In both crystals of X:C and X:T, two dodecamers are associated to form a right-handed double helix with B-form conformation similar to those of the unmodified duplexes. The carboxymethyl groups of the damaged nucleotides are protruded into the major groove of the duplex suggesting that carboxy-methylation has no significant effects on the DNA conformation. In the X:C duplex, X and its complementary C base form a pair to each other through the two hydrogen bonds, $N^1(X)\ldots N^4(C)$ and $N^2(X)\ldots N^3(C)$, so that the two bases are displaced in different directions, X toward the major groove side and C toward the minor groove side. The wobbling directions are reversed from those found frequently in G:T pairs. In addition, this pairing is further stabilized by an additional hydrogen bond between the carboxyl oxygen and the paired C amino group. In the X:T duplex, however, the X residue forms a pair with T in a Watson-Crick type geometry with propeller twisting to release the O…O interaction. A model building of DNA polymerase in complex with X-containing DNA has suggested that these pairing modes found in the present study are acceptable for incorporation of dCTP or dTTP opposite X by the polymerase. It implies that the X residues modified in a DNA template not only direct the incorporation of complementary dCTP but also allow the non-complementary dTTP to be incorporated into the newly synthesized DNA strand. Therefore, it can be concluded that the latter Watson-Crick type X:T pair formation induces GC-to-AT transition mutation of genes demonstrated by *in vitro* and *in vivo* experiments, as an origin of increased risk of gastrointestinal cancer.

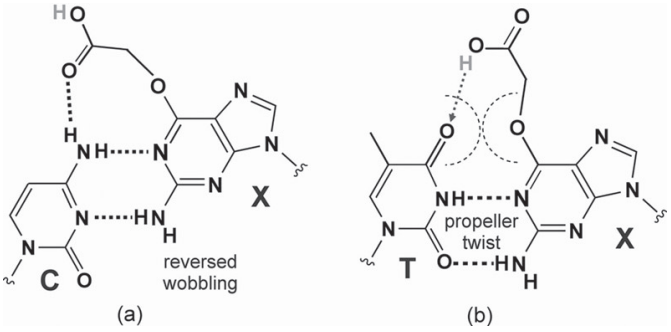

Fig. 1. Two pairing modes found in X:C(a) and X:T(b)

Keywords: crystal structure, damaged DNA, mutagenesis

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Crystal structure of the human thioredoxin reductase - thioredoxin complex implicates movement of the C-terminal redox center by 20 Å upon catalysis

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We present the first crystal structure of human TrxR1 (hTrxR) in complex with its substrate thioredoxin (Trx).

The human thioredoxin system comprises the homodimeric flavoenzyme thioredoxin reductase, its characteristic substrate thioredoxin and NADPH. TrxR is crucially involved in the regulation of cellular redox reactions, growth and differentiation. Its importance in various diseases renders TrxR1 a highly interesting drug target. During catalysis electrons are transferred from the cofactor NADPH to FAD, then to the N-terminal active site cysteines and from there to the C-terminal active site to be finally delivered to Trx at the molecule´s surface. We used X-ray crystallography to depict crucial conformations of the TrxR carboxyterminal amino acid chain at different stages in the catalytic cycle of the enzyme. In the complex structure the C-terminal redox center is found about 20 Å apart from the N-terminal redox center. Our structure and the analysis of hTrxR1 mutants shows that the enzyme recruits a swinging C-terminal arm for electron transport to its substrates, which is stabilized by a guiding bar for controlled transfer. Furthermore, essential residues of the interface region were characterized both structurally and functionally.

The three-dimensional structure of the hTrxR1-hTrx1 complex provides an important template for future drug design, and contributes to our understanding of redox regulatory processes in eukaryotes.

[1] K. Fritz-Wolf, S.Kehr , M. Stumpf, S. Rahlfs, K. Becker. Revised manuscript has been submitted to Nature communications (28.3.2011)

Keywords: complex, mobility, redox biology

MS16.P05

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Ligand Efficieny Indices as a navigation tool in the transthyretin protein chemico-biological space to find new amyloidogenic inhibitors

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We have previously reported the design and synthesis of ligands that stabilize Transthyretin protein (TTR) [1] in order to obtain therapeutically active compounds for Familial Amyloid Polyneuropathy (FAP). We are hereby reporting a drug design strategy to optimize these ligands to target Familial Amyloid Cardiomyopathy (FAC). The strategy comprises: i) a SAR analyses of the ligands described previously for the TTR tetramer, classified in chemical classes and mapping them in Chemico-Biological Space (CBS) using Ligand Efficiency Indices (LEIs)[2]; ii) optimization through docking in the TTR tetramer three-dimensional structure model; and iii) improvement of physicochemical/pharmacokinetic/selectivity properties.

We have focused in the optimization of TTR amyloid inhibitors exploring new methods to guide the proposed drug discovery strategy. Our approach is based on using Ligand Efficiency Indices (LEIs) [2], [3], [4] to navigate and evaluate the efficiency of the existing TTR ligands reported on the Protein Data Bank, combining a binding efficiency index (BEI) [4], based on the measured binding affinity related to the Molecular Weight (MW) of each compound, with a surface efficiency index (SEI) based on Polar Surface Area (PSA). We will illustrate the use of these indices, combining three crucial variables (potency, MW and PSA) in a 2D graphical representation, to perform a retrospective mapping of SAR data for a current TTR inhibitors database, taking as starting point of the analysis a good crystallographic ligand (iododiflunisal). We will also demonstrate how LEIs can be used for prospective strategies of optimization and drug design efforts for new TTR inhibitors [5].

