Hot News

Discovery of VIRIP – a Natural HIV Entry Inhibitor

Preventing entry of HIV into host cells is a key strategy for controlling viral replication. To date, there is only one approved HIV entry inhibitor drug, enfuvirtide (Fuzeon®; T-20), although several others are in development. German researchers have recently reported the identification of a naturally occurring peptide in human blood that blocks HIV entry (Kirchhoff, et al. Cell 2007;129:263-75). The investigators screened a comprehensive library of more than one million small peptides generated from human blood filtrate, the residue left after kidney dialysis. They found that a 20-residue peptide sequence designated "virus inhibitory peptide," or VIRIP, a fragment of alpha-1-antitrypsin, which is the most abundant circulating serine protease inhibitor, reduced cellular HIV infection by 99%, and inhibited multiple strains of HIV-1, including those resistant to current antiretroviral drugs.

Further analysis showed that VIRIP blocks viral entry by interacting with the gp41 fusion peptide, a conserved region of the HIV-1 envelope glycoprotein. By making a few amino acid substitutions, the antiretroviral potency of VIRIP could be increased significantly. Also, VIRIP appeared nontoxic even at high concentrations *in vitro*, was effective against HIV strains that use either CCR5 or CXCR4 coreceptors, and did not promote development of resistant virus in cell cultures. Thus, VIRIP seems to be a highly specific natural inhibitor of the HIV-1 gp41 fusion peptide, and might lead to the development of a new class of antiretroviral drugs.

Since it is a peptide, however, a VIRIP-derived drug would likely need to be injected, like enfuvirtide, unless it can be discovered how to produce a small-molecule compound with the same mechanism of action. In addition to treatment of HIV infection, VIRIP might also be used as microbicide to prevent infection, and studies are ongoing to prove this further utility of the compound. The agent has been licensed by Viro Pharmaceuticals, a German biotechnology company, which is conducting animal studies to determine whether VIRIP can safely be tested in humans. For selected VIRIP derivatives, the lack of toxicity has already been confirmed in animals.

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Efavirenz to Nevirapine Switch in HIV-Infected Patients with Dyslipidemia

Many antiretroviral therapies, including efavirenz, are associated with increased serum concentrations of LDL-cholesterol. In a 52-week randomized study, French researchers (Parienti, et al. Clin Infect Dis 2007;45:263-6) found that switching from efavirenz to nevirapine was associated with a significant decrease in LDL-cholesterol levels, compared with continuation of efavirenz therapy. As highlighted in the most recent National Cholesterol Education Program (NCEP) guidelines (JAMA 2001;285:2486-97), serum LDL-cholesterol is the most important lipid fraction that must be considered for any assessment of cardiovascular risk and accordingly the main target for therapeutic interventions. In the French trial, the switch to nevirapine was associated with no severe adverse events and therefore could be advised in patients with cardiovascular risk factors showing a negative cardiovascular profile using efavirenz.

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SPRING: A New Trial to Evaluate Tipranavir in Heterogeneous Treatment-Experienced HIV Populations

There is an urgent need for safe, simple, and more effective regimens for the treatment of antiretroviral-experienced HIV-positive patients, especially women, Blacks, Hispanics and Asians. To address this need, Boehringer-Ingelheim has initiated a trial, named SPRING (**S**afety, efficacy and **P**harmacokinetics of tip**R**anavir boosted with low dose ritonavir (500/200 mg) twice daily **IN** 400 racially and **G**ender diverse, antiretroviral-experienced HIV patients). The study will be conducted at 72 sites across eight countries (United States, Canada, Mexico, Germany, Italy, Spain, Argentina, and Brazil) and enroll 200 women and 200 men, including Whites, Blacks, Hispanics, Asians, and American Indians. SPRING has been approved as a phase IIIb, open-label, multicenter, multinational trial with a primary endpoint of treatment response at 48 weeks, defined as plasma HIV-RNA < 50 copies/ml.

An additional relevant aspect of SPRING is the inclusion of therapeutic drug monitoring (TDM). In fact, it will be the largest randomized controlled trial to evaluate the utility of TDM in antiretroviral-experienced HIV-positive patients. A subset of 200 patients will be evaluated to assess the impact of TDM on the efficacy and safety of tipranavir coadministered with ritonavir. For this purpose, measurement of specific plasma drug levels at certain intervals of time will be made and medication dos-

ages will be adjusted to fit within specific therapeutic ranges.

Overall, the study will provide insights about the efficacy of antiretroviral treatment with tipranavir, which might vary across races and genders. Worldwide, there are more HIV-positive women than ever before, with nearly 18 million now living with the disease. Racial and ethnic minorities are also being disproportionately affected by HIV. SPRING reflects the commitment of Boehringer-Ingelheim to assess patient's demands at epidemic scale and not just in the richest countries. All patients recruited in SPRING will be adults older than 18 years with prior exposure to at least three antiretroviral drug classes and with documented resistance to at least one protease inhibitor. At screening, patients should have a CD4 count ≥ 50 cells/mm^3 and plasma HIV-RNA > 1000 copies/ml.

All 400 patients entering SPRING will begin with the standard dose of 500 mg of tipranavir coadministered with 200 mg of ritonavir twice daily in conjunction with an optimized backbone regimen. Half of patients will continue to receive this regimen for 48 weeks. The other 200 patients will be allocated into the TDM arm and may have their dose of tipranavir or ritonavir modified, depending on plasma drug concentrations. With this pharmacokinetic intervention, it is proposed that the risk of hepatotoxicity, particularly in patients with underlying chronic hepatitis B or C, will be diminished, avoiding overexposure without compromising virologic activity.

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