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# Harnessing the Potential of Small RNAs for HIV-1 Gene Therapy – A Polycistronic approach

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Combinational therapy with small RNA agents against multiple viral targets is critical to efficient inhibition of viral production. We have previously validated this approach by expressing multiple anti-HIV RNAs from independent Pol III promoters within a single gene therapy construct, however, the high transcription rate of Pol III promoters often leads to toxicity as a consequence of saturating the endogenous RISC machinery. An alternative approach takes advantage of an endogenous polycistronic miRNA cluster driven by a Pol II promoter which has been engineered as a multiplexing platform. We tested combinations of different classes of therapeutic anti-HIV RNAs expressed within the context of an intronic MCM7 platform replacing the endogenous miRNAs with siRNAs targeting HIV-1 *tat* and *rev* messages, a nucleolar-localizing RNA ribozyme that targets the conserved U5 region of HIV-1 transcripts for degradation, or nucleolar TAR and RBE RNA decoys. We demonstrate the versatility of the MCM7 platform for expression and efficient processing of all RNA elements. Three of the combinatorial constructs tested potently suppressed viral replication during a one-month HIV challenge, with greater than five-logs of inhibition compared to unprotected HIV-1 infected CEM T-cells. One of the most effective constructs contains an anti-HIV siRNA combined with a nucleolar-localizing U5 ribozyme and nucleolar-localizing TAR RNA decoy. To the best of our knowledge, this is the first successful demonstration of functional combinations of different types of small inhibitory RNAs expressed from a single intron transcriptional unit.

## Biography

Dr. Janet Chung received her Bachelor of Science degree in Chemical Engineering from the University of Texas at Austin and subsequently completed her Ph.D with Dr. Thomas James in Department of Pharmaceutical Chemistry from University of California, San Francisco. Her thesis focused on structure-based small molecule drug discovery utilizing RNA targets. She is currently a research fellow in Dr. John Rossi's lab at City of Hope developing RNA-based HIV-1 gene therapies. Dr. Chung has published ten peer-reviewed articles with the latest publication in Human Gene Therapy describing the novelty of multiplexing si/snoRNAs as potent antiviral strategy.

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