

## Mass spectrometry for nucleic acids biophysics

Valérie Gabelica

ARNA Laboratory, Inserm & University of Bordeaux, France

[valerie.gabelica@inserm.fr](mailto:valerie.gabelica@inserm.fr)

There is now increasing evidence that specific nucleic acid structures modulate gene expression levels both at the transcriptional and at the translational level. In particular, G-quadruplex (G4) structures are attractive targets for anticancer strategies, since several studies showed that their stabilization by ligands caused proliferation arrest, telomere deprotection and changes in gene expression. Understanding the structure-function relationships in G4 DNA and RNA in order to target them requires innovative biophysical tools to probe the general and specific features of the structures adopted by a wide variety of sequences, their macromolecular assemblies, and their interactions with drugs.

Current biophysical assays for ligand binding to G-quadruplexes include melting assays, fluorescence displacement assays, and direct titrations monitored by spectrophotometry, surface plasmon resonance, or isothermal titration calorimetry. These in-solution methods however suffer from the fact that the signal reflects the weighted average contribution of all species simultaneously present.

This presentation will survey native mass spectrometry and ion mobility spectrometry approaches that can be used as biophysical tools to probe small molecule ligand interactions with G4 structures. We will also describe the fundamental principles underlying correct interpretation of mass spectrometry-derived data for biophysics. First, MS is uniquely well suited to detect and quantify G4-drug interactions in a direct binding assay. With mass and intensity measurement, one can characterize the binding affinity and specificity of ligands to a variety of targets. We will also highlight how some details, such as cation binding, can also give insight into nucleic acid folding, ligand binding mode, and ligand-induced changes in folding. Finally, ion mobility spectrometry is a key method for studying the conformational space of the nucleic acids, and ligand-induced conformational changes.