Native mass spectrometry study of the displacement of proteins bound to DNA G-quadruplexes by small molecules

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G-quadruplexes (G4s) are nucleic acid structures made of stacked guanine quartets, four guanines interacting via hydrogen bonds. G4s are over-represented in key regions of the genome such as in promoters of oncogenes or in telomeres. When formed in gene promoters, it is proposed that the G4 would act as an obstacle for the replication of the gene by acting as a knot.

Many studies report the use of small molecules (called ligands, L) to stabilize G4s and affect these biological events. However, while G4:L interactions are often investigated, whether ligands are able or not to disrupt interactions between G4s and proteins (P) remain poorly studied.

We investigated G4:P interactions and ternary complexes like G4:P:L using native mass spectrometry (native MS). Thanks to advances in soft ionization methods, native MS has become an indispensable tool for the study of biomolecules and noncovalent biomolecule complexes. MS can provide unambiguous information about the stoichiometries of the complexes and their respective abundances. Quantification allows one to determine equilibrium constants.

We have developed a competition experiment in which some of the most potent G4 binders reported in the literature compete with a helicase, an enzyme that recognize G4s and unwind them. We found that these ligands, indeed, compete for the same G4 binding sites as the protein. Therefore, we confirm that they are potential anticancer drugs. Based on this principle, we have screened a chemical library for G4 ligands able to displace the bound protein.