**Tracking Ligand Binding Kinetics with G-Quadruplex DNA**

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G-quadruplex DNA (GqDNA) structures are formed by guanine-rich DNA sequence in the presence of monovalent cations. These structures play vital roles in various biological processes, which contain specific binding sites for small molecules (ligands), enabling anti-cancer activities and gene regulation upon interacting with GqDNA within the cell. Understanding the kinetics of ligand interaction with GqDNA in cell-like crowded environments is paramount in biology and pharmacology, as it elucidates the influence of molecular crowders on the reaction rates governing these interactions. In this talk, I will discuss how using fluorescence correlation spectroscopy (FCS) and molecular dynamics (MD) simulations can track the kinetic steps of ligands’ binding/unbinding with GqDNA structures in the absence and presence of saccharide and EG/PEG crowders [1-5]. Experimental results indicate that saccharide and PEG crowders control the ligand binding kinetics with the GqDNA differently: Atomistic MD simulations on GqDNA/ligand in absence and presence of crowders reveal the critical role of electrostatic forces and long-lived water-mediated hydrogen-bond-bridges in stabilizing the ligand/GqDNA complex, which is significantly disrupted by the EG/PEG crowders, leading to the destabilization of the complex [1]. Unlike polysaccharide crowders, the EG/PEG crowders affect association and dissociation rates. Metadynamics simulations uncovered the rate-limiting steps that govern such kinetics of ligand/GqDNA interactions, matching well with the FCS results.

References:

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