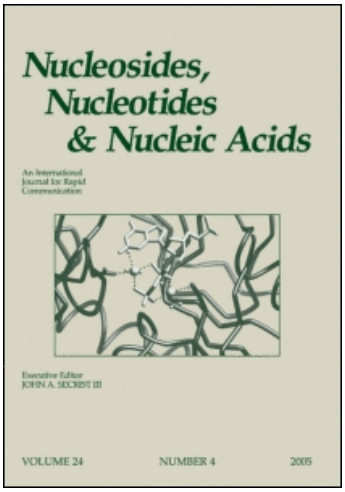

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INHIBITION OF HIV-1 INTEGRATION BY MONO- & BI-FUNCTIONALIZED TRIPLE HELIX FORMING OLIGONUCLEOTIDES

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ABSTRACT : HIV-1 DNA integration is carried out by integrase, a viral protein which binds to specific sequences located on both extremities of the HIV-1 DNA LTR. Inhibition of integration was observed with submicromolar concentrations of mono- or bi-functionalized 11-mer oligonucleotide-intercalators, which were designed to form an alternate strand triple helix with the U5 LTR end containing two adjacent purine tracts on opposite strands 5'-**GGAAAA**TCTCT-3'/3'-CCTTTT**AGAGA**-5'.

Integration of an HIV-1 DNA copy into the genome of a newly infected cell is an essential step in the replicative life cycle of the virus. Integration is carried out by the integrase, a viral protein which directs two distinct reactions: 3'-processing of the proviral DNA removing a dinucleotide GT at each 3' end and strand-transfer which results in the joining of each processed 3'-end to 5'-phosphates in the target DNA. Those two reactions can be modeled in vitro, by using purified recombinant integrase[1].

The integrase-binding site located on the HIV-1 U5 LTR end contains two adjacent purine tracts on opposite strands 5'-**GGAAAA**TCTCT-3'/3'-CCTTTT**AGAGA**-5', in

parallel orientations. A single strand oligonucleotide 5'-GGTTTTTGTGT-3' linked with the intercalator oxazolopyridocarbazole (OPC) forms a stable triplex with the target DNA and inhibits the two integrase mediated-reactions[2].

In order to optimize the inhibition efficiency, different third strand oligonucleotide sequences and intercalator structures were synthesized[3]. Oligonucleotide-acridine conjugates inhibitory effect on integrase 3'-processing activity is displayed on **TABLE 1.** Oligonucleotides alone do not have any effect on integrase 3' -processing activity. Functionalization at 5' end is more effective than at 3'. Finally, bifunctionalization leads to the best inhibition ($IC_{50} \cong 0.5$ μM). Bi-functionalized (GT)-oligonucleotide-OPC gives rise to the same inhibition of 3'-processing activity and a stronger inhibition of strand transfer. The branched oligonucleotide OPC-5'-GGAAAAC*AGAGA-5'-OPC which can form a thermodynamically stable triple helix with an unusual parallel orientation of the third strand[4], leads to an marked inhibition of integration. Further studies need to be carried out to determine the exact mechanism of the inhibition and the role of both oligonucleotide and intercalator moieties.

TABLE 1. Acr: acridine, OPC: oxazolopyridocarbazole.

Compound	IC50 (μM)	
	Processing	Integration
5'-GGTTTTTGTGT-3'	>5	>5
5'-Acr-GGTTTTTGTGT-3'	1	nd
5'-GGTTTTTGTGT-Acr-3'	2.5	nd
5'-OPC-GGTTTTTGTGT-OPC-3'	0.5	0.5
5'-GGTTTTAGAGA-3'	>5	>5
5'-GGTTTTAGAGA-Acr-3'	>5	5
5'-Acr-GGTTTTAGAGA-Acr-3'	0.5	1
5'-OPC-GGAAAACAGAGA-OPC-3'	1	0.5

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REFERENCES

1. Craigie, R.; Mizuuchi, K.; Bushman, FD.; Engelman, A. *Nucleic Acids Res*, **1991**, *9*, 2729-2734

2. Bouziane, M.; Cherny, D.; Mouscadet, J.-F.; Auclair, C. *J. Biol. Chem.*, **1996**, *271*, 10359-10364.

3. Gottikh, M.; Volkov, E; Romanova, E; Oretskaya, T; XIIIth International Round Table.

4. 2. Ouali, M.; Bouziane, M.; Ketterle, C.; Gabarro-Arpa, J.; Auclair, C.; Le Bret, M. *J. Biomol. Struct. Dynam.*, **1996**, *13*, 835-853.