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Mechanism of multivalent nanoparticle encounter with HIV-1 for potency enhancement of peptide triazole virus inactivation

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Introduction: Initial entry of HIV-1 into host cells remains a compelling and yet elusive target for developing agents to prevent infection. This step is mediated by a sequence of interactions of a trimeric gp120/gp41 envelope (Env) protein complex with host cells, including initial gp120 encounter with the cellular receptor CD4 and a chemokine co-receptor usually either CCR5 or CXCR4. A peptide triazole class of entry inhibitor leads has been shown to bind to gp120 with close to nanomolar affinity, to suppress protein ligand interactions of the Env protein at both its CD4 and co-receptor binding sites and to inhibit cell infection by a broad range of virus subtypes. Further we have also shown that gold nanoparticle conjugated peptide triazoles lead to 20 fold enhanced potency of their anti-viral effects against HIV-1. Previously bowman et al. has shown that multivalent display of HIV inhibitors on gold nanoparticles (AuNPs) has lead to a substantial amount of poency enhancement. This study will lead to the study of size dependency and density dependency on the gold nanoparticle peptide triazole conjugates to further understanding of their mechanism of action leading to enhanced potency.

Materials and Methods: The AuNPs were synthesized using a modified citrate reduction method to obtain size-controlled, stable and monodisperse AuNPs. The peptide (KR13) was conjugated to the AuNP using a direct gold-thiol covalent link. The size and extent of polydispersity of the AuNP-KR13 conjugates were measured using Transmission Electron Microscopy (TEM) and Dynamic Light Scattering (DLS). The HIV-1 viral entry inhibition potencies of KR13 and AuNP-KR13 conjugates were compared using a single-round pseudoviral infection luciferase reporter assay using lab synthesized pseudoviruses. We subsequently tested the effects of KR13 and AuNP-KR13 on the virus particle itself by measuring release of the nucleocapsid protein p24 using ELISA analysis of cell-free virion inhibition.

Results and Discussion: Compared to peptide triazole alone, the 20 nm AuNP-KR13 conjugate exhibited a close to 20-orders of magnitude enhancement of infection inhibition activity (Table) and further with increasing size of AuNP, the potency was enhanced further with the 120 nm AuNP-KR13 having nearly 1600 fold enhancement (Table). KR13 and AuNP-KR13 conjugates are specific for HIV-1 envelope. There was no significant *in vitro* cytotoxicity observed for either KR13 or AuNP-KR13 conjugates. Further the residual virion that was generated upon treatment with KR13 was immunoreactive while the residual virion generated upon AuNP-KR13 treatment was completely inactive. The mechanism was studied by observing the morphological changes caused by both KR13 and AuNP-KR13 on the HIV-1 virion using TEM.

Conclusions: In summary, we report the ability of modified peptide triazole inhibitors that target HIV-1 gp120 to physically disrupt virus particles in the absence of host cells. At conditions similar to those at which both KR13 and AuNP-KR13 conjugates inhibited HIV-1 BaLpseudovirus infection of HOS.T4.R5 cells, it also caused release of HIV-1 gag p24 when incubated with virus alone. Both inhibition of cell infection and p24 release were enhanced substantially by increasing diameter of the multivalent display of KR13 on gold nanoparticles. The mechanism of action of AuNP-KR13 is evidently different from KR13 leading to cell free virus transformation leading to further insights towards virus-cell fusion mechanisms.

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