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Structure of Guinea Pig 11β Steroid Dehydrogenase 1 with Glycyrrhetinic Acid
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11β steroid dehydrogenase 1(11βHSD1) catalyzes the conversion of glucocorticoid cortisone to cortisol, amplifying the local concentration of cortisol in select tissues. Increasing evidence in the literature implicates 11βHSD1 in the metabolic syndrome consisting of diabeties, visceral obesity, and hyperlipidemia[1]. In addition, inhibition of 11βHSD1 ameliorates hyperglycemia and increases insulin sensitivity in diabetic animal models[2]. 11βHSD1 is thus a target for drug intervention in diabetes. We present the structure of Guinea Pig 11βHSD1 with Glycyrrhetinic Acid, a natural product inhibitor. We also discuss the mechanism of 11βHSD1 in relation to other steroid dehydrogenases and the implications of the structure for structure based drug design.

[1]Masuzaki H., Paterson J., Shinyama H., Morton N., Mullins J., Seckl J., Flier J., *Science*, 2001, **294**, 2166. [2] Alberts P., Nilsson C., Selen G., Engblom L.O., Edling N.H., Norling S., Klingstrom G., Larsson C., Forsgren M., Ashkzari M., Nilsson C.E., Fiedler M., Bergqvist E., Ohman B., Bjorkstrand E., Abrahmsen L.B., *Endocrinology*, 2003, **144**, 4755.
Keywords: diabetes, structure-based drug design, dehydrogenase steroid nucleotide

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Farnesyl Pyrophosphate Synthase: Clinical Target for Bone Diseases
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Osteoporosis affects one in three women and one in five men over the age of 50. Bisphosphonate therapy, which inhibits bone resorption, reduces the risk of fracture by 50% within one year.

Nitrogen-containing bisphosphonates are known inhibitors of farnesyl pyrophosphate synthase (FPPS) and are currently used to treat osteoporosis, Paget's disease of the bone, and malignant bone tumors. FPPS resides at a branchpoint of the isoprenoid pathway due to the fact that the farnesyl pyrophosphate product can undergo either chain-elongation or cyclization, or may be utilized for protein prenylation. Since the post-translational addition of a farnesyl moiety is essential to activate many intracellular signaling proteins, inhibition of FPPS leads to apoptosis. Why some nitrogen-containing bisphosphonates are more potent inhibitors, and hence more effective drugs, is poorly understood.

The structure of human pyrophosphate synthase in complex with magnesium and the bisphosphonate risedronate shows the binding mode for this important class of inhibitors. Risedronate occupies the chain-elongation site but not the isopentenyl pyrophosphate site. Two aspartate clusters chelate the magnesiums that mediate ligand binding and are involved in catalysis. Although predictions suggested two inhibitors binding to each protein chain, isothermal titration calorimetry and the crystal structure clearly indicate a one-to-one stoichiometry.

Since this is the first example of a mammalian FPPS, it will provide the basis for more accurate structure-assisted drug design.
Keywords: transferases, protein-drug interaction, drug design

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Structure of *S*-Adenosyl-L-Homocysteine Hydrolase from *Plasmodium falciparum*
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The human malaria parasite *Plasmodium falciparum* is responsible for the death of more than a million people each year. The emergence of strains of malaria1 parasite resistant to conventional drug therapy has stimulated searches for antimalarials with novel modes of action. *S*-Adenosy1-L-homocysteine hydrolase (SAHH) is a regulator of biological methylations. Inhibitors of SAHH affect the methylation status of nucleic acids, proteins, and small molecules. *Plasmodium falciparum* SAHH (PfSAHH) inhibitors are expected to provide a new type of chemotherapeutic agent against malaria. Despite the pressing need to develop selective PfSAHH inhibitors as therapeutic drugs, only the mammalian SAHH structures are currently available. Here, we report the crystal structure of PfSAHH complexed with the reaction product adenosine [1].

[1] Tanaka N., et al., *J. Mol. Biol.*, 2004, **343**, 1007-1017.
Keywords: crystal structure, malaria, drug design

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Crystal Structure of Oxido Squalene Cyclase
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Oxido Squalene Cyclase (OSC) catalyses the synthesis of the steroid scaffold which is a key step in the synthesis of cholesterol. In a single highly selective reaction OSC forms lanosterol from the linear substrate oxido squalene.

The 2.1Å structure of this human monotopic integral membrane protein shows how OSC is inserted to the membrane. The hydrophobic substrate can reach the active site that is deeply buried in the center of the enzyme through a channel that opens into the membrane. The structure gives also new insights into the way OSC catalyzes the interesting cyclization reaction. Analysis of the mode of inhibitor binding to the active site cavity will help in the design of new OSC inhibitors as anticholesteremic drugs.

Also the high level expression, purification and crystallization of this human membrane protein will be described. Analytical ultra centrifugation was used to characterize the aggregation state of OSC and was helpful in predicting crystallizability.
Keywords: cholesterol, cyclase, membrane protein

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Crystal Structure of the N-terminal Ankyrin Repeat Domain of Human RNase L
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Ribonuclease L (RNase L) is implicated in both the molecular mechanisms of interferon action and the fundamental control of RNA stability in mammalian cells. RNase L is catalytically active only after binding an unusual activator molecule containing a 5'-phosphorylated 2',5'-linked oligoadenylate, (pp)p(A2'p5')2A (2-5A), in the N-terminal half. RNase L consists of three domains, namely the N-terminal ankyrin repeat domain, the protein kinase homology domain, and the C-terminal ribonuclease domain. The N-terminal ankyrin repeat domain is responsible for 2-5A binding, and the C-terminal domain is responsible for catalytic activity.

We have determined the crystal structure of the N-terminal ankyrin repeat domain (ANK) of human RNase L complexed with the activator 2-5A at 1.8 Å resolution [1]. The ANK folds into eight ankyrin repeat elements and forms an extended curved structure with a