

Poster presentation

Inhibition of HIV-1 Entry by Inducing a Nonproductive Conformational Change in gp120

Weihong Lai^{*‡}, Li Huang, Phong Ho, Xiong Yuan and Chin-Ho Chen

Address: Department of Surgery, Duke University Medical Center, Durham, North Carolina 27710, USA

Email: Weihong Lai^{*} - wh.lai@duke.edu

^{*} Corresponding author [‡]Presenting author

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Conformational change in HIV-1 gp120 is a dynamic process essential for HIV-1 entry. It is not clear whether the dynamic nature of gp120 could be exploited to abort the viral entry machinery. Here we show that a small molecule entry inhibitor, IC9564, induces a conformational change in gp120 and locks the envelope into fusion incompetent conformation. Binding of IC9564 to HIV-1 envelope results in the exposure of CD4i epitopes that are ally concealed in gp120. As a result of the conformational effect, IC9564 significantly enhances the neutralizing activity of 17b that binds to an epitope overlapping chemokine receptor binding site. Unlike CD4, IC9564-induced conformational change in gp120 does not trigger a conformational change in gp41. In fact, IC9564 inhibits CD4 induced conformational changes in gp41. The binding site of IC9564 remains elusive due to the fact that mutations in both gp120 and gp41 could change IC9564 sensitivity. Nevertheless, a common effect of these mutations is that conformation of gp120 is changed to conceal conserved epitopes such as CD4i. In summary, IC9564 exploits the dynamic nature of HIV-1 gp120 by inducing a nonproductive conformational change in gp120 and prevents HIV-1 from entering the cells.