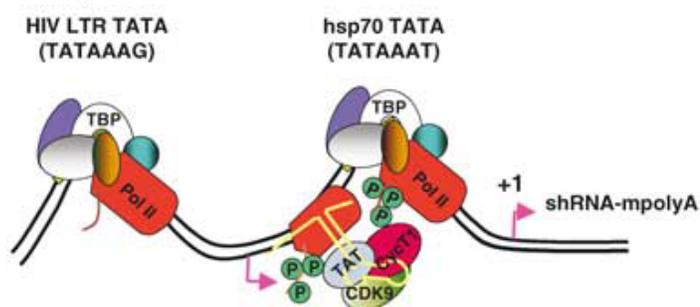


TAR-Mediated Inducible Method for Controlling siRNA Expression

LTRhsp-shRNA



DESCRIPTION

Small interfering RNA (siRNA) is a potent inhibitor of targeted gene expression. These short single-stranded ribonucleotides, produced from double-stranded or hairpin RNA (shRNA), incorporate into a ribonucleoprotein complex that selectively silences genes complementary to the siRNA. The ability to selectively “switch-off” disease causing genes represents immense therapeutic potential, however pooling of siRNA in non-target tissue can

cause side effects such as immune response, diminished blood vessel growth, and disrupted organ function.

City of Hope has developed a method to minimize off-target effects by repurposing a mechanism found in HIV replication to trigger siRNA expression only in the presence of a target-specific marker. TAR, an RNA hairpin element in HIV, prohibits HIV replication until it binds to Tat, a protein produced by HIV. The Tat-TAR complex then recruits transcription factors to perform HIV replication. City of Hope has developed nucleotide constructs that also contain a TAR element; however, when TAR-mediated inhibition is deactivated, either by Tat or other TAR-binding molecules, rather than replicating HIV, the construct expresses therapeutic shRNA. Because Tat is expressed in HIV infected cells, this technology provides an ideal mechanism for delivering targeted HIV therapy. shRNA sequences can be designed to silence genes required for HIV transcription or replication. Furthermore, the system creates a negative feedback loop; as HIV activity lessens, so too will Tat-activated shRNA expression and the risk of off-target effects. However if HIV activity flares up again, shRNA expression springs back into action to bring the viral load back down.

KEY ASPECTS

- TAR-mediated siRNA expression creates method for silencing genes without off-target siRNA effects
- Method diverts HIV replication mechanism to express siRNA only in the presence of a specific marker

INTELLECTUAL PROPERTY

Title	US Patent Number	Issued
Inducible Systems and Methods for Controlling siRNA Expression	8,138,327	3/20/12
Title	US Patent Application	Filed
Inducible Systems and Methods for Controlling siRNA Expression	13/425,065	3/20/12

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