Structure and Dynamics in Non-canonically H-Bonded RNAs

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We are investigating effects of salt conditions on structure in G-rich nucleic acids that are implicated in neurodegenerative diseases. We have observed frequency shifts using FTIR and confirmed structure change in short G-repeat sequences. Using 2D IR spectroscopy, we will examine vibrational coupling and ultrafast dynamics in these RNA complexes.

Guanine-rich nucleic acid sequences form tetrameric complexes termed G-quadruplexes or G-quads (Fig 1), which are prevalent in normal human genomes where they are involved in processes such as gene regulation. RNA G-quads have been implicated in neurodegenerative diseases where they are found in expansion regions of genes associated with conditions such as ALS.[1] These G-quads can form higher order structures that have a propensity to aggregate making them difficult to identify. 2D IR is appealing for this system because it can be used to study insoluble, disordered systems and is sensitive to sugar conformation and base pairing. We will establish a method and model system for characterization of G-quads and aggregates in G-repeat RNA sequences using 2D IR to probe the hydrogen bonding network of the systems. 2D IR spectra of short G-repeat sequences will be collected under varying salt conditions to probe the structural changes in each system. We have used electrophoretic methods to identify tetrameric structures in small RNA G-repeat model systems such as UG_4U, and we have also observed higher order aggregates in larger repeat sequences. We have observed a K^+-dependent shift in the FTIR spectrum of model G-repeat RNA sequences (Fig 1), and this shift is also seen in the more complex sequences which tend to aggregate. 2D IR has shown that nucleotide base vibrations are delocalized and the amount of delocalization greatly influences IR spectra.[2] The Hoogsteen base pairing exhibited by G-quads will give a 2D IR spectrum different from that of the Watson-Crick pairing.[3] We will also vary waiting times to examine hydrogen-bonding and metal chelate dynamics in these systems, which will help identify these structures in more complex, disease-related sequences.

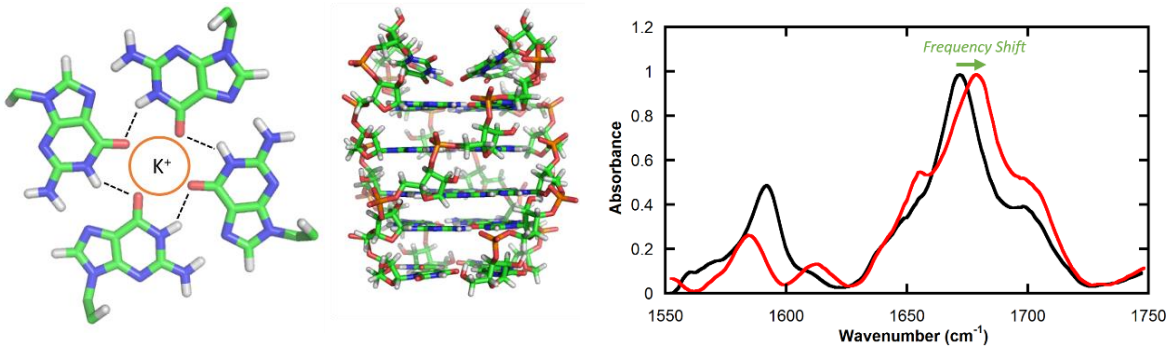

Figure 1- Single layer of G-quardruplex with K^+(left). Solution NMR Structure of UG_4U in a G-quadruplex structure (PDB ID: 1RAU) (middle). (right) Shift in frequency for UG_4U RNA sample in presence of K^+(red) and Li^+(black).

(1) Dodd, D. W.; Tomchick, D. R.; Corey, D. R.; Gagnon, K. T. *Biochemistry* **2016**.
(2) Peng, C. S.; Jones, K. C.; Tokmakoff, A. *J. Am. Chem. Soc.* **2011**, *133*, 15650.
(3) Greve, C.; Elsaesser, T. *The Journal of Physical Chemistry B* **2013**, *117*, 14009.