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Biological relevance and targeting of *i*-motif DNA

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i-Motifs of DNA (hereafter, *i*-DNA), known *in vitro* for nearly three decades, are unusual, four-stranded structures, in which cytosines are intercalated *via* a stack of hemi-protonated C–C base pairs (CH^+:C) (Fig. 1A, B). Some of these structures have been well characterized *in vitro* and, because *i*-DNA may mirror other four-stranded G-rich structures (G-quadruplexes) present in gene promoters or at telomeres, their biological relevance is being investigated.

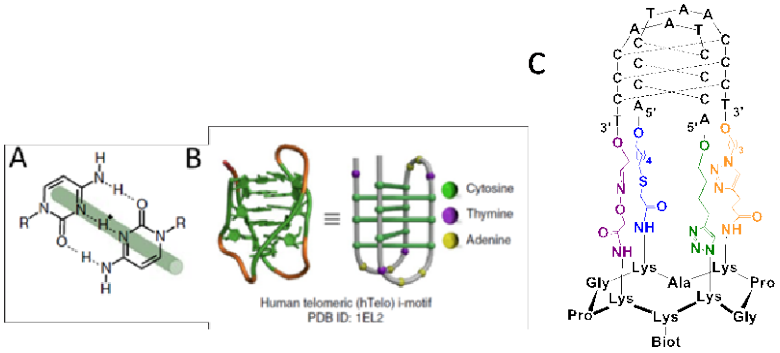

Figure 1. A/ Hemi-protonated C-C base pair. B/ Schematic structure of the telomeric i-DNA. C/ Structure of constrained i-motif

However, our knowledge about *i*-DNA biology is still limited: the main challenges in this regard being the strong pH dependency, flexibility, and polymorphism of *i*-DNA, that introduce potential bias into studies. In particular, low-pH conditions that are required for the formation of *i*-DNA can lead to the protonation of many ligands (including small molecules or proteins), strongly increasing their non-specific nucleic acid binding. In this context, we have developed a peptide-DNA conjugate (Fig. 1C) being able to fold into a stable *i*-motif at room temperature and, most importantly, at near-neutral pH.[1]

The stabilized mimic of the *i*-motif adopted by the telomeric sequence was used to study the interactions with already reported ligands (TMPyP4, mitoxantrone, IMC-48, berberine, *etc*) at physiologically relevant pH by Bio-Layer Interferometry (BLI) and CD. We demonstrated that none of the reported ligands were shown to discriminate between folded and unfolded *i*-motif structures.[2]

In conclusion, the constrained i-motif reveals to be a powerful tool for studying i-motif structure.

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2. Bonnet, H.; Morel, M.; Devaux, A.; Boissieras, J.; Granzhan, A.; Elias, B.; Lavergne, T.; Dejeu, J.; Defrancq, E. *Chem. Commun.* **2022**, *58*, 5116-5119. DOI : 10.1039/D2CC00836J

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