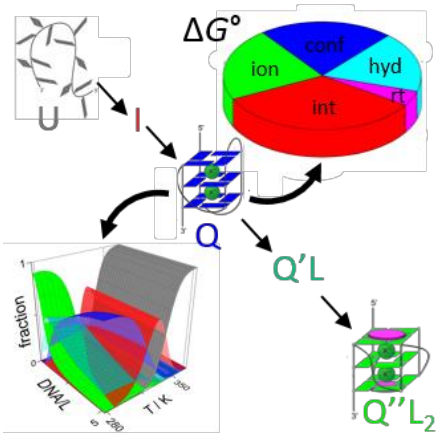
What drives DNA folding into G-quadruplex structures and their recognition by ligands?

Jurij Lah

Faculty of chemistry and chemical technology, University of Ljubljana, Večna pot 113, 1000 Ljubljana, Slovenia, e-mail: jurij.lah@fkkt.uni-lj.si

Guanine rich DNA sequences can fold into complex structures called G-quadruplexes in which four guanines form square planar structure stabilized by eight Hoogsteen hydrogen bonds, stacking interactions between the neighboring G-quartets and coordinated cations. They can be found in telomeres where they decrease the activity of the enzyme telomerase, which is responsible for maintaining the length of telomeres and is involved in around 85% of all cancers [1]. Formation of stable G-quadruplexes in the region of the telomeric single-stranded overhangs has been found to inhibit telomerase activity. Therefore, telomeric G-quadruplexes are emerging as promising targets for anticancer agents able to inhibit the telomerase activity by binding to the G-quadruplex structures.

Here we present our study of a human telomeric (ht) DNA fragment folding/unfolding [2] and its recognition by ht-quadruplex specific and non-specific ligands. The mechanism of folding and ligand binding was characterized thermodynamically and structurally using calorimetric (DSC, ITC) and spectroscopic (CD, fluorescence) methods and native gel electrophoresis. We will demonstrate how the global model analysis of a wide variety of experimental data enables the description of ht-DNA fragment behavior in aqueous solution at various conditions (temperature, salt concentration, ligand concentration) and characterization of thermodynamic forces driving the ht-DNA fragment folding and binding (Figure).



[1] Neidle S.; Balasubramanian S. *Quadruplex Nucleic Acids*, **2006**, Cambridge.
[2] Bončina, M.; Lah, J.; Prislan, I.; Vesnaver, G. *J. Am. Chem. Soc.* **2012**, *134*, 9657-9663.