s8a.m6.p7.la **Guanine-specific binding at an intercalated DNA junction.** J.R. Hobbs (a), J.H. Thorpe (a), W.A. Denny (b), P. Charlton (c) and C.J. Cardin (a) (corresponding author) (*a) Department of Chemistry, The University of Reading, Whiteknights, Reading RG6 6AD, UK. (b) Auckland Cancer Society Research Centre, Faculty of Medicine and Health Science, The University of Auckland, Private bag 92109, Auckland, New Zealand. (c) Xenova plc, 240 Bath Road, Slough, UK.*
Keywords: proteins, nucleic acids.

Some DNA-intercalating tricyclic carboxamides have the unusual ability [1] to poison both topoisomerase I and topoisomerase II [2], the structurally diverse enzymes that generate transient single or double strand breaks in the DNA phosphodiester backbone to allow the passage of one or two DNA strands during replication [3]. The crystal structure of an acridine-4-carboxamide with the DNA sequence CG(5BrU)ACG reveals a novel quadruplex-like intercalation cavity. The drug/DNA complex was crystallised in the presence of Co^{2+} ions, and was solved by MAD phasing at 2.0 Å and refined with SHELXL to R 19.5%.

In this complex two CG base pairs are linked by G2/G12 N2-N3 hydrogen bonds to form the base (and roof, by symmetry) of the cavity. One of these base pairs (C1/G12) is formed by a Holliday junction-like strand exchange of the terminal C1, so that the overall architecture is two such linked cavities. The DNA backbone conformation linking the cavities resembles that of the Holliday junction [4], with a C3'-*endo* sugar conformation (δ 78°) and a χ angle of -155° at G2 of the junction. The Co^{2+} ions cause unpairing at the other end of the duplex, and a *trans* Co^{2+} ion links two guanine residues through the N7 position of G6; a second Co^{2+} ion is bound to G8. There is no direct association of either with the junction. The carboxamide sidechain of the drug binds specifically to guanine in the major groove, with a preference for the anomalous G12, so that the drug is hemi-intercalated into this strand. The Holliday junction is known to generate a high affinity binding site for intercalators [5], but no such structure has been crystallographically characterised to date.

We have previously shown [6] that related 9-aminoacridinecarboxamides (topoisomerase II poisons) can intercalate into duplex DNA, with the carboxamide side chain oriented by H-bonding to the cationic ring nitrogen of the acridine to lie in the major groove and specifically bind to adjacent guanines.

This structure suggests a plausible model for the interaction of this class of compound with topoisomerases, that may contribute to their unusual dual topoisomerase poisoning ability and their functionally distinct mode of action. The hemi-intercalative binding seen here suggests a mode of binding where the phosphotyrosine linkage in the trapped cleavable complex would take the place of the Holliday junction-like feature seen in the above complex.

[1] Malonne, H and Atassi, G., *Anti-Cancer Drugs* 1997, *8,* 811-822.
[2] Denny, W.A., *Exp. Opin. Inv. Drugs* 1997, 6, 1845-1851.
[3] Feinberg, H, Lima, C.D. and Mondragon, A., *Nature Structural Biology* 1999, *6*, 918-922 and references therein .
[4] Ortiz-Lombardia, M., Gonzales, A., Eritja, R., Aymami, J., Azorin, F., and Coll, M., *Nature Structural Biology* 1999, *6*, 913-918.
[5] Lilley, D.M.J., in 'DNA-Protein: Structural Interactions', IRL Press 1995, p. 127, and refs therein.
[6] Todd, A.K., Adams, A., Thorpe, J.H., Denny, W.A., Wakelin, L.P.G., and Cardin, C.J,, *J. Med Chem.* 1999, *42*, 536-540.

s8a.m6.p8.la **The High Resolution Crystal Structure of the Nucleosome Core Particle: Sequence-Dependent DNA-Bending and Plasticity of Histone-DNA Binding.** C.A. Davey and T.J. Richmond, *Institut für Molekularbiologie und Biophysik ETHZ, ETH-Hönggerberg, CH-8093 Zürich, Switzerland.*
Keywords: nucleosome, histone, DNA-bending.

The crystal structure of the nucleosome core particle containing a 147 base pair (bp) DNA (NCP-147) has been solved at 1.9 Å resolution and refined to an R-value of 20.8 % (R_{free}=27.5%). The weakly diffracting NCP crystals necessitated merging of data from 44 crystals collected at an intense synchrotron source to yield a complete data set at this resolution. The DNA of the NCP-147 is significantly better ordered than previous constructs[1,2], which for the first time has allowed detailed elucidation of the conformational parameters and solvent structure of nucleosomal DNA and full characterization of the direct and water-mediated histone-DNA contacts. The DNA of the NCP is not bent uniformly, but rather displays a variety of context-specific effects relating to double-helix orientation with respect to histone-octamer, di-nucleotide step identity, as well as more distant sequence-environment. Structural analysis has revealed the general mechanism for DNA-wrapping and provided insight towards the basis of sequence-dependent positioning and stability. Furthermore, in conjunction with the apparent plasticity observed for histone binding of identical sequences and the DNA distortions present in two NCP-constructs containing different 146 bp DNAs[1,2], we propose a model for histone octamer movement along the DNA superhelix.

[1] Luger, K., Mäder, A.W., Richmond, R.K., Sargent, D.F., and Richmond, T.J. 1997. Crystal structure of the nucleosome core particle at 2.8 Å resolution. *Nature.* 389: 251-260.
[2] Luger, K., Mäder, A.W., Sargent, D.F., Richmond, T.J. 1998. The atomic structure of chromatin's nucleosome core particle at 2 Å resolution. *ESRF Newsletter.* 31: 9-11.