially important for catalysis.