HIV LTR G-4 – G-quadruplexes in the HIV-1 genome: novel targets for the development of selective antiviral drugs

G-quadruplexes (G-4) are polymorphic nucleic acid structures identified in gene promoters where they act as transcription regulators. G-4s have been found in eukaryotic and prokaryotic organisms, while very little information is available on viruses. The applicant research group has recently shown that HIV-1, which integrates into the human chromosomes and exploits cellular factors to activate transcription, takes advantage of G-4-mediated transcription regulation. G-4 disruption stimulates promoter activity while G-4 stabilization by small molecules inhibits it, showing a striking parallelism between HIV-1 LTR and eukaryotic promoter G-4s. Preliminary results indicate that similar G-4 structures form also in the viral RNA genome before retrotranscription. Available G-4 ligands, developed as anticancer drugs targeting DNA G-4, recognize both viral and cellular G-4s. Therefore, they cannot be straightforwardly used as anti-HIV compounds. The aim of this project is to develop highly specific anti-HIV-1 drugs targeting LTR DNA and/or RNA G-4s, using both reversible G-4 ligands and G-4-selective alkylating/cleaving agents, triggered by external stimuli. These approaches will be taken: a) to increase selectivity by 1) screening of ligands against LTR G-4s to select the best hits among libraries of G-4 ligands; 2) conjugation of the most promising leads to modified nucleic acids complementing LTR G-4 loop/flanking regions, to deliver the drug to its target; b) to stabilize binding by conjugation of the ligands to 3) an alkylating/cleaving subunit, and 4) an activable moiety (such as quinone methides) that alkylates the target only once the drug has reached it. Physico-chemical, biomolecular, cellular and viral assays will be used to tests the compounds. This approach should deliver reversible and irreversible ligands that selectively inhibit viral transcription and/or reverse transcription, thus preventing virus production and/or integration into the host genome.

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