STRAATEGIES AND SOFTWARE FOR ENGINEERING PROTEIN TUNNELS AND DYNAMICAL GATES

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Improvements in the catalytic activity, substrate specificity or enantioselectivity of enzymes are traditionally achieved by modification of enzymes' active sites. We have recently proposed that the enzyme engineering endeavors should target both the active sites and the access tunnels/channels [1,2]. Using the model enzymes haloalkane dehalogenases, we have demonstrated that engineering of access tunnels provides enzymes with significantly improved catalytic properties [3] and stability [4]. User-friendly software tools Caver [5], Caver Analyst [6], CaverDock [7] and Caver Web [8], have been developed for the computational design of protein tunnels/channels; FireProt [9] and HotSpot Wizard [10] for automated design of stabilizing mutations and smart libraries. Using these tools we were able to introduce a new tunnel to a protein structure and tweak its conformational dynamics. This engineering strategy has led to improved catalytic efficiency [2], enhanced promiscuity or even a functional switch (unpublished). Our concepts and software tools are widely applicable to various enzymes with known structures and buried active sites.