and other beta-pore-forming toxins. This homology and its trimeric form will allow us to make some conclusions regarding the formation of complexes with Claudin at tight junctions.

[1] R.J. Carman. *Reviews of Medical Microbiology,* **1997**, *8*, S46-S48. [2] K. Miyamoto, Q. Wen, B.A. McClane. *Journal of Clinical Microbiology*, **2004**, *42*, 1552-1558. [3] B.A. McClane. *Trends in Microbiology*, **2000**, *8*, 145-146. [4] U. Singh, C.M. Van Itallie, L.L. Mitic, J.M. Anderson, B.A. McClane. *Journal of Biological Chemistry*, **2000**, *275*, 18407-17. [5] C.M. Van Itallie, L. Betts, J.G. Smedley, III, B.A. McClane, J.M. Anderson. *Journal of Biological Chemistry*, **2008**, *283*, 268-274. [6] J.M. Smedley, III, F.A. Uzal, B.A. McClane. *Infection and Immunity*, **2007**, *75*, 2381-2390.

Keywords: toxin, food, hairpin

MS.17.1

Acta Cryst. (2011) A**67,** C53

Designer enzymes

Donald Hilvert, *Laboratory of Organic Chemistry, ETH Zürich, Zurich (Switzerland).* E-mail: hilvert@org.chem.ethz.ch

Protein design is a challenging problem. We do not fully understand the rules of protein folding, and our knowledge of structure-function relationships in these macromolecules is at best incomplete. Nature has solved the problem of protein design through the mechanism of Darwinian evolution. From primitive precursors, recursive cycles of mutation, selection and amplification of molecules with favorable traits have given rise to all of the many thousands of gene products in every one of our cells. An analogous process of natural selection can be profitably exploited in silico and in the laboratory on a human time scale to create, characterize and optimize artificial catalysts for tasks unimagined by Nature. Recent progress in combining computational and evolutionary approaches for enzyme design will be discussed, together with insights into enzyme function gained from studies of the engineered catalysts.

Keywords: enzyme, computational design, evolution

MS.17.2

Acta Cryst. (2011) A**67,** C53

Molecular probes as starting point for structure-based lead development

Andreas Heine, Jürgen Behnen, Helene Köster, Tobias Craan, Sascha Brass, Gerhard Klebe, *Institute of Pharmaceutical Chemistry, Philipps-University Marburg, Marburg, (Germany).* E-mail: heinea@mailer.uni-marburg.de.

In addition to high-throughput screening and structure-based drug design, fragment- based approaches have recently become increasingly popular for lead development in pharmaceutical drug research. Here, a small but well selected library of low molecular weight compounds (< 300 Da) is screened by biophysical methods such as surface plasmon resonance (SPR), nuclear magnetic resonance (NMR) or X-ray crystallography.

In this study, we started with even smaller, highly-soluble probe molecules, such as aniline, urea, N-methylurea, propanediol, bromophenol and phenol. These probe molecules were selected to experimentally map out protein binding pockets by detecting hot spots of binding with respect to hydrophobic and hydrophilic properties. Furthermore, they should be applicable to a wide range of target proteins. As model protein the zinc protease thermolysin was selected. Subsequently, our studies were extended to additional proteins such as protein kinase A (PKA), D-xylose isomerase (DXI), 4-diphosphocytidyl-2C-methyl-D-erythritol synthase (IspD) and the aspartyl protease endothiapepsin (ETP). The obtained crystal structures clearly show that the probe molecules could be located in these protein binding pockets. These probe molecules form similar interactions as larger ligands containing analogical chemical features and therefore are deemed suitable for hotspot detection.

Next, the structure of PKA in complex with phenol was used as template for docking of a virtual in-house fragment library of about 4000 entries. With one promising candidate a crystal structure was subsequently determined. Using the structural information and the experimental hot spot analysis, a putative lead skeleton was obtained that was translated into a synthetically accessible compound class. Of the synthesized compound series, one first representative showed an affinity of 70 μM. Based on this complex structure further lead optimization is in progress.

Keywords: probe molecules, fragments, drug design

MS

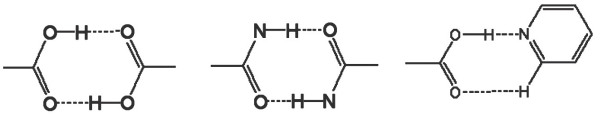
MS.17.3

Acta Cryst. (2011) A**67,** C53-C54

Supramolecular synthons in crystal engineering

Kumar Biradha, *Departament of Chemistry, Indian Institute of Technology, Kharagpur, 721302, West Bengal, (India).* E-mail: kbiradha@yahoo.com

Crystal engineering deals with creation of novel materials using controlled arrangements of molecules in the crystal lattice using intermolecular interactions.[1], [2] Various common functional groups such as carboxylic acids, amides, phenols and other weak hydrogen bonding functional groups known to form certain recognition motifs in a repetitive manner (Scheme 1). These motifs were termed as supramolecular synthons signifying the importance of such motifs in the aggregation of molecules in the crystal lattice. Supramolecular synthons are defined by Desiraju as "structural units within supermolecules which can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interaction" [1]. In this talk the utility of synthons and robustness and interference effects of popular synthons will be discussed in detail by using some of our recent results [3-11]. Further the discovery of new synthons and transfer of supramoleuclar synthons observed in organic molecules into coordination polymers will also be discussed.



Scheme 1: Popular strong hydrogen bonding synthons

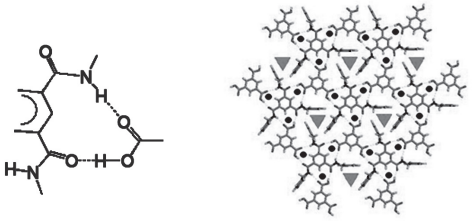


Figure 1: A new robust synthon in the generation of two-dimensional layer between two chemical components.

[1] G.R. Desiraju, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2311. [2] K. Biradha, *CrystEngComm*. **2003**, *5*, 374. [3] S. Samai, J. Dey, K. Biradha, *Soft Matter*