structures and discuss further design strategies for highly selective family 3 glycoside hydrolase inhibitors.

Keywords: glycosyl hydrolases, antibiotic resistance, structure-based drug design

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The crystal structure of AKR1C1 in complex with an active-site inhibitor

Urmi Dhagat[1], Satoshi Endo[2], Akira Hara[2], Ossama El-Kabbani[1]
[1]Monash University, Medicinal Chemistry, 381 Royal Parade, Parkville, Melbourne, Victoria, 3052, Australia, [2]Laboratory of Biochemistry, Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu 502-8585, Japan, E-mail：urmi.dhagat@vcp.monash.edu.au

Hydroxysteroid dehydrogenases (HSDs) regulate a wide range of physiological processes including reproduction, development and homeostasis. AKR1C1, is a 20α-HSD involved in the conversion of progesterone to 20-hydroxyprogesterone. Increased activity of AKR1C1 in the endometrium and in breast tissues leads to the formation of tumor-promoting metabolites and to the development of endometriosis, breast cancer and endometrial cancer. At present, there are few known inhibitors that specifically bind and inhibit the adverse actions of AKR1C1. Here we present the first crystal structure of AKR1C1 in complex with potent inhibitor 3,5-dichlorosalicylic acid (IC_{50} = 44 nM). The crystal structure was solved at a resolution of 1.8 Å, with clear electron density corresponding to the inhibitor bound in the active site. The details of the enzyme-inhibitor interactions and selectivity against members of the AKR1C subfamily will also be discussed. The structural information obtained from this study will help speed up the drug design process for the development of more selective and potent compounds that can be used in the treatment of endometriosis and cancer.

Keywords: aldo-keto reductases, enzyme inhibitors, drug design

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Eimeria tenella lactate dehydrogenase as a target for anti-parasitics

Victoria Fairweather[1,2], Robert Schwarzenbacher[2], Leo Brady[1]
[1]University of Bristol, Department of Biochemistry, School of Medical Sciences, University Walk, Bristol, Bristol, BS8 1TD, UK, [2]University of Salzburg, Department of Molecular Biology, Billrothstr. 11, 5020 Salzburg, Austria, E-mail：v.fairweather@bristol.ac.uk

Eimeria species are parasitic Apicomplexa protozoans that cause gastrointestinal coccidiosis infections in birds, and are associated with general morbidity and intestinal lesions. These parasitic infections lead to major losses within the broiler industry, a situation that is deteriorating due to emerging resistance to available therapeutics. By analogy with other Apicomplexa obligate parasites, in the intracellular stages of its lifecycle the Eimeria parasite relies heavily on glycolysis for ATP production, and hence on homolactic fermentation - the action of lactate dehydrogenase (LDH) - to restore the NADH/NAD^+ balance. These parasites are therefore extremely sensitive to LDH inhibition. In common with the LDH of the malaria causing parasite Plasmodium falciparum (PfLDH), Eimeria tenella LDH (EtLDH) has a characteristic five amino acid insert in a loop directly adjacent to the active site. As a consequence, we reasoned that compounds we have previously designed to specifically inhibit PfLDH should cross-react with EtLDH. We are therefore undertaking crystallisation and structural analysis of EtLDH and its inhibitory complexes in order to explore the possibility of targeting EtLDH for novel veterinary therapeutics.

Keywords: lactate dehydrogenase, Eimeria tenella, enzyme inhibitors

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Crystal structure and structure based drug design of HU (histone like protein) from *M.tuberculosis*

Ramakumar Suryanarayanarao[1], Tuhin Bhowmick[1], Soumitra Ghosh[2], Ramagopal A Udupi[3], Nagaraja Valakunja[2]
[1]Indian Institute of Science, Physics, Raman Avenue, Bangalore, Karnataka, 560012, India, [2]Microbiology and Cell Biology Department, Indian Institute of Science, Bangalore-560012, India, [3]Albert Einstein College of Medicine, Bronx, New York, 10461, USA, E-mail：ramak@physics.iisc.ernet.in

HU is an architectural protein for bacterial chromosome compaction and organization.HU is one of the most ubiquitous proteins in the bacterial cell.It is a small basic protein, binding non-specifically throughout the nucleoid. While the sequence of HU is highly conserved through most of the bacterial species, the HU in M.tuberculosis has a sequence longer than other HUs whose crystal structures have been elucidated (Anabaena (1P71): 94 residues). It has a sequence length of 214 amino acid residues suggesting the presence of an extra domain.As the protein has a possible role in overall gene architectural modification and a global control of gene expression, it makes this HU an important candidate for structural study. For the first time a complete functional N-terminal Domain of HU from M.tuberculosis [H37Rv] (1st 100 amino acid residues) containing the sub-domains for DNA binding and dimerization was crystallized,the crystals diffracted to 2.04Å. Crystal unit cell contains biological dimer of N-terminal region of HU protein. The structure was solved by molecular replacement method. The final *R*cryst and *R*free are 20.6% and 25.0%. As the sequence is highly conserved among the other important mycobacterium species, like M.leprae, M.bovis, M.smegmatis etc., this structure is a good representative HU structure for the whole class and serves as an attractive target for drug design. Two types of drug molecules, one which can interfere with DNA-binding and other with HU dimerization, were designed computationally, utilizing the solved crystal structure of HU. The designed compounds interact with HU with high binding energies, as estimated computationally and could serve as lead molecule for drug design. Details of the 3-D models of HU-drug interactions will be discussed.

Keywords: Mycobacteria, histone like protein, structure aided drug design

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Structure-based design of anticancer prodrug PABA/NO

Xinhua Ji[1], Ajai Pal[2], Ravi Kalathur[1], Xun Hu[2], Yijun Gu[1,2], Joseph Saavedra[1], Gregory Buzard[1], Aloka Srinivasan[1],