BCHM 421/422 – 2018/2019

Project #1 Outline: DNA's most well-known folding pattern is that of the double helix, but in the past 20 years, an intriguing folding motif called the 'guanine quadruplex' has emerged as a critical element in 'the life' of nucleic acid molecules. From replication, where a new molecule of DNA is born, to transcription, where the genetic information is read, on its way to proteins, to senescence, where the cell ages and finally dies, guanine quadruplexes are often transiently present.[1] Even RNAs are subject to this exotic structure. [2] But what are they? They are formed by the spontaneous gathering of groups of four guanines ('quartet') that hydrogen-bond to each other (Figure 1, middle), forming a flat, aromatic surface that likes to stack with another such quartet, forming a 'quadruplex' (Figure 1, right), helped by stabilizing metal ions.

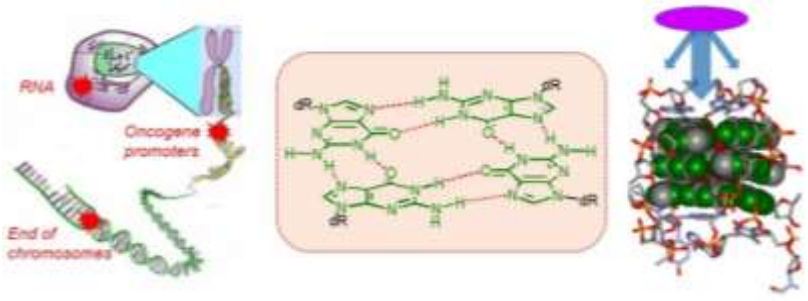

Figure 1: Location of quadruplexes in DNA (oncogene promoters, end of chromosomes), and RNA (cytoplasm); chemical structure of a guanine quartet; NMR structure of 3 quartets stacked into a guanine quadruplex (human end of chromosome sequence in Na^+ buffer). The purple oval and blue arrows: binding site for the proposed small molecules.

Among other roles, guanine quadruplexes (G4) are important in all aspects of cancer, but are also emerging as regulating elements in infections (*e.g.* HIV, Zika virus) and neurological disorders.

For all these reasons, forcing the fold of guanine quadruplexes, using ligands that stabilize these structures, is a very active field of research.[3,4] The Petitjean lab has just discovered a very simple family of ligands that vastly prefer guanine quadruplexes over duplex DNA (represented by the purple blob on Figure 1 right). This is important, as any such drug candidate would have to find its quadruplex target in a sea of duplex DNA (Figure 1 left). Now that we have a selective binder, we need to tune it so it turns off specific detrimental processes, such as tumour-inducing protein production, while leaving healthy pathways turned on.

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Project Title: Refining guanine quadruplex binders

Keywords (3-5):

1. **DNA targeting**
2. **Quadruplex**
3. **Oncogene silencing**
4. **Organic synthesis**
5. **Spectroscopies (UV-vis, fluorescence, NMR)**

Project Goals: This project deals with decorating guanine quadruplex binders with extra contact points aimed at distinguishing elements from 'bad' guanine quadruplexes (diagonal blue arrows in Figure 1 right). Priority will be given to the guanine quadruplexes found in the c-myc and c-kit oncogene promoters, and those found at the end of human chromosomes.

Experimental Approaches: The student will reinforce their practical skills in organic synthesis (including chemistry of important heterocycles, and peptide synthesis), and in analytical characterization of synthetic molecules (^{1}H and ^{13}C NMR, mass spectrometry). They will also be introduced to the characterization of the target DNA and RNA sequences (circular dichroism, ^{1}H NMR) and DNA and RNA binding studies (fluorescence, UV-vis, ^{1}H NMR and possibly crystallography).

References:

[1] P. Murat, S. Balasubramanian, *Curr. Opin. Genetics Dev.* **2014**, 25, 22–29.

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[3] S. Balasubramanian, L. H. Hurley, S. Neidle, *Nat. Rev. Drug Discov*. **2011**, 10, 261–275.

[4] A. De Cian, L. Lacroix, C. Douarre, N. Temime-Smaali, C. Trentesaux, J.-F. Riou, J.-L. Mergny, *Biochimie* **2008**, 90, 131–155.