

POSTER 40

APTAMER INHIBITION OF HIV-1 REVERSE TRANSCRIPTASE VARIANTS: A SYNTHETIC BIOLOGY APPROACH

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Nucleic acid aptamers bind lentiviral reverse transcriptases with very high affinity. They inhibit RT enzymatic activity in vitro, and their intracellular expression reduces HIV-1 replication by multiple logs in cell culture. To sustain multi-year to lifetime protection by these aptamers in a gene therapy context will require that they retain inhibition in the face of viral evolution. It is therefore important to understand the nature of, and propensity for, aptamer resistance to aptamers.

We have demonstrated that RT inhibition varies with both aptamer structure and RT amino acid sequence. Biochemical resistance to “specialist” aptamers is conferred by a single amino acid substitution in the RT, while “universalist” aptamers inhibit RT from highly diverse primate lentiviruses, including HIV-1 groups M and O, SIVcpz and HIV-2. Our recent work has identified several RNA aptamers with novel secondary structures and a guanosine quadruplex ssDNA aptamer with broad cross-clade inhibition. Distinct modes of nucleic acid-protein contacts are suggested by the patterns of RT-dependent reactivity during hydroxy radical footprinting and in-line probing assays.