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Microbicides that Can Pop HIV-1

Arangassery Rosemary Bastian*

Department of Biochemistry and Molecular Biology, Drexel University, College of Medicine, USA

Introduction

The human immunodeficiency virus which is the viral precursor that is responsible for the disease that is still a challenge and an epidemic, AIDS [1-3]. Several top physicians as well as scientists in the field have been trying to combat this virus and trying to inhibit the infection and spread of the disease. Due to the constant mutation tendencies of the HIV virion it has become a big challenge to target this virus and eradication of the virus infection all together [4]. Our group at Drexel University College of medicine has developed several inhibitors that target the virus directly that not only leads to very potent entry inhibitors but further have gone a step further to create microbicides that target the virion envelope and lead it to irreversible self-destruction [5-7]. This innovative approach has led to the development of a class of microbicides that can be used at several stages of AIDS progression which include, initial entry, reduction of new virus production as well as cell-cell transmission of the virion leading to complete virus abolition of the disease progression.

Host cell infection by HIV-1 is mediated by cell receptor interactions with trimeric envelope glycoprotein (Env) spikes that are exposed on the virus membrane surface. Env is the only virus-specific protein on the virion surface, and is essential for cell receptor interactions and subsequent virus-cell fusion [8-10] (Figure 1). Hence, Env presents an obvious target to attack the virus directly in order to block the cascade of integrated binding and conformational change steps that lead to host cell infection. Env-specific inhibitors that could inactivate the virus before receptor encounter would hold great promise of preventing AIDS transmission and progression. The proteins of the HIV-1 Env include gp120 and gp41 on the viral envelope spike and the cell surface receptors include CD4 and a chemokine receptor, either the CCR5 or CXCR4. The fusion inhibitor T20 [11], and the CCR5 inhibitor maraviroc [12] are approved drugs used currently for salvage therapy in HIV-infected patients, though trials are ongoing to assess their addition to first line regimen (Figure 1). T20 targets the N-terminal heptad repeat region of gp41, blocking gp41 conformational changes essential for 6-helix bundle formation and membrane fusion. This inhibitor however has a relatively short time window to act on the transiently exposed N-helix of gp41 at the cell-virus synapse. In addition, T20 is logistically difficult to administer, as it can only be given parentally, and adverse reactions at sites of injection are common. Maraviroc only blocks R5-tropic HIV-1 and its use requires that CXCR4-tropic viruses are not present [12]. While there are other small molecule entry inhibitors [13,14], peptidomimetics [15,16] and anti-CD4 antibodies [17,18] that block or interfere with proteins at the cell-virus interface, they are still not advanced to clinical use as a first line regimen.

These groups of microbicides are called peptide triazole inhibitors, made with amino acids just like proteins in the body and hence they are very biocompatible [19]. They have been engineered by using a technology called click chemistry to create a pharmacophore [19] that binds close the CD4 binding pocket hence making it a 98% conserved region among the several drug resistant mutants strains of the virus that are currently present. The peptide triazoles compete with the CD4 as well as co-receptor binding site which therefore inhibits the virus from initial contact with the host cell, blocking its entry [6,20-22]. The peptide triazoles revert gp120 to an alternate inactivate state which will not proceed towards CD4 or co-receptor binding, hence blocking virus cell fusion as shown in (Figure 2). This class of peptides was further developed to create the virolytic class of the peptide triazole inhibitors called peptide triazole thiols [3,5]. These virolytic peptides have an additional characteristic in addition to entry inhibition, which is the cell-free virolysis. This unique effect of the peptide triazole thiol is still under investigation but we have shown that the cysteine in the C-terminus is very crucial for this lytic effect [3]. We have confirmed that these virolytic peptides do not have any cellular cytotoxicity by conducting a cell viability assay as shown in previous data [3,5]. Further we also have demonstrated that this effect follows a similar pathway as regular virus fusion with the host cell. This was proven by showing that peptide induced virus breakdown followed a similar time-line as virus fusion as demonstrated in Bastian et al. [3]. Also further the fusion inhibitor, T20 that targets HIV-1 spike protein gp41 and blocks the 6 helix bundle formation of the virion, also inhibits the peptide induced virus breakdown. These two striking results have led to exploration of how the peptide triazole thiols are hi-jacking the virus fusion machinery and mocking the virion to think it is fusing with a cell but instead leading to complete release of the protein (p24) that is in the virus nucleus into the surrounding environment. One additional component that makes there peptides very unique is that they can target multiple clades of the HIV-1 virus including the founder viruses. Several inhibitors that are currently in the pipeline have very few specific clades that they are more active against, and therefore are limited to their inhibitory action. The results of these are elaborated in the Bastian et al. paper [3].

