Identification of new compounds targeting the HIV-1 replication complex at sub-nanomolar concentrations

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Once a target cell is infected by HIV-1, the viral reverse transcriptase (RT) copies the genomic RNA to synthesize the viral DNA. The viral structural nucleocapsid protein (NC) encoded by Gag is an essential cofactor of the reverse transcription reaction since it chaperones RT along the genomic RNA template from the initial stage to the completion of viral DNA synthesis that necessitates two strand transfers to generate the long terminal repeats (LTR). NC was also found to control the timing of reverse transcription, in a spatiotemporal manner. New potential drugs or virucides against HIV-1 replication continue to be needed, which prompted us to look for compounds aimed at inhibiting NC. Here we report that the NC chaperoning activity can be extensively inhibited by modified oligonucleotides (mODN) in vitro. These mODN were delivered intracellularly using a peptide-based-nanoparticle-device (PBND) and found to impede HIV-1 replication in TCD4+ cells and macrophages at a concentration as low as 0.1-0.2 nM. In addition, these mODN were acting as virucides on cell-free virus. Detailed analysis shows that cDNA synthesis was impaired and that partially resistant viruses with mutations in NC and RT emerged after 8 months passaging in cell cultures. A pNL4.3 molecular clone bearing these mutations was found to replicate in the presence of 100 nM mODN, albeit at a level 6-7 times lower than wild type virus. Such small modified ODN appear to be a new type of highly potent inhibitors of HIV-1 replication.

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