Retrovirology



Poster presentation



# Design of RANTES-derived Peptides With Enhanced HIV-inhibitory Activity and Derivation of Resistant HIV-1 Strains

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*from* 2005 International Meeting of The Institute of Human Virology
Baltimore, USA, 29 August – 2 September 2005

Published: 8 December 2005

*Retrovirology* 2005, **2**(Suppl 1):P113 doi:10.1186/1742-4690-2-S1-P113

We previously identified the major structural determinants of CCR5 binding and HIV blockade in RANTES, describing linear RANTES-derived peptides with biological activity in the low micromolar range (Nardese et al., 2001). To deepen our understanding of RANTES structure-function relations and obtain more potent antiviral peptido-mimetics, we have extensively mutagenized the prototypic peptide, R11-29. This presents two clusters of hydrophobic residues at its termini, (corresponding to RANTES N-loop and b1-strand) connected by a positively-charged linker. Single or multiple alanine substitutions within the N- or C-terminal hydrophobic clusters resulted in a dramatic loss of antiviral activity, whereas deletion of selected residues within the hydrophilic linker had no major functional consequences. Based on RANTES 3D structure, we designed a series of modified peptides, resulting in a progressive increase in specific antiviral activity. These peptides also displayed anti-inflammatory properties blocking RANTES-elicited lymphocyte chemotaxis. Through serial passages in culture in the presence of increasing concentrations of the most effective antiviral peptides, we have derived variants of the R5 HIV-1 isolate BaL resistant to the peptide inhibitory activity. Complete sequencing of the envelope genes from such variants is currently underway. Our results provide new insights into the structure of the receptor-binding region of RANTES and identify new antiviral peptides that may be instrumental in the development of effective HIV-1 entry inhibitors.