Lipid-conjugated HIV-1 Fusion Inhibitor Exhibits Enhanced Potency and Increased Serum Half-life

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Human immunodeficiency virus type 1 (HIV-1) Env subunit gp41, mediates fusion Sciences between the viral envelope and target cell membrane. GP41 changes conformation by inserting the fusion peptide into the cell membrane, resulting in the formation of a six-helix bundle (6-HB) between the N- and C-terminal heptad repeats (NHR and CHR) bringing the viral and cell membranes into proximity for fusion. T20 (Enfuvirtide), which is a peptide derived from the CHR, is the only clinically available HIV-1 fusion inhibitor, but it suffers from low potency and short half-life, which urgently calls for next-generation drugs. T-cell lipid rafts are enriched in the receptor (CD4) and co-receptors (CCR5/CXCR4) for HIV. To target these sites of active fusion and increase drug potency, a C-16 lipid moiety was incorporated into the current leading fusion inhibitor YIK. Addition of a lipid motif may also prolong the half-life of the peptide inhibitor through binding to serum albumin. Inhibition of 6-HB formation, cell-cell fusion and infection assays were used to assess the anti-HIV potency of YIK-C16. YIK-C16 was twice as potent as YIK in inhibiting cell-cell fusion and 6-HB formation and 10-fold more effective than YIK at preventing HIV-infection. Importantly it retained biological activity for up to ~15 h while YIK lost activity after 2 h. Cell viability assays revealed no cytotoxic effects of YIK-C16. These results suggest that the lipopeptide YIK-C16 shows promise for further development as a new anti-HIV drug with improved anti-HIV-1 activity and prolonged half-life.

Awards Won: