Abstract for general public

De novo design, synthesis and evaluation of catalytic mini-proteins

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Mini-proteins, defined as oligopeptides that form well-defined tertiary structures with the molecular mass not exceeding 10 kDa, show numerous exceptional features related to their structures and functions. Due to recently described effective *de novo* design strategy, the field of mini-proteins gains significant attention of scientific community. Rational design allows incorporation various demanding functions, e.g. inhibition of protein-protein interactions. Although the possibility of construction of catalytically active mini-proteins has been also proven, the known examples concerns only model reactions, and therefore this area remains still poorly explored.

This proposal concerns *de novo* design of mini-proteins incorporating cavities and their use for construction of enzyme-like catalysts. Challenging cavity-containing mini-proteins will be constructed using secondary structures incorporating conformationally constrained beta-amino acid residues. Interactions between secondary structures will be maintained by hydrophobic interactions in some cases supported by disulfide bridges. Subsequently, the application of developed cavity-containing mini-proteins for construction of enzyme-like catalysts will be explored. Iterative optimization of catalytic activity by computer-aided modifications of both substrate binding cleft and distant residues will provide access to proficient catalysts. We will focus on three groups of reactions: (a) aldol condensation and related reactions mediated by enamine intermediate; (b) conjugate additions and cycloadditions proceeding via iminium intermediate.

High potential of mini-proteins for development of functional molecules will provide a possibility to rationally create catalyst with unique properties. Combination of advantages of low-molecular-weight catalysts (synthetic availability, understanding of the catalytic process, wide variety of catalyzed reactions) with advantages of enzymes (extended structure, high proficiency, high regio- and stereo-selectivity) will be possible and, in consequence, will allow exploration of new areas of science. Results will also provide insight in the catalytic process of native enzymes.