DNA Quadruplexes & Applications to Telomeres
By
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Abstract:
DNA is prone to structural polymorphism: besides the famous double-helix, other structures, involving 3 or 4 strands may be formed. G-quadruplexes constitute an example of such unusual nucleic acids structures. They result from the hydrophobic stacking of several quartets; each quartet being a planar association of four guanines held together by 8 hydrogen bonds. Stable tetramolecular quadruplexes may be formed with short oligomers. The melting of these quadruplexes is kinetically irreversible, allowing us to study association and dissociation processes independently [1]. We analyzed the properties of parallel quadruplexes with a single thymine at the 5’ and 3’ extremities such as TG4T and TG5T, and sequence variants, in which each guanine of the central block was systematically substituted by a different base and promising base analogs have been identified [2].

Quadruplexes may find applications in areas ranging from nanotechnology (as nanodevices; [3]), biotechnology (as molecular beacons; [4]) to medicinal chemistry. Using a FRET assay [5], we have identified several series of G4 ligands [6]. Selectivity of these ligands towards G-quadruplexes was assessed by FRET competition experiments. Quadruplex ligands not only bind to preformed quadruplexes, but increase the association rate of these structures, acting as G4 chaperone agents [7] whereas some proteins can actively unwind quadruplexes [8]. We are currently trying to understand the rules that govern quadruplex stability [9].

Telomeres and telomerase represent, at least in theory, attractive targets for cancer therapy [10]. The 3’ G-rich telomeric overhang may adopt a G-quadruplex structure that blocks telomerase. We recently challenged the assumption that quadruplex ligands are telomerase inhibitors [11]. These molecules are actually more effective inhibitors of telomeric DNA amplification than extension by telomerase. We also demonstrate that the popular telomeric repeat amplification protocol (TRAP) is completely inappropriate for the determination of telomerase inhibition by quadruplex ligands [11]. Finally, these compounds may also target non-human telomeric overhangs, provided that a G-rich motif is present [12].


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Time: 11.00am to 12.00 noon
Venue: PAP Meeting Room (SBS B3n-19)