Abstract of Presentation

Note: This paper should be typed in "Times New Roman" of 12pt.

Presentation Title(Should be no more than 20 words):

Plasticity of protein structures as challenge for structure-based drug discovery

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Abstract :

Today, drug discovery as well as protein crystallography utilize modular and genomics-driven high-throughput technologies that integrate expression/purification, crystallization, structure determination, computational chemistry methods and high throughput screening to improve the efficiency of the process.

Many of our structural data revealed an enormous amount of conformational flexibility in enzyme active sites. This leads to novel ideas for the design of low molecular weight inhibitors and emphasises the importance for the ongoing support of drug design projects with experimental structural data. Opportunities and challenges will be discussed on a few examples.

Proteases are involved in many essential intracellular and extra-cellular processes, including the life cycle of pathogenic organisms and many viruses. The critical role of many proteases in the development of diseases is also established and high resolution structures of many representatives of cysteine-, serine-, metallo- and aspartic proteases are available. Therefore proteases are perhaps the largest class of enzymes that have been used as targets for structure based drug design. Among the most successful applications to date are drugs against the HIV protease and human renin that stop viral replication and regulate the blood pressure, respectively. The structure based approach to develop orally active and bioavailable renin inhibitors will be reviewed [1].

Repeat proteins are ubiquitous protein-protein interaction molecules fundamental to many biological processes [2]. This feature was exploited *in vitro*, by designing ankyrin repeat proteins (DARPin) and combinatorial libraries thereof [3]. By using ribosome display [4] we selected DARPins having high affinity (nM range) and specificity for proteases, kinases as well as membrane proteins and used them for co-crystallization of the target

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protein. The methodology and the structures of an ARP-kinase complex and an ARP-caspase-2 complex will be presented, showing the usefulness of this novel technology for structural biology as well as for drug design.

[1] Rahuel, J., et al. and Grütter, M.G. Structure-based drug-design: the discovery of novel nonpeptide orally active inhibitors of human renin. ChemBiol., 7, 493-504 (2000).

[2] Forrer, P., Stumpp, M. T., Binz, H. K. & Plückthun, A. A novel strategy to design binding molecules harnessing the modular nature of repeat proteins. FEBS Letters **539**, 2-6 (2003).

[3] Kohl, A., Binz, H. K., Forrer, P., Stumpp, M. T., Plückthun, A. & Grütter, M. G. Designed to be stable: crystal structure of a consensus ankyrin repeat protein. Proc. Natl. Acad. Sci. USA **100**, 1700-1705 (2003).

[4] Binz, H. K., Amstutz, P., Kohl, A., Stumpp, M.T., Briand, C., Forrer, P., Grütter, M. G. & Plückthun, A. High affinity binders selected from designed ankyrin repeat protein libraries. Nature Biotechnology, **22**, 575-582 (2004).