Tailoring noncovalent interaction networks to modulate protein stability, dynamics, and selectivity

Supervisors / institute:
Main supervisor: Prof. Dr. Holger Gohlke, Pharmaceutical and Medicinal Chemistry
Co-supervisor: Prof. Dr. Jörg Pietruszka, Bioorganic Chemistry

Project background and description:
Noncovalent interaction networks are key determinants of a protein's structural stability, dynamics, and selectivity. In the proposed project, the structural stability, dynamics, and selectivity of two protein systems, an aldolase and a pyruvate orthophosphate dikinase (PPDK), shall be modulated based on rationally tailoring noncovalent interaction networks.
Aldolases are an important class of enzymes that catalyse C-C bond formation. While widely used as "green catalysts" in organic synthesis, issues of enzyme stability and selectivity are still of concern. Here, aldolases with new and altered selectivity shall be designed based on an understanding of the stereochemical outcome of the aldolase-catalysed reaction and to what extent this is influenced by noncovalent interaction networks between aldolase and substrates as well as within the enzyme. This work will be performed in close collaboration with the group of Jörg Pietruszka (bioorganic chemistry and protein biochemistry).
PPDK is both an attractive target for the development of herbicides and antiparasitic drugs. During catalysis, a phosphate needs to be shuttled over 45 Å between PPDK's two catalytic domains, presumably by a large-scale swivelling motion. Stalling this motion will help to shed light onto the details of the swivelling mechanism and will open up an avenue for herbicide and antiparasitic drug development. Three strategies will be pursued: I) residues that form interdomain "interaction weak spots" shall be identified and the weak spots strengthened by mutagenesis; II) small-molecule stabilizers of the interdomain interactions shall be identified by structure-based virtual screening; III) hinge regions shall be stiffened based on an understanding of the protein's static properties. This work will be performed in close collaboration with the group of Georg Groth (protein crystallography and biochemistry).
Key technologies available in the Gohlke group will be applied and further developed for this. These include the analysis of static protein properties by means of Constraint Network Analysis (CNA) [1], coarse-grained and molecular dynamics simulations [2], and rational approaches for finding small-molecule modulators of protein-protein interactions [3].

Aims of the project:
- Elucidation of the swivelling mechanism of PPDK and identification of small-molecule stabilizers of protein-protein interactions as potential herbicides and antiparasitic drugs
- Rational design of aldolases with new and altered stereoselectivity

Requirements:
- Diploma, MSc or equivalent degree in biophysics, biochemistry, bioinformatics, chemistry
- A strong background in computational biophysics and molecular bioinformatics

Additional information:
Group web page: http://cpclab.uni-duesseldorf.de/
[1]: http://cpclab.uni-duesseldorf.de/publications/c18_gohlke.pdf
[2]: http://cpclab.uni-duesseldorf.de/publications/ahmed_a._jcim_2011.pdf
[3]: http://cpclab.uni-duesseldorf.de/publications/JCIM_2012_52_120-133.pdf