

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<sup>1</sup>(X)...N<sup>4</sup>(C) and N<sup>2</sup>(X)...N<sup>3</sup>(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.

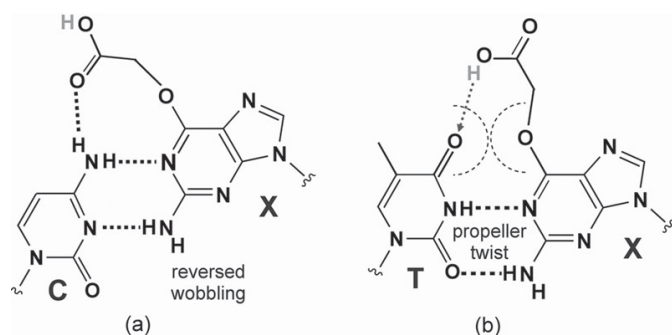


Fig. 1. Two pairing modes found in X:C(a) and X:T(b)

**Keywords:** crystal structure, damaged DNA, mutagenesis

### MS16.P04

*Acta Cryst.* (2011) A67, C287

**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

*Acta Cryst.* (2011) A67, C287-C288

**Ligand Efficiency Indices as a navigation tool in the transthyretin protein chemo-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 Chemo-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].

[1] T. Mairal, J. Nieto, M. Pinto, M.R. Almeida, L. Gales, A. Ballesteros, M.J. Saraiva, A.M. Damas, A. Planas, G. Arsequell, G. Valencia, et al., *PLoS ONE*,