neurons against toxic substances in CSF from human infected patients with moderate to severe dementia. Mitochondrial potential was used to assess neuronal functionality. Didox nearly prevented the toxic CSF effect from moderate-severe dementia HIV patients on the mitochondrial potential of cultured fetal neurons.

These results demonstrate that this series of RRIs, particularly Didox, have multi-faceted actions that can be beneficial to HIV patients. They can impair HIV replication through inhibiting proviral DNA synthesis and potentiate NRTIs. Additionally, these RRIs can inhibit NF-kB activation. Lastly, they have the potential to impede the development of HIV dementia.

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Human Immunodeficiency Virus Type 1 Does Not Escape from Novel Single-Stranded Dnazyme Expression-Mediated Inhibition

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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. The DNAzyme is similar to hammerhead ribozymes, at least in terms of its secondary structure, with two binding arms and a catalytic loop that captures the indispensable catalytic metal ions. We designed a vector to produce single-stranded DNA. Human inmmunodeficiency virus type 1 (HIV-1) reverse transcription was used to construct a DNAzyme expression vector against the HIV-1 env V3 loop (Kusunoki et al., 2003). Initiation of HIV-1 reverse transcription requires the formation of a complex containing the viral RNA, tRNALys-3, and reverse transcriptase. The expression vector contains the HIV-1 primer binding site and tRNALys-3 at the 3′ end of its RNA transcript, thus enabling the synthesis of a single-stranded DNA by HIV-1 reverse transcriptase. We demonstrated that the lentiviral vector-mediated DNAzyme expression suppressed HIV-1 replication in SupT1 cells. Furthermore, HIV-1 did not escape from novel single-stranded DNAzyme expression-mediated inhibition. This lentiviral vector-mediated DNAzyme anti-genes are promising tools for HIV-1 gene therapy for the treatment of HIV/AIDS.

Reference

Kusunoki, A., Miyano-Kurosaki, N., Takaku, H., 2003. Biochem. Biophys. Res. Commun. 301, 535–539.

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Characterization of a New Class of Polycyclic RSV Inhibitors

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Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and pneumonia in children under one year of age and is a leading cause of severe lower respiratory infections in infants and young children. Prophylactic antibodies such as Synagis® (palivizumab) effectively reduce the incidence and severity of RSV disease in high-risk pediatric populations but the only antiviral treatment available for patients with RSV disease is ribavirin, a nucleoside analog with suboptimal clinical efficacy and safety profile.

RSV enters cells in the lung using a fusion glycoprotein (RSV-F), found on the virus's outer envelope. Biota has developed small-molecule, orally available, synthetic drugs that specifically target RSV-F, preventing it from functioning and therefore stopping RSV infection from spreading.

We will present in vitro cellular data evaluating the antiviral activity and cytotoxicity of this potent class of RSV inhibitors. Mechanism of action will be reported including functional assays and genotypic and phenotypic analysis of resistant mutants. Cross-resistance data with known fusion inhibitors and modelling studies to establish the proposed binding site will be presented. The compounds display promising oral bioavailability and efficacy in rodent models of RSV infection.

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HIV Coreceptor Switch Induced by Antagonism to CCR5

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HIV resistance to CCR5 antagonists in cell culture has been observed in the absence of coreceptor switch, but it is unclear whether inhibition of HIV-1 replication with a CCR5 antagonist will lead to an increased rate of emergence of CXCR4 variants.