Potential new drugs plug brain's biological 'vacuum cleaner' and target HIV

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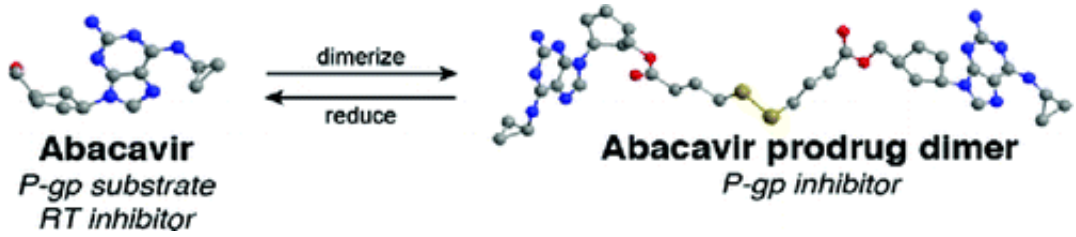

In an advance toward eliminating pockets of infection in the brain that help make HIV disease incurable, scientists report the development of new substances that first plug the biological vacuum cleaner that prevents anti-HIV drugs from reaching the brain and then revert to an active drug to treat HIV. They describe the advance, which allows medications to cross the so-called "blood-brain barrier" (BBB) and treat brain diseases, in the *Journal of the American Chemical Society*.

Jean Chmielewski, Christine Hrycyna and colleagues explain that Human Immunodeficiency Virus infection remains incurable because HIV can sneak through the BBB -- a network of special blood vessels and cells that protects the brain from many harmful substances -- while many of the most powerful anti-viral medications cannot. A pump at the BBB suctions anti-viral medicines away like a biological vacuum cleaner, leaving a reservoir of HIV in the brain. To overcome this hurdle

and get rid of the last footholds of HIV, the researchers set out to develop a new group of drugs that can plug up the vacuuming mechanism and then sneak across the BBB to fight HIV.

Their approach involves gluing two anti-HIV drug molecules together with a "tether." This dual drug plugs up the BBB vacuum cleaner and can then sneak across the BBB. Once across, the tether disintegrates, freeing the two drug molecules to kill the virus. "This overall strategy represents a platform technology that may be readily applied to other therapies with limited brain penetration," such as anticancer and anti-schizophrenia drugs, say the researchers.

More information: Toward Eradicating HIV Reservoirs in the Brain: Inhibiting P-Glycoprotein at the Blood–Brain Barrier with Prodrug Abacavir Dimers, J. Am. Chem. Soc., Article ASAP. DOI: 10.1021/ja206867t

Abstract
Eradication of HIV reservoirs in the brain necessitates penetration of antiviral agents across the blood–brain barrier (BBB), a process limited by drug efflux proteins such as P-glycoprotein (P-gp) at the membrane of brain capillary endothelial cells. We present an innovative chemical strategy toward the goal of therapeutic brain penetration of the P-gp substrate and antiviral agent abacavir, in conjunction with a traceless tether. Dimeric prodrugs of abacavir were designed to have two functions: inhibit P-gp efflux at the BBB and revert to monomeric therapeutic within cellular reducing environments. The prodrug dimers are potent P-gp inhibitors in cell culture and in a brain capillary model of the BBB. Significantly, these agents demonstrate anti-HIV activity in two T-cell-based HIV assays, a result that is linked to cellular reversion of the prodrug to abacavir. This strategy represents a platform technology that may be applied to other therapies with limited brain penetration due to P-glycoprotein.