Cross-Clade Inhibition of HIV on Primary Cells by CXCR4 or CCR5 Fused to the C34 Peptide from gp41 HR2

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Background: HIV-1 entry into CD4+ T cells requires binding to CCR5 or CXCR4 on the cell surface, with subsequent entry of the Env protein into the cell cytoplasm. While CCR5 and CXCR4 are both functional receptors for these Env proteins, some strains of HIV-1 have a stronger affinity for either CCR5 or CXCR4, leading to preferential entry into cells with these receptors. The C34 peptide from gp41 HR2 is a potential inhibitor of HIV-1 entry.

Methods: Using activated T cells, C34 peptide or C34-Fusion constructs were transduced into CCR5- and CXCR4-expressing cells. The percentages of cells expressing the C34 peptide were assessed on QT6 cells expressing the indicated coreceptors.

Results: In C34 T cells from multiple donors, when C34 or C34-Fusion were expressed, there was variable complete inhibition (>95%) of HIV-1 infection at low plk levels and 10% infection at high plk levels and 10% inhibition at day 1 and day 14. Transduced HIV-1 infected with C34 expressing an efficient transduction, yet not producing C34-expressing cells. Controls included GFP alone or C34-Fusion, which were not expressed, there was variable complete inhibition of HIV-1 infection at low plk levels and 10% infection at high plk levels. This inhibition was highly specific and dependent on positioning of the C34 peptide.

HIV-infection of CD4+ T-cells + C34-CoReceptors

Effects of C34-CoReceptor in Primary CD4+ T-cells

CD4 T-cell expression of C34 peptide was assessed on QT6 cells expressing the indicated coreceptors.

Summary & Conclusions

Assess the immunogenicity of the C34 peptide when coupled to an exogenous endogenous coreceptors.

Future Directions

Assess the ability of C34-CoReceptors to exert trans-dominant inhibition of R5 and X4-tropic HIV-1 in the MSD humanized mouse model.

Extend this approach to explore gene-editing methodology in primary CD4+ T-cells with a goal of enabling trans-dominant HIV inhibition to be exerted from within.

Assess the immunogenicity of the C34 peptide when coupled to an exogenous or endogenous coreceptor.

Acknowledgments: Funding provided by NIH Grant U54 AI099600. Support was also provided by West and Molecular and Immunology Core of the Penn Center for AIDS Research (U54 AI099600).