MS85 BIOLOGICAL MOLECULES AS TARGETS FOR DRUG DESIGN
Chairpersons: Stefania Di Marco, William (Bill) Stallings

MS85.30.1
Acta Cryst. (2005). A**61**, C108
AChBP Structures for Understanding Ligand Binding in Nicotinic Receptors
Titia K. Sixma, Patrick H Celie[a], Remco Klaassen[b], Pim van Nierop, Sarah E. van Rossum-Fikkert[a], August B. Smit[b], *[a]Netherlands Cancer Instiute Amsterdam, The Netherlands. [b]Neurobiology, Free University, Amsterdam, The Netherlands.* E-mail: t.sixma@nki.nl

Acetylcholine-binding protein (AChBP) from the mollusc Lymnaea stagnalis is at present the only high-resolution model for the ligand-binding domains of the ligand-gated ion channel family, which includes nicotinic acetylcholine, 5HT3, GABAA, GABAC and glycine receptors.

Here we present crystal structures from remote homologs from other molluscs that will define the variabilities in the binding sites. We will also explore a series of crystal structures of nicotinic receptor agonists and other ligands. These define how cation-pi interactions as well as remote electrostatic compensation contribute to ligand binding in the receptors. These structures also explain the many different data from ligand-binding studies on this pharmaceutically important class of neuronal receptors.

Comparison of these structures will be valuable for improving structure-function studies of ligand-gated ion channel receptors, including signal transduction, homology modeling and drug design.
Keywords: ligand-gated ion-channels, acetylcholine, toxin

MS85.30.2
Acta Cryst. (2005). A**61**, C108
Classical and Non-classical Structure-based Drug Design
Joseph W. Becker, *Department of Medicinal Chemistry, Merck Research Laboratories, Rahway NJ 07065, USA.* E-mail: joseph_becker@merck.com

Structure-based drug design is usually described as an iterative process in which knowledge of the three-dimensional structure of a receptor-ligand complex reveals details of the binding interface that can be improved by chemical modification of the ligand. These structure-based changes as evaluated by *in vitro* or *in vivo* assay, and improved ligands are subjected to additional cycles of structure determination, improvement and evaluation. Our studies on caspase-3, PTP-1B and other targets provide examples of such classical structure-based drug design. On occasion, however, structural studies lead to surprising results that produce unexpected effects on the inhibitor-development process. In both the caspase and PTP projects, early structures revealed that the apparent improvement in binding potency was inconsistent with program goals and this knowledge led to termination of the compound classes involved. In work on both nuclear receptors and kinases, knowledge of structure-based selectivity led to the design of novel assays that have effectively discriminated compounds on their biological properties. These studies demonstrate that structure-based drug design studies can not only lead to ligand optimization but to prioritization of compound classes and to the design of novel methods of discriminating among compounds based on their biological properties.
Keywords: structure-aided drug design, nuclear receptors, protein kinases

MS85.30.3
Acta Cryst. (2005). A**61**, C108
Structure Based Drug Design of Novel Inhibitors of cGMP Phosphodiestearse, PDE5
Chris Phillips, David G Brown, *Pfizer Global Research and Development, Sandwich UK.* E-mail: brown_dg@sandwich.pfizer.com

PDE5, a cGMP specific PDE, has been recognised in recent years as an important therapeutic target. It is composed of the conserved C-terminal, zinc containing, catalytic domain, which catalyses the cleavage of cGMP, and an N-terminal regulatory portion, which contains two GAF domain repeats [1]. Each GAF domain contains a cGMP-binding site, one of high affinity and the other of lower affinity [2]. PDE5 activity is regulated through binding of cGMP to the high and low affinity cGMP binding sites followed by phosphorylation, which occurs only when both sites are occupied [3]. PDE5 is found in varying concentrations in a number of tissues including platelets, vascular and visceral smooth muscle, and skeletal muscle. The protein is a key regulator of cGMP levels in the smooth muscle of the erectile corpus cavernosal tissue. Inhibition of PDE5 inhibits the breakdown of cGMP allowing the levels of cGMP, and hence smooth muscle relaxation, to be maintained [2]. Sildenafil, the active ingredient of Viagra® and a potent inhibitor of PDE5, has attracted widespread attention for the effective treatment of male erectile dysfunction.

We present here the application of the structures of PDE5 [4-9] to design novel inhibitors. The use of the complexes provides additional important structural information on the binding modes of multiple series of inhibitors. The structures also highlight the diverse chemical nature of inhibitors within this gene target and wider gene family, and the subtle structure activity relationships which assist the design of more potent and specific inhibitors to treat the many diseases where PDE's play a role.

[1] Beavo J. A., *Physiological Reviews*, 1995, **75**, 725-748. [2] Corbin J. D., Francis S. H., *Journal of Biological Chemistry*, 1999, **274**, 13729-32. [3] Thomas M. K., Francis S. H., Corbin J. D., *J. Biol. Chem.*, 1990, **265**, 14971-8. [4] Brown D.G. et al., *International Patent Application*, 2003, WO 2003/038080. [5] Sung B-J. et al., *Nature*, 2003, **425**, 98-105. [6] Huai Q. et al., *J. Biol. Chem*.,2004, **279**, 13095. [7] Zhang et al., *Mol. Cell*, 2004, **15**, 279. [8] Brown D.G. et al, *International Patent Application*, 2004, WO 2004/097010. [9] Card G.L. et al., *Structure*, 2004, **12**, 2233.
Keywords: structure based drug design, novel inhibitors, phosphodiesterase

MS85.30.4
Acta Cryst. (2005). A**61**, C108-C109
Structure-guided Drug Discovery for Protein Kinases Using Fragment-based Lead Identification/Lead Optimization
Stephen K. Burley, *Chief Scientific Officer and Senior Vice-President Research, Structural GenomiX, Inc., 10505 Roselle Street, San Diego, CA 92121.* E-mail: sburley@stromix.com

Structural GenomiX, Inc. (SGX) has developed an integrated target-to-lead platform that combines high-throughput X-ray crystallography with a fragment-based approach to lead identification/optimization. The proprietary *FAST*™ (Fragments of Active Structures) process exploits crystallographic screening to detect, visualize, and identify small ligands (MW 150-200) that are bound to the target protein. Each member of the *FAST*™ fragment/scaffold library was designed to be amenable to rapid chemical elaboration at two or three points of chemical diversity using high-throughput organic synthesis. Initial lead optimization involves using our knowledge of the co-crystal structure of the target-fragment complex and advanced computational chemistry tools to guide synthesis of small focused linear (one-dimensional) libraries. These linearly elaborated fragments/scaffolds are then evaluated with *in vitro* biochemical and cellular assays and co-crystallography. Thereafter, optimal variations at each point of chemical diversity are combined to synthesize focused combinatorial (two- or three-dimensional) libraries that are again examined with assays and co-crystallography. (The potential chemical diversity of the fully elaborated *FAST*™ fragment/scaffold library far exceeds 160 million compounds.) These focused combinatorial libraries typically contain multiple novel compounds of low molecular weight (<350) that bind the target protein at low nM IC_{50} and already display considerable selectivity. Thereafter, compound series are prioritized for further medicinal chemistry and compound development efforts using the results of *in vitro* and *in vivo* ADME and *in vitro* toxicology studies in concert with structural information. Successful applications of the *FAST*™ fragment-based lead discovery/optimization process will be presented