pockets. This separation might be possible to accept three HMTGs on a gp120 at the same time.

Keywords: lectin proteins; HIV drug design; protein structure analysis

FA1-MS07-P08

Conformational Change of Adenosine Deaminase During Ligand-Exchange in Crystal State.
Takayoshi Kinoshita[a], Toshiji Tada[a], Isao Nakanishi[b]. *[a]Graduate School of Science, Osaka Prefecture University, Japan. [b]Department of Pharmaceutical Sciences, Kinki University, Turkey, Japan.*
E-mail: kinotk@b.s.osakafu-u.ac.jp

Adenosine deaminase (ADA) perpetuates chronic inflammation by degrading extracellular adenosine which is toxic for lymphocytes. ADA has two distinct conformations: open form and closed form [1]. From the crystal structures with various ligands, the non-nucleoside type inhibitors bind to the active site occupying the critical water-binding position and sustain the open form of apo-ADA. In contrast, substrate mimics do not occupy the critical position, and induce the large conformational change to the closed form. However, it is difficult to predict the binding of (+)-erythro-9-(2-hydroxy-3-nonyl)adenine (EHNA), as it possesses characteristic parts of both the substrate and the non-nucleoside inhibitors. The crystal structure shows that EHNA binds to the open form through a novel recognition of the adenine base accompanying conformational change from the closed form of the PR-ADA complex in crystalline state [2]. The open form crystal structure of the EHNA-ADA complex supports our hypothesis that the occupancy at the trigger-water-position is critical for determining the open/closed conformational alternation, rather than the nucleoside framework binding. We believe that the structural penetration of the EHNA-ADA complex and structural comparison of the other inhibitor-ADA complexes will support the discovery of novel ADA inhibitors by structure-based drug design.

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Keywords: adenosine deaminase; EHNA; conformational change

FA1-MS07-P09

The Structure of the Ca^{2+}-ATPase Bound to Cyclopiazonic Acid Reveals a Complexed Divalent Ion.
J. Preben Morth[a], Mette Laursen[a], Maike Bublitz[a], Karine Moncoq[c], Claus Olesen[b], Jesper Vuust Moeller[b], Howard S. Young[c], Poul Nissen[a]. *[a]Department of Molecular Biology, Aarhus, University, Denmark. [b]Department of Physiologyand Biophysics, Aarhus University, Denmark. [c]Department of Biochemistry and National Institute for Nanotechnology, University of Alberta, Canada.*
E-mail: jpm@mb.au.dk

We have determined the structure of the sarco(endo) plasmic reticulum Ca^{2+}-ATPase (SERCA) in an E2.Pi-like form stabilised as a complex with MgF_4^{2-}, an ATP analogue (AMPPCP), and cyclopiazonic acid (CPA) . The structure determined at 2.5 Å resolution leads to a significantly revised model of CPA binding compared to earlier reports [1,2] showing that a divalent metal ion is required for CPA binding through coordination of the tetramic acid moiety at a characteristic kink of the M1 helix found in all P-type ATPase structures which is expected to be part of the cytoplasmic cation access pathway. Our model is consistent with the biochemical data on CPA [3] function and provides new measures in structure based drug design targeting Ca^{2+}-ATPase from e.g. pathogens. We also present an extended structural basis of ATP modulation pinpointing key residues at or near the ATP binding site. A structural comparison to the Na^+,K^+ -ATPase reveals that a Phe93 side chain occupies the equivalent binding pocket of the CPA site in SERCA suggesting an important role of this residue in stabilization of the potassium-occluded E2 state of Na^+,K^+-ATPase.

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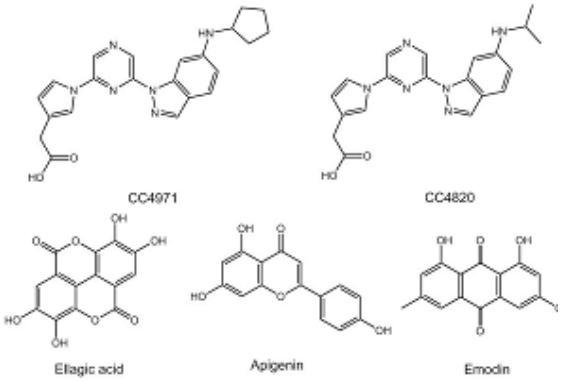
Keywords: drug design; ATPase; membrane channel transport

FA1-MS07-P10

An Approach for Producing a CK2alpha Inhibitor Using X-ray, Calculation and ITC.
Yusuke Sekiguchi[a], Harumi Fukada[b], Tetsuko Nakaniwa[a], Takayoshi Kinoshita[a], Shinya Nakamura[c], Isao Nakanishi[c,d], Kazuo Kitaura[d], Hiroaki Ohno[d], Yamato Suzuki[d], Akira Hirasawa[d], Gozoh Tsujimoto[d], Toshiji Tada[a]. *[a]Graduate School of Sciences. [b]Graduate School of Life and Environmental Sciences, Osaka Prefecture University. [c]Department of Pharmaceutical Sciences, Kinki University. [d]Graduate School of Pharmaceutical Sciences, Kyoto University.*
E-mail: sekiguchi07@b.s.osakafu-u.ac.jp

