

The existence, prevalence and functional relevance of four-stranded nucleic acid structures (G-quadruplex-DNA/RNA) in human cells

Synopsis: Beyond the canonical duplex structure of DNA (so-called Watson-Crick duplex, dsDNA or B-DNA structure), nucleic acids can adopt locally and transiently a series of alternative structures comprising 2, 3 or 4 strands. Among these noncanonical (non-B-type) structures, the four-stranded G-quadruplex-DNA/RNA (or G4-DNA/-RNA, or G4) is at the heart of an intensive research effort aiming at both understanding when, where and why G4s fold in human cells, and deciphering the cellular consequences of this folding. To this end, the use of cell-permeable small molecules (or G4 ligands) has been pivotal: ligands can indeed perturb cellular equilibria in which G4s are involved, which provides readouts amenable to mechanistic interpretations. This approach, which fully abides by the very definition of chemical biology, will be discussed in this lecture: the development of a series of biomimetic G4 ligands will be presented and their use as molecular tools to gain insights into G4 biology highlighted. The roles that G4s play in normal/abnormal cell circuitries will be depicted and their relevance as genetic targets for therapeutic interventions in both cancers and age-related diseases disclosed.

Selected reviews: *RSC Chem. Biol.* **2021**, 2, 47; *Cell Chem. Biol.* **2021**, 28, 436; *Nucleic Acids Res.* **2022**, 50, 12636; *Acc. Chem. Res.* **2023**, 56, 350

Selected references: *J. Am. Chem. Soc.* **2021**, 143, 12567; *Nucleic Acids Res.* **2021**, 49, 10275; *Nat. Protoc.* **2022**, 17, 870; *JACS Au* **2022**, 2, 1588

Contacts: D. Monchaud, Institut de Chimie Moléculaire de Université de Bourgogne (ICMUB), CNRS UMR6302, 9, Avenue Alain Savary, 21078 Dijon, France ; david.monchaud@cnr.fr; <https://sites.google.com/site/monchaudchembiolab/>