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Guanine quadruplexes : formation, stability and interaction

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Guanine quadruplexes (G4) are non-canonical four-stranded nucleic acid structures formed by guanine-rich DNA and RNA sequences. Theses polymorphic structures are built from the stacking of several G-quartets and could be involved in many fields, in biotechnology as well as in nanotechnology. The study of modified tetramolecular G4 presented in this manuscript participated to the understanding of tetramolecular G4 formation. Especially, we showed that the insertion of 8-methyl-2'-deoxyguanosine at the 5'-end of the sequence accelerate G4 formation and increase its stability. Besides, we demonstrate here that short guanine rich L-DNA strands (mirror image of natural DNA) form a tetramolecular G4 with the same properties than their enantiomer, but with opposite chirality. The study revealed also self-exclusion between two enantiomers (D- and L- form), showing the controlled parallel self-assembly of different G-rich strands. This work introduced also a simple and stable system to observe tetramolecular antiparallel G4 formation, called "synaptic DNA", into a DNA origami nanostructure.

In vivo, such structures appear to be implicated in genome dynamics, and especially at telomeres. During this thesis, we dedicated a study to the comparison of G4 folding and stability of known telomeric sequences from different organisms. The present study allowed enriching the dataset necessary to build and refine algorithms predicting G4 stability. Last but not least, we developed a G4 ligand screening method onto 96-well plates allowing the comparison of different biological relevant sequences. The G4 stabilisation by specific ligands in some genome regions may prevent cancer cell proliferation, making it an attractive target for anticancer therapy.

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