This novel finding is not only creating a new class of virus targeted inhibitors but also can answer some unknown questions about virus fusion with a host cell that is yet to be answered. We have also led to several virucidal constructs developments that relate to this finding that are leading to the creation of inhibitors that can completely and irreversible destruct the virion at the site of initial contact with the host [23]. Our current research is focused on several aspects of this potent class of virus disrupting inhibitors. We had previously shown that multivalent display of this virolytic peptide triazole thiols lead to a 20 fold enhancement of the antiviral effects making it a much more potent inhibitor [5]. But recently we found that if we use nanotechnology to

***Corresponding author:** Arangassery Rosemary Bastian, Department of Biochemistry and Molecular Biology, Drexel University, College of Medicine, 245N 15th Street, New College Building, Room No. 11102, Philadelphia, PA 19102, USA, E-mail: rab65@drexel.edu

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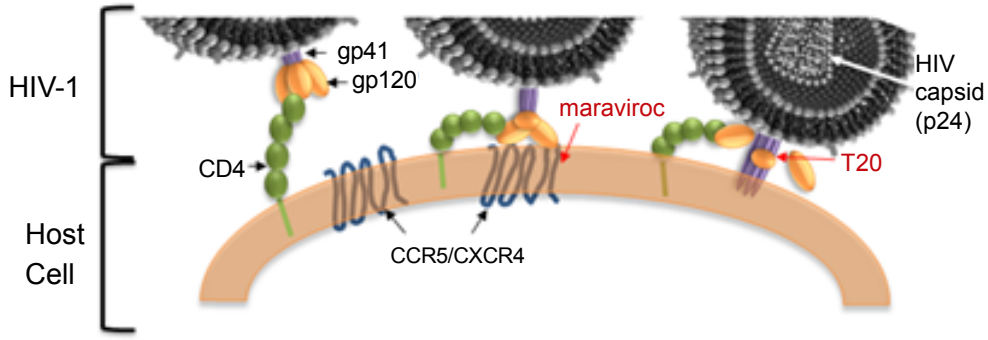

Figure 1: Fusion of HIV-1 with host cell. The HIV proteins gp120 and gp41, together known as the HIV-1 spike interacts with the receptor CD4 and coreceptor CCR5 or CXCR4. The gp120 sheds off the spike and the gp41 is exposed on the cell surface. Gp41 follows a 6-helix bundle formation and the virus and cell surface fuse and the capsid is released. The inhibitors that are currently approved for therapy that target HIV-1 fusion with cell are indicated in red with maraviroc that targets the co-receptor, CCR5 binding to gp120 and T20 (enfurvitide) that targets gp41 blocking 6-helix bundle formation and therefore fusion of the two membranes.

