OFFICIAL ABSTRACT and CERTIFICATION

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 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.

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