A wide range of minor groove binding ligands (MGBLs) with good sequence discrimination ability are of interest as potential therapeutic agents in variety of human diseases such as cancer, along with anti-bacterial and/or anti-parasitic activities. These MGBLs are highly selective to A:T base pairs of the minor groove of the DNA. Some of these compounds are in phase III clinical trials while some are currently in use for their veterinary applications.

Nucleic acids require structured water molecules in order to maintain their stability, polymorphism and flexibility of the duplex DNA. The binding of ligands into the minor groove of DNA involves the displacement of the native (drug-free) structured water molecules. These ligands have been studied extensively over the last two decades using a number of methods. However, for many of these systems understanding regarding water interactions and protonation states of the DNA-ligand complex and components remains unclear. This critical information is important for understanding the stability and recognition of DNA ligand complexes. Crystallographic methods have been used to determine the molecular structure of small molecules bound to DNA sequences, in order to better understand the details of molecular recognition by DNA.

Some of the MGBLs have shown to be effective inhibitors of a number of minor and major groove binding protein-DNA interactions (e.g. OTF 1, Antp HD, HMG-A2, etc.) [2]. Studies have been done with major groove binding transcription factor NF-kB which will add additional detail towards the biological significance and activity for the MGBLs. In this project we aim to build a library of information relating drug-DNA-water interactions to sequence specificity and drug design using X-ray crystallography as well as kinetics (e.g. from SPR) data and gel shift assays. This information is valuable for rational drug design in future.


Keywords: crystallography, DNA, drug

**MS16.P02**


**Specificity and efficiency in activity of anti-HIV actinohivin for sugar binding**

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In order to overcome the present multi-drug resistance problem in treating HIV/AIDS pandemic, a new lectin actinohivin (AH) was found to exhibit a potent anti-HIV activity through binding the high-mannose type glycans (HMTG) which are bound to gp120 of HIV. X-ray analyses of AH and its complex with (1,2)-mannobiose (M2) which is the terminal end of three branches (D1, D2 and D3) of HMTG revealed that AH is composed of tandem repeated three structural modules associated with a pseudo three-fold symmetry[1]. In each module, M2 is accommodated through the specific hydrogen bonds with D, Y and N residues equivalent between the three modules. In this study, the structural features were revised, as seen in Fig. 1(a), based on which essential residues for specific inter-actions were confirmed by mutation experiments[2]. In addition, dimerization effect of AH on anti-HIV activity was examined by increasing the number of HMTG-binding sites in a molecule, because gp120 is covered with many HMTGs, as seen in Fig. 1(b). Several dimeric AH (AH2) derivatives were prepared and their anti-syncytium formation and anti-HIV activities were evaluated.

D15, Y23, L25, N28 and Y32 (in module 1) and the corresponding residues in the other modules were identified to be essential for AH activity. Among them, D, Y and N residues participate in recognition of M2. By superimposing the three terminal ends of D1 branches onto the bound M2, a model of gp120 bound to several AHs has been constructed. This model suggests that the AH affinity to gp120 is amplified in col-laborative binding when it forms a dimer as a cluster. Among several AH2s (see Fig. 1(c)), those linked by a head-to-tail fashion showed higher (20 folds at maximum) in anti-syncytium formation activity and (2–30 folds) in anti-HIV activity than those of AH monomer. These activities vary depending on the linker sequence. Therefore, the anti-HIV activity of AH can be improved as a microbicide to prevent HIV transmission.

Keywords: X-ray structure, anti-HIV activity, actinohivin

**MS16.P03**


**Crystal structures of DNA containing X relevant to gastrointestinal cancer**

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Red meat stimulates endogenous intestinal N-nitrosation of glycine and its derivatives that can induce DNA mutations by reacting with DNA to form O-carboxymethylguanine (hereafter X) which is associated with increased risk of gastrointestinal cancer. In order to obtain insights into the pairing geometry of DNA duplexes containing X (modified or damaged nucleotide) and to further understand its biological implications, we have determined the crystal structures of two DNA dodecamers with the sequences d(CGCGAATTCGCG) (hereafter X:C) and d(CGCGAATTCGCG) (hereafter X:T) by X-ray analyses.

![Image](image_url)