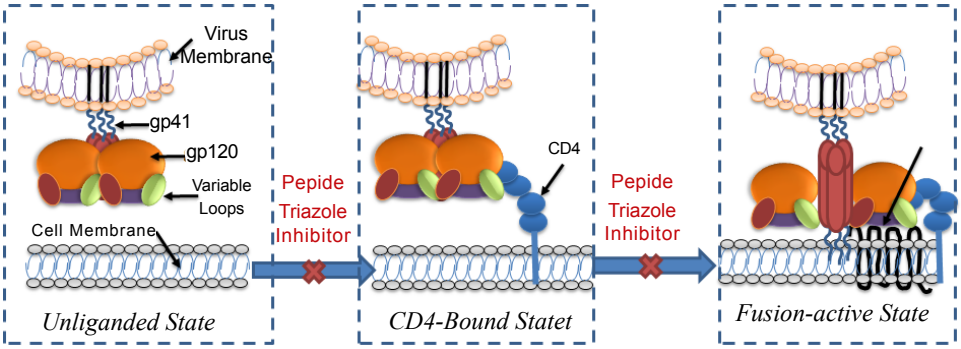

Figure 2: The schematic representation of the peptide triazole mode of action. It is an allosteric diverter that puts the gp120 protein in an inactive state that is insensitive to CD4 and CCR5 binding leading to complete inhibition of HIV fusion and therefore entry of the virion into the host cell.

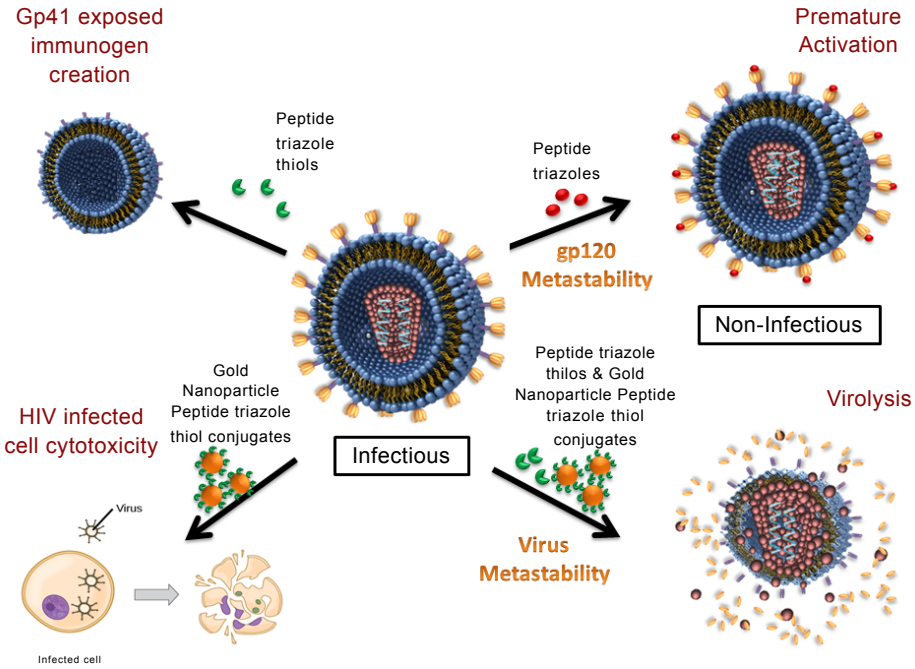

Figure 3: Schematic representation of the different effects of peptide triazoles and its conjugates. It summarizes the different stages of HIV infection.

present an increased local concentration of this virolytic inhibitor on a single virion we can lead to nearly 200 fold potency enhancement of virolysis compared to peptide alone and also further we saw that this leads to disruption of the infected cells that act as a virus producing factory.

Therefore (Figure 3) summarizes the effects of peptide triazole inhibitors as well as their multivalent gold nanoparticle conjugates and shows how they target different stages of the virus infection as well as how they act as a multi level process that can be used as microbicides to exterminate the disease completely. This therefore is a innovative approach that can be developed further for longer bioavailability as well as microbicidal preparations in order to create a multi-process inhibitor that can target the virus and lead to pre-infective inactivation and complete breakdown of the virus.

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