



Method for determining co-receptor selectivity of Human Immunodeficiency Virus-1

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INTRODUCTION:

HIV-1 enters the target cells by consequent utilization of CD4 and the chemokine receptor. The CXCR4 and CCR5 are the two predominant chemokine co-receptors utilized by the HIV-1, which mediates interaction with the chemokine receptor on the target cells through its third variable loop (V3) of the envelope protein, gp120. The sequence of the V3 loop dictates recognition of different chemokine receptor. The usage of either CXCR4 or CCR5 receptor determines the viral tropism and the viruses are termed as either "X4"-tropic or "R5"-tropic viruses, respectively. The R5-tropic viruses are predominantly found in the early stages of infection, while the X4-tropic viruses are associated with the late stage of AIDS progression. In addition to the protease and reverse transcriptase inhibitors, the basic knowledge of viral tropism has introduced co-receptor antagonist in the arsenal of drugs against HIV-1. CCR5 antagonists are being currently tested in Phase III trials, while the CXCR4 antagonists are in the early development stage. Hence, accurate prediction of co-receptor usage by HIV-1 will not only help in determining disease progression but also in customizing co-receptor antagonist therapy for the infected individual. "11/25 rule" to determine viral tropism exists and is based on the charge of amino acid residues of the crown of the V3 loop of gp120 protein; however, this rule has very low predictive accuracy. Therefore, there is an urgent need for predictive algorithm to accurately determine either X4 or R5 tropic viruses in order to assess the disease progression and support therapy with new regimen of co-receptor antagonist drugs.

DESCRIPTION OF PROJECT: As outlined in this patent, Drs. Cardozo and Zolla-Pazner describe a structural basis for predicting X4 or R5-tropic HIV-1 based on the charged patch on the surface of V3 loop. The resultant new rule or algorithm was derived after 3D-computational modeling of the V3 loop of 71 primary HIV-1 isolates from the 'gold-standard' library that were experimentally verified for co-receptor usage. The new rule, "11/24/25", states that if a positively charged amino acid is present at either 11, 24 or 25 position of the V3 loop, an X4-tropic virus is present, otherwise an R5-tropic virus is present; this rule has overall prediction accuracy of 95.2%.

APPLICATIONS:

Sample of a body fluid or cells of a tissue from the subject can be used to obtain either nucleotide or amino acid sequence of the V3 region that includes amino acid residues 11, 24 and 25. The "11/24/25" rule will help in determining selectivity for co-receptor usage for HIV-1 in the subject. The accurate determination of viral-tropism for CXCR4 or CCR5 receptor will be useful in different aspects of disease management including clinical diagnosis, customizing the treatment with the new co-receptor antagonist drugs and rational vaccine design.

PATENT STATUS:

A U.S. patent application (20070072200) has been filed covering