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Keywords: transthyretin, amyloid, chemico-biological space.

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Structural basis for inhibition of interferon alpha signaling pathway and its therapeutic potential in SLE patients

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Increasing evidences suggest that the type I interferon (IFN) plays a critical role in the etiopathogenesis of systemic lupus erythematosus (SLE), which makes it a promising therapeutic target for the treatment of the disease. By screening a large size non-immune human antibody library, we have developed a human single-chain antibody (ScFv) AIFNα1bScFv01 and corresponding whole antibody AIFNα1bIgG01, that recognizes recombinant human interferon alpha1b (hIFNα1b) with high specificity and high affinity. The IgG antibody can down-regulate the expression of *ISG15* and *IFIT-1* induced by either recombinant hIFNα1b or naive IFN-α presented in SLE patient's sera. The crystal structure of AIFNα1bScFv01-hIFNα1b complex solved to 2.8 Å resolution reveals that both Pro26-Gln40 region in loop AB and Glu147-Arg150 region in helice E of hIFNα1b contribute to binding with AIFNα1bScFv01. Four residues of above two regions (Leu30, Asp32, Asp35 and Arg150) are critical for the formation of antigen-antibody complexes. AIFNα1bScFv01 shares partial epitopes of IFNα1b with its receptor IFNAR2. AIFNα1bIgG01 has a much higher affinity for IFNα1b than IFNAR2 (K_D = 0.747 nM versus 100 nM), making it unavailable for binding to IFNAR2 and preventing the activation of IFN-α-mediated signaling pathway. Thus, AIFNα1bIgG01 exhibits its neutralizing activity through competition with IFNRA2 to bind with IFN-α. Our results highlight the potential use of the human antibody for modulating the activity of IFN-α in SLE.

Keywords: SLE, IFNα, ScFv antibody

MS16.P07

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Structure of peptide inhibitor of human islet amyloid polypeptide fibrillization

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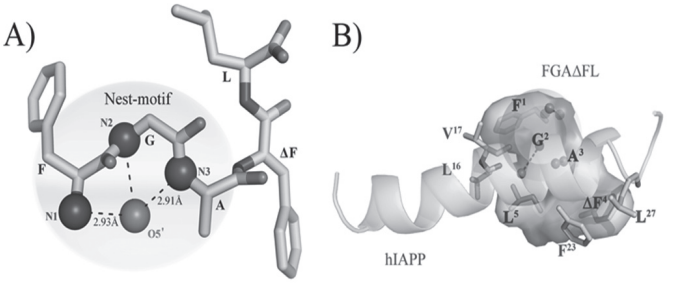
Type-2 diabetes mellitus (T2DM) accounts for more than 90% of all diabetes worldwide. Over 100 million people worldwide have T2DM, and the prevalence is increasing dramatically in both the developed and developing countries. Amyloid deposits have been observed in a vast majority of the T2DM patients and these are primarily on account of misfolding and aggregation into fibrils of human islet amyloid polypeptide (hIAPP), a 37 residue endocrine hormone secreted by pancreatic *β*-cells. It has been suggested that intermediates produced in the process of fibrillization are cytotoxic to insulin producing *β*-cells. Hence, the inhibition of misfolding/fibrillization of hIAPP could be a possible strategy to mitigate T2DM. The misfolding of hIAPP involves structural transition from its native state (coil and/or helical and/or transient helical conformation) to *β*-sheet conformation. We have targeted hIAPP fibrillization by designing short peptides containing the helix inducing *α,β*-dehydrophenylalanine (ΔPhe or ΔF) amino acid and the fibrillization inhibition was monitored by thioflavin-T assay and electron microscopy. We find that the short peptides inhibit fibrillization without any cytotoxic effect as tested on RIN4fm pancreatic cell line. Of these, the penta-peptide, FGAΔFL is the most effective inhibitor of hIAPP fibrillization. We successfully crystallized the penta-peptide and solved its 3D structure at atomic resolution using direct methods. Molecular conformation of the peptide reveals the occurrence of a nest-motif (Fig. A) involving the stretch FGA in the penta-peptide and a type-I *β*-turn. To gain structural understanding and visualize the probable interactions of the hIAPP with FGAΔFL, molecular docking studies were performed using AutoDock4. Here, we considered the penta-peptide as receptor and $hIAPP_{6-30}$ (PDB: 2KB8) as ligand. The best ligand pose was selected from the cluster with the highest occurrence and the lowest binding energy (-6.41 kcal/mol). The interactions stabilizing FGAΔFL-hIAPP complex, are nest-motif interactions, hydrophobic interactions and aromatic interactions (Fig. B). We propose, on the basis of FGAΔFL crystal structure and molecular docking, that the penta-peptide binds to the helical conformation of hIAPP which is considered as transient in nature and/or preferred in membranous environment. Here, the penta-peptide binds at the C-terminal of helical $hIAPP_{6-30}$, stabilizes the helical conformation and makes the transition from alpha to beta structure unfavourable, thereby curtailing the fibrillization process. Thus, the crystal structure of the penta-peptide inhibitor together with computational docking studies provides an atomic level picture of the possible mechanism by which the penta-peptide manifests its fibrillization inhibition activity. Further studies are underway in our laboratories to develop even more potent inhibitors of hIAPP fibrillization and the details will be presented.



Keywords: diabetes, amyloid, inhibitor

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Studies of nucleotide metabolism from blood fluke *Schistosoma mansoni*

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