Thus, ESN-196 is a unique CCR5 agonist compound with potent activity in inhibiting R5 HIV-1 replication in PBMCs and monocytes. Small-molecule CCR5 agonists offers significant advantages over the known peptide agonists where clinical utility is limited, in part, due to pharmacokinetic liabilities. Moreover, the concept of agonist-induced CCR5 receptor internalization may offer potential advantages over the receptor-blockade (i.e. antagonist) approach.

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Human Immunodeficiency Virus Type 1 Does Not Escape From Novel Single-Stranded DNAzyme Expression-Mediated Inhibition

Yuichiro Habu[1,2,*], Ryuichi Sugiyama[1], Hiroshi Takaku[1]

[1] *Chiba Institute of Technology, Narashino, Japan;* [2] *Colorado State University, Fort Collins, USA*

Recently, several groups reported that the antiviral activity of shRNA targeting the HIV-1 gene is abolished due to the emergence of viral quasispecies harboring a point mutation in the shRNA target region. This finding is particularly relevant for viruses that exhibit significant genetic variation due to error-prone replication machinery, and the risk might be more severe for RNA viruses and retroviruses than for DNA viruses. On the other hand, ribozyme technologies are also major tools for inactivating genes in gene therapy. One model, termed deoxyribozyme (Dz), is especially useful because it can bind and cleave any single-stranded RNA at purine/pyrimidine junctions.

In the present paper, we describe the inhibition of HIV-1 replication by a lentiviral vector-transduced DNAzyme. Human immunodeficiency virus type 1 (HIV-1) reverse transcription was used to construct a DNAzyme expression vector against the HIV-1 env V3 loop. As initiation of HIV-1 reverse transcription requires the formation of a complex containing viral RNA, tRNALys-3, and reverse transcriptase, we included a HIV-1 primer binding site and tRNALys-3 at the 3′-end of its RNA transcript in the expression vector, thus enabling the synthesis of single-stranded DNA. We demonstrated that lentiviral vector-mediated DNAzyme expression suppressed HIV-1 replication in SupT1 cells. Furthermore, HIV-1 arrests escape from novel single-stranded DNAzyme expression-mediated inhibition in long-term-assay. Such lentiviral vector-mediated DNAzyme anti-genes are promising tools for HIV-1 gene therapy in the treatment of HIV/AIDS.

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In Silico Screening for Anti-HIV-1 Compounds Targeting to Human Cyclin T1

Takayuki Hamasaki[1,2,*], Masanori Baba[1]

[1] *Center for Chronic Viral Diseases, Kagoshima University, Kagoshima, Japan;* [2] *Japanese Foundation for AIDS Prevention, Tokyo, Japan*

Considering the drug resistance and side effects of long-term HAART, it is still mandatory to develop anti-HIV-1 drugs with novel mechanisms of action. At present, entry inhibitors, reverse transcriptase inhibitors, an integrase inhibitor, and protease inhibitors are available for the treatment of HIV-1 infection. However, the drugs targeting the transcription from HIV-1 proviral DNA to mRNA have not been developed yet. The HIV-1 transcription process is essential for virus replication and is regulated by a complex composed of p-TEFb (cyclin T1/CDK9), Tat, and TAR RNA. Thus, the formation of this complex could be a potential target for the inhibition of HIV-1 replication. The crystal structure of cyclin T1 (protein data bank ID:2pk2) has been reported. Furthermore, the crystal structure of a complex composed of cyclin T1, Tat, and TAR RNA (protein data bank ID:2w2h) has recently been elucidated. These structures provide essential templates for the design of potential inhibitors. We examined *in silico* screening of compound libraries to identify potential inhibitors of cyclin T1 using the molecular docking simulation software MOE. The molecular surface of cyclin T1 was analyzed and searched for potential sites to which compounds could bind. Then, the docking simulation of cyclin T1 with the library compounds was performed. Approximately 200,000 compounds were screened, and 124 compounds having the optimum docking scores were selected. Consequently, most compounds were assumed to interact with the amino acid residues composed of the Tat/TAR RNA binding surface. We are currently evaluating the anti-HIV-1 activity of the selected compounds in vitro and further screening small-molecule compounds that bind to the Tat/TAR RNA binding surface of cyclin T1.

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Predicted Models of Resistance and Hypersensitivity Conferred by Natural Polymorphisms of HIV-1 Integrase

Raymond Hewer[1,*], Telisha Traut[1,2], Judy Coates[1], Bradley Williams[2]

[1] *Mintek, Johannesburg, South Africa;* [2] *University of Johannesburg, Johannesburg, South Africa*

Viral resistance remains a significant factor in the treatment of HIV patients and the development of anti-HIV drugs. In addition to resistant viral mutants that arise from drug-induced pressure, natural polymorphisms have been reported in isolated viral strains and suggested to influence susceptibility to drugs. Although less common than in protease and reverse transcriptase, inter- and intra-subtype diversity is evident in integrase from drug-naïve viral strains. In this study, the effect of natural polymorphisms in altering the binding affinity of inhibitors to integrase was evaluated via in silico molecular modelling. In total, the binding of 10 integrase inhibitors described in recent literature including Raltegravir and Elvitegravir to subtype B and subtype C integrase models was scored before and after the insertion of single or multiple point mutations. Findings from this study detail the inhibitors that are more susceptible to natural polymorphisms than others; demonstrate that both single and multiple point mutations can confer hypersensitivity to certain inhibitors; and identify several differences between the docking of compounds to subtype B and C mutants. These findings could be of relevance in the design of future inhibitors and to personalised antiviral treatment.

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Synergistic Inhibition of Bovine Leukemia Virus Replication In Vitro by Ribavirin and alpha-Interferon

Jeffrey Isaacson[1,*], Charles Wood[2], Jay Reddy[2]

[1] *Nebraska Wesleyan University, Lincoln, USA;* [2] *Nebraska Center for Virology, University of Nebraska, Lincoln, USA*

Bovine leukemia virus (BLV) is an oncogenic retrovirus that infects cattle. It is classified in the human T-cell leukemia virus (HTLV) group, although BLV mainly infects B cells rather than T