

Super-Tat Proteins for use in Research, Diagnostic and Therapeutic Applications

Background

The human immunodeficiency virus (HIV) Tat protein stimulates the expression of early genes of the virus by binding directly to a stem and loop TAR RNA element, present at the 5' end of the virus. Tat protein also interacts with cellular transcriptional factors and cytokines, such as tumor necrosis factor-alpha (TNF-alpha), and alters the expression of a variety of genes in HIV-1-infected and non-infected cells. Tat function requires its binding to (P-TEFb), a cellular positive transcription elongation factor b.

Tat protein is secreted by HIV infected cells and extracellular Tat has been implicated in the progression of AIDS. Also, extracellular Tat exerts a variety of pleiotropic effects on target cells by binding to cell surface receptors such as VEGF, and chemokine receptors. For example, extracellular Tat has been shown to act on quiescent CD4 cells rendering them susceptible to HIV infection. Thus, inhibition of extracellular Tat represents a viable approach to stem the progression of AIDS. Variants of Tat protein, with enhanced or reduced activity, would be useful tools in advancing the current knowledge of HIV replication, pathogenesis, and progression of AIDS. **The present invention relates to new variants of the Tat protein that exhibit higher transcriptional activation than wild-type TAT.**

Description of the Technology

New variants of the wild-type Tat were generated via the site directed mutagenesis of a single amino acid in a key domain of the protein. The new variants exhibit 5-fold higher transcription activation and 3.5-fold higher P-TEFb binding activity than wild-type Tat. The enhanced P-TEFb binding and transcription activation of Super-Tats would enable the use of lower levels of the protein in research and clinical applications, thereby minimizing the toxic side effects known to be associated with the use of high doses of wild-type Tat.

Advantages

- 5-fold higher transcription activation
- Enhanced activity of Super-Tat allows the use of lower amounts of the protein in research and therapeutic applications
- 3.5 fold higher P-TEFb binding

Applications

- As research tools -to study viral replication -for HIV propagation -to deliver peptides, proteins or other agents into cells in cell culture since Tat is internalized by cells
- structural studies
- In therapeutic applications including the inhibition of viral transcription
- For the production of antibodies for vaccine development, research and therapeutic applications.
- For the preparation of conditioned medium from cells expressing Super-Tats -for use

in diagnostic assays to detect HIV infection

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- as a growth medium to culture HIV. Use of the conditioned medium would decrease the time required for viral replication
- to purify Super-Tats
- Chemical synthesis of Super-Tats for activation of latent HIV

Deliverables

- . • Sequences of variants of Super-Tat
- . • Vectors containing Super-Tats for bacterial and mammalian expression systems.
- . • Cell lines expressing Super-Tats
- . • Multiple variants of Tat exhibiting – fold enhanced activity
- . • Methods for production of Super-Tats

Patent Status

- . • A PCT application filed.
- . •PCT application published on September 4, 2003. Publication No.: WO 03/072709.

Licensing Opportunity

- This technology is available on a non-exclusive basis for research purposes and on an exclusive basis for diagnostic or therapeutic uses.

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