

## A Novel Antisense Strategy for Anti-Retroviral Intervention

### Background

There are a number of approaches to the prevention and treatment of AIDS disease. The HAART approach involving a combination of protease inhibitors, nucleoside and non-nucleoside analogs as reverse transcriptase inhibitors, has been very successful in reducing the viral load. However, the rapid emergence of drug resistant genetic variants is a major obstacle in the eradication of viral infection. Thus, a treatment strategy that targets the conserved regulatory elements of the HIV replication cycle would prove to be a viable alternative to HAART.

The HIV-1 virus encodes a powerful transactivator protein termed as Tat that exerts its regulatory effect by binding to a stem and loop RNA element called transactivation responsive element (TAR), at the 5' end of HIV-1 primary transcripts. Previous research has demonstrated that Tat stimulated gene expression can be abolished by abrogating Tat-TAR interaction. Thus, Tat and TAR represent useful drug targets for therapeutic intervention of HIV infection. Previous cell culture studies at UMDNJ laboratory have demonstrated that a 15-mer polyamide nucleotide analog (PNA) has the potential to interfere with Tat-TAR interaction thereby eliminating transactivation of genes. PNAs are analogs of nucleic acid with peptide backbone replacing sugar phosphate backbone in a nucleic acid. These analogs bind to RNA or DNA in sequence specific manner to inhibit translation and replication. **The current strategy was aimed at enhancing the biodelivery and antiviral efficacy of potential anti-TAR PNA by conjugating them with membrane transducing peptide vectors that efficiently enters into the cell and blocks transactivation by Tat protein, consequently inhibiting HIV replication.**

### Description of the Technology

Studies at UMDNJ have identified conserved TAR RNA sequences that can be targeted for blocking Tat-TAR interaction. Other important regulatory regions such as the primer-binding site (PBS) and its upstream A-loop region, the repeat (R) region at the 5' end and the dimerization site (DIS) of the viral genome are also being targeted by a similar approach. Appropriate length of the PNA targeting to these regions have been identified and are being conjugated with a number of membrane transducing peptide vectors to enhance their biodelivery and antiviral efficacy.

Studies with four anti-TAR PNAs have narrowed down the optimum length requirement of anti-TAR PNA to effectively sequester the TAR sequence and block Tat mediated transactivation to a 16 mer PNA. Conjugation of this PNA with a membrane transducing peptide called transportan, significantly enhanced its biodelivery into HIV-1 infected lymphocytes and blocked HIV-1 replication by inhibiting transactivation of transcription. **Most importantly, the anti-TAR transportan conjugate could effectively internalize into the virion particles rendering them replication incompetent. The present class of HIV-1 drugs exert their therapeutic function on HIV-1 infected cells only. The significance of the present approach is that it can inactivate the circulating HIV-1 virions in the plasma in addition to blocking HIV replication in HIV-1 infected cells.** Thus a cocktail of PNA-MTD conjugates targeting multiple regulatory elements of HIV-1 genome may potentially act as effective prophylactic agents to block HIV-1 infection, thereby, representing a novel antisense approach in HIV viral intervention. This strategy may have application to other viral infections.

### Advantages

- Can be used broadly in the treatment of other retroviral infections

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- . •Targets the conserved RNA element of the retrovirus
- . •Reduces the emergence of drug resistant mutants due to genetic variability

### **Applications**

- . •For the treatment of HIV infections
- . •In retroviral intervention

### **Deliverables**

- Anti-HIV-1 PNAs conjugated with membrane transducing peptide vectors.

### **Patent Status**

- PCT application filed. (Application No.: PCT/US2003/034708)

### **Licensing Opportunity**

- This technology is available for exclusive license.

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