located at the interface between A-band and M-line. It has been shown by Centner et al. [2] that MURF-1, a member of the RING finger proteins, binds to the two Ig-domains A168 and A169 in proximity to the kinase. Thus, its binding might be involved in the regulation of titin kinase. The structure of this tandem Ig domain has been solved. Ig domains, also in titin, are involved in many protein-protein interactions and this interconnects titin with other muscle proteins and pathways. Here, we will present new structures near titin kinase and from a downstream signaling pathway of titin kinase (Gautel et al., unpublished data).

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Keywords: muscle proteins, immunoglobulin structure, protein interaction

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Carving a Beanstalk: the Structure of ΔS2 from Human Myosin II

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S2 is the flexible coiled coil that connects light meromyosin to the N-terminal motor domain of myosin II. S2 interacts with other proteins of thick filament and can lead to fatal familial hypertrophy (FFH) when mutated. We have determined the structure of a 126-residue N-terminal fragment of S2 in two different crystal forms. The WT protein diffracted to 2.7 Å resolution in a $C222_1$ cell of a=40, b=46, c=373 Å. Cryo-protection was difficult and data could only be reduced in XDS. Phases were derived from 2-λ MAD data collected from a mercury derivative. Only SHELXD with SHARP generated interpretable electron density maps. The protein is a parallel dimeric coiled coil of 187 Å lying stretched out along the c-axis.

The FFH-associated E924K-mutant crystallised in P1 with a=40, b=42, c=98 Å; α=91, β=93, c=107°. Molecular replacement was not successful and crystals were highly radiation sensitive, giving non-traceable electron density maps when anomalous phasing from SeMet-labelled or heavy-atom-soaked crystals was employed. It was, however, possible to locate 4 mercury atoms from anomalous data. These co-ordinates together with the position of cysteine residues in the WT structure were used in a semi-brute-force approach to derive the relative orientation of two coiled coils in the asymmetric unit. The model was refined to 2.5 Å with R=27.3 and R_{free}=34.9 %. The two extended coiled coils run anti-parallel with neighbouring molecules lying head-to-tail such that they form quasi-endless filaments.

Keywords: coiled coil proteins, MAD, brute force

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Preliminary X-ray Analysis of RNA Oligomers Containing CUG Repeats

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Human genome contains so many different types of repetitive sequences. Some of them are tandem repeats of trinucleotides, and their unusual expansions cause genetic diseases including type 1 myotonic dystrophy (DM1) and Huntington's disease (HD). The unit sequence for DM1 is CTG in the 3'-untranslated region of the myotonic dystrophy protein kinase (DMPK) gene, and that for HD is CAG in the ORF of exon-1 of the HD gene.

The two complementary sequences may induce increase or decrease of the repeats during DNA replication or repair of DNA. The direct origin of DM1 is, however, the transcribed RNA fragments with CUG repeats, which forms a specific structure and inhibits other protein syntheses. In the present study, structural versatility of such DNA and RNA fragments has been examined.

In the case of $(CUG)_n$, native PAGEs show that the even repeat (n=even number) is more stable than the odd repeat. This may be ascribed to the structural difference at the hairpin head. The PAGEs also suggest that duplex formation is dependent on coexisting cationic species and their concentration. Crystal data of $(CUG)_6$ are *a*=*b*=39.6 and *c*=141.0Å, space group *R*32 and one oligomer in the asymmetric unit. An approximate crystal structure has been solved by molecular replacement techniques at 1.9 Å resolution and shows that the fragment forms a duplex similar to an A-form RNA.

Keywords: RNA structure, X-ray analysis, genetic disease

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Crystal Structures of Two Minor Groove Binders Complexed with d(CGCGAATTCGCG)$_2$

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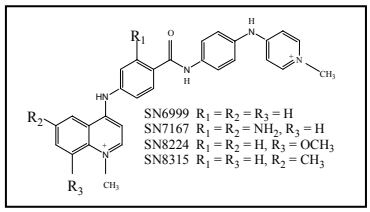
Quinolinium quaternary salts (QQS) are anticancer drugs [1] and bind reversibly in the minor groove of AT rich sites in DNA. The crystal structures of SN6999 [2] and SN7167 [3] complexed with CGC[e^{6}G]AATTCGCG and CGCGAATTCGCG respectively have been solved previously at a resolution of about 2.5 Å. We have recently solved the structures of two new QQS compounds, SN8224 and SN8315, complexed with the dodecamer CGCGAATTCGCG. These two structures are at higher resolution (1.6 and 1.8 Å) and crystallise in similar conditions. We are able to compare the four complex structures and reach conclusions about minor groove requirements for QQS compounds bound to unmodified DNA.



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Keywords: DNA, minor groove binders, anticancer drugs

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A new Highly Symmetric DNA G-4 Quadruplex/ Drug Structure

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Guanine-rich DNA telomeres occur at the 3' ends of chromosomes. They can associate into four-stranded assemblies known as stacked G-4 quadruplexes. It has been found that the enzyme telomerase protects tumour cells but not normal cells from telomere loss during replication. Telomerase has therefore become an exciting new target for anti-cancer drug design. Small molecules which can stabilise the formation of G-4 quadruplexes may inhibit telomerase activity.

We recently determined the crystal structure of the daunomycin complex with the telomeric sequence d(TGGGGT) [1]. We now report the 1.08 Å structure of daunomycin complexed to d(GGGG). The crystals are tetragonal, space group I4, a = b = 40.21, c = 49.83 Å. The final R is 16.1%. The asymmetric unit contains 2 independent strands of d(GGGG), 4 drug molecules, and eight Na and 2 Mg cations. The crystallographic 4-fold axis generates the biological unit which consists of 2 high-symmetry G-4 quadruplexes between which are 4 layers of daunomycin molecules with 4 daunomycins per layer.