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

Patrycja D. Pytel[a], George R. Clark[a], Christopher J. Squire[b], [a]*Department of Chemistry, The University of Auckland, Auckland, New Zealand.* [b]*School of Biological Sciences, The University of Auckland, Auckland, New Zealand.* E-mail: p.pytel@auckland.ac.nz

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.

[1] Clark G.R., Pytel P.D., Squire C.J, Neidle S., *J. Amer. Chem. Soc.*, 2003, **125(14)**, 4066-4067.

Keywords: G4-quadruplexes, DNA-drug interactions, telomeres