Protein kinase CK2alpha is a highly pleiotropic serine/threonine protein kinase. CK2alpha plays important roles in cell growth, proliferation, and survival, while it is highly expressed in a wide variety of tumors.(1) Furthermore, CK2alpha is a target protein for glomerulo nephritis (GN) therapy, because an administration of either anitisense oligodeoxynucleotide against CK2alpha or low molecular weight CK2alpha-specific inhibitors effectively prevents the progression of renal pathology in the rat GN models. (2)
To design a novel and potent CK2alpha inhibitor, we determined four X-ray crystal structures of CK2alpha-inhibitor complexes (cc-04791, cc-04820, apigenin, ellagic acid), and measured enzyme kinetic parameters using ITC (Isothermal Titration Calorimetry) for the respective

inhibitors. Thermodynamic data, specifically enthalpy (ΔH) and entropy (ΔS), reveal the forces that drive complex formation. Furthermore, binding affinity - K_d in range of millimolar to nanomolar is a powerful information for drug design targeting highly homologous kinases. Supported with computational analysis, these data show the specific contributions of some important residues in ligand-binding, and lead to design a potent inhibitor.



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Keywords: CK2; kinase inhibitor; drug design

FA1-MS07-P11

Structural Characterization of Human Glutathione Transferase A1-1 in Complex with the Anti-cancer Drug Chlorambucil. Lykourgos Chiniadis[a], Kostas Bethanis[a], Nikos Labrou[b], Irene Axarli[b], Katholiki Skopelitou[b], Michael Karpusas[a]. [a]*Physics Lab., Department of Science, Agricultural University of Athens.* [b]*Lab. of Enzyme Technology, Department of Agricultural Biotechnology, Agricultural University of Athens.*
E-mail: kbeth@aua.gr

The glutathione transferases (GSTs) are detoxification enzymes that protect the cell from a wide range of potentially harmful electrophilic compounds [1]. Although this action of GSTs protects the organism from harmful environmental toxins, it results also in neutralization of certain therapeutic drugs such as chlorambucil, an anti-cancer drug used to treat chronic lymphocytic leukemia (CLL) [2]. Design of GST inhibitors that mimic chlorambucil binding may be useful in improving the bioavailability of chlorambucil when they are co-administered with the drug. To enable structure-based design of such inhibitors, human GST A1-1 was crystallized in the presence of glutathione and chlorambucil and its structure was determined at 2.3 Å resolution. Chlorambucil is observed to form a conjugate with glutathione, adopting a conformation different from the one observed in the structure of GST P1-1 and to induce local conformational changes in nearby protein residues. In addition it reacts with the only cysteine residue of the enzyme, in agreement with biochemical evidence.

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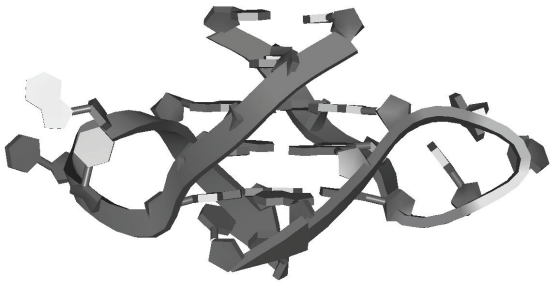
Keywords: glutathione transferase; anticancer drugs; crystallographic structure determination

FA1-MS07-P12

Targeting Telomeric RNA Quadruplexes. Gavin Collie[a], Stephen Neidle[a], Gary Parkinson[a]. [a]*CRUK Biomolecular Structure Group, The School of Pharmacy, London, UK.*
E-mail: gavin.collie@pharmacy.ac.uk

Following the discovery that mammalian telomeres are transcribed into telomeric-repeat containing RNA [1],[2], there has been a move to determine the role these molecules play in telomere regulation. We report here the first crystal structure of a telomeric RNA G-quadruplex, providing atomic-resolution insights into RNA-quadruplex folding. The structure, formed from the sequence r(U_{Br}AGGGUUAGGGU), folds as a bimolecular, parallel stranded G-quadruplex with linking propeller-type external loops, a topology previously observed for the equivalent telomeric DNA sequence [3].
As telomeric DNA G-quadruplexes are well established targets for small molecule anti-cancer therapeutics, it is reasonable to consider telomeric RNA G-quadruplexes as potential targets too. The structure reported here provides the basis for computer aided drug design, and will hopefully allow the differences between RNA and DNA G-quadruplexes to be identified and exploited for improved specificity of quadruplex-interacting ligands. These issues will be addressed and the structural basis for drug design explored.



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Keywords: RNA structure; anticancer drug structural study; drug targets