HIV entry inhibitors: mechanisms of action and resistance pathways

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Entry inhibitors represent a new generation of antivirals for the treatment of HIV infection. Several compounds which block the attachment of HIV gp120 to either the CD4 T cell receptor or the CCR5/CXCR4 co-receptors are currently in clinical development. Most of these compounds have different molecular structures and specific mechanisms of action. These agents are eagerly awaited by a growing number of patients carrying viruses resistant viruses to many of the current available reverse transcriptase and protease inhibitors. For enfuvirtide, the first and, so far, only entry inhibitor approved for clinical use, the main mechanism of resistance is the selection of changes within a 10 amino acid segment encompassing residues 36–45 within the HR1 region of gp41. For other entry inhibitors, multiple changes in different gp120 domains (V1, V2, V3, C2 and C4) have been associated with loss of susceptibility to these agents, although in most cases with limited cross-resistance.

Keywords: antivirals, gp120, CCR5, CXCR4

Introduction

Viral entry currently represents one of the most attractive targets in the search for new drugs to treat HIV infection. Thanks to the advances in the knowledge of the molecular basis of the mechanisms involved in the entry process, it has been possible to split it into several steps and design molecules to block each one of them. The main steps in the viral entry process are (i) attachment of the viral gp120 to the CD4 T cell receptor, (ii) binding of the gp120 to CCR5 or CXCR4 co-receptors and (iii) fusion of the viral and cellular membranes (Figure 1).

Entry inhibitors are a new family of antiretrovirals presently represented only by one drug, enfuvirtide, the first fusion inhibitor, but many other compounds are in the process of clinical development and certainly will be part of the therapeutic armamentarium within the next few months or years. These compounds are eagerly awaited and may prove beneficial for the growing number of HIV-infected individuals who have developed resistance to the currently available reverse transcriptase (RT) and protease inhibitors.

The threat of resistance is always present in HIV therapeutics, and there is no doubt that HIV will develop resistance to entry inhibitors also. However, the good news is that no cross-resistance with the currently available antiretrovirals is expected given their distinct mechanisms of action. Herein, we review in detail how HIV entry inhibitors block each stage of the entry process and which are the mechanisms by which resistance may develop (Table 1).

CD4–gp120 binding

The identification in 1984 of the CD4 molecule as the major receptor used by HIV to enter into cells was a breakthrough in the knowledge of HIV biology. The first step in the HIV entry process is initiated by the binding of HIV gp120 to CD4 on the target cell surface. The viral protein gp120 is composed of an inner and an outer domain connected by a bridging sheet, a four-stranded antiparallel β-sheet. In those domains are localized five conserved (C1–C5) and five variable (V1–V5) regions (Figures 2 and 3). The most critical regions involved in the viral entry process are V1/V2, V3 and C4. The three-dimensional functional structure of gp120 has been characterized and shown to contain intramolecular disulphide bonds, which are critical for the interaction with the CD4 receptor and any potential drug inhibitor.

The CD4 receptor binds between the outer and inner domains of HIV gp120. Its binding creates a cavity that is well-protected and conserved among different HIV strains. Moreover, this cavity does not contain glycosylation sites. These unique characteristics have encouraged its study as a therapeutic target in the search for new agents that may specifically bind and block the initial step of HIV infection.

Electrostatic forces mainly drive the CD4–gp120 binding, with the positive charge at the primary end of CD4 attracted to the primary negative charge cavity of HIV gp120. Furthermore, van der Waals’ forces and hydrogen bonds help to stabilize the CD4–gp120 interaction. The CD4 phenylalanine is the only residue that...
binds to this cavity; hence, the cavity of HIV gp120 has been designated as the Phe-43 cavity. This residue is quite significant in CD4–gp120 binding because it is estimated that it alone accounts for 23% of the total energy of CD4–gp120 binding. Following the CD4–gp120 binding, the gp120 conserved core undergoes conformational changes, moving from the rigid to a flexible state, allowing a subsequent interaction with the chemokine co-receptors. The Phe-43 cavity in HIV gp120 was initially pursued as a potential target for small molecules that could bind it and block the HIV entry.

**CD4–gp120 binding inhibitors and their mechanism of action**

There are many molecules able to inhibit gp120–CD4 binding, they have different structures and mechanisms of action. **PRO-542** (CD4-IgG2) is a tetravalent soluble recombinant antibody-like fusion protein that incorporates four copies of the virus-binding CD4 domain and mimics the CD4 receptor. It is one of the gp120–CD4 binding inhibitors in more advanced stages of clinical development. Currently it is being evaluated in Phase II trials. Phase I studies concluded that PRO-542 was well tolerated without apparent dose-limiting toxicities. Moreover, pre-clinical studies combining PRO-542 