Repurposed Derferiprone to Treat HIV

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Technology description

This invention describes a method for inhibiting viral replication in eukaryotic cells and of inducing apoptosis of virally-infected cells by treatment with agents that inhibit the formation of hypusine. Eukaryotic initiation factor 5A (eIF-5A) is the only cellular protein known to contain the unusual amino acid hypusine. EIF-5A is a cellular cofactor of HIV-1 Rev proteins. Rev binds to eIF-5A and to crucial unspliced and incompletely spliced viral mRNAs that encode the structural proteins that form the virion core and capsid. Rev shuttles its partners from the nucleus to the cytoplasm, where they are translated preferentially due to eIF-5A. HIV and other lentiviruses, as well as hepatitis B virus and human T-cell leukemia virus, depend on this parasitization of host eIF-5A.

The dependence of these viruses on eIF-5A and eIF-5A's dependence in turn on hypusine led investigators led by Dr. Hartmut Hanauske-Abel (formerly at Cornell and now at the University of Medicine and Dentistry of New Jersey) to investigate methods of treating HIV infection by interfering with the formation of active eIF-5A.

Hypusine is formed by a post-translational modification of lysine at position 50 in a proform of eIF-5A. The hypusine modification includes two steps: the transfer of the aminobutyl moiety of spermidine to the -NH2 group of lysine by deoxyhypusine synthase, followed by hydroxylation by deoxyhypusine hydroxylase, resulting in the active form of eIF-5A.

This invention provides for the use of hydroxypyridones, deoxyhypusine hydroxylase inhibitors, hypusine inhibitors, and most generally, inhibitors of eIF-5A for the treatment of infection with HIV and all other viruses dependent upon eIF-5A.

Although the compounds employed are not novel, the mechanism of action is different from currently marketed AIDS therapeutics and such drugs would be first in class.

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