

THE MINIMAL PRIMARY STRUCTURES OF RNA APTAMERS SELECTED TO BIND HIV-1 REVERSE TRANSCRIPTASE

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ABSTRACT

Human Immunodeficiency Virus (HIV) reverse transcriptase (RT) is the most common molecular target of current HIV treatments. Oligonucleotide aptamers bind and inhibit the RNA- and DNA-dependent polymerization activities of HIV RT. Libraries consisting of aptamers including 32, 70 or 80 nucleotide variable regions were previously screened by Systematic Evolution of Ligands by Exponential Enrichment (SELEX) against RT. Roughly half of the resulting aptamers were represented by pseudoknots with well defined signature sequences (the Family I), but also additional pseudoknots with little sequence convergence (Family II), and non-pseudoknot aptamers (Family III).

Nucleic acid aptamers bind RT in the primer/template binding site. Aptamers are generally non-toxic and non-immunogenic molecules making them enticing drug prospects. Many aptamers inhibit DNA dependent DNA polymerization by RT from several phenotypically different recombinant viruses, but inhibition depends on a single amino acid mutation at position 277 for other aptamers. Aptamers that are un-reactive to the identity of this amino acid represent a group which may inhibit RT from other viruses as well.

In this work I present a set of aptamers with unknown secondary structure which in some cases inhibit polymerization activity by RT from two HIV subtypes with different polymorphisms at position 277. I identify the minimal primary structure containing a pseudoknot in many of these aptamers sequences. I present evidence that in at least one aptamer, the structure responsible for binding RT is not a pseudoknot, which is highly uncommon in RNA anti-RT aptamers. For at least one other aptamer I show that a pseudoknot is the important binding element, but binding is increased in the presence of additional flanking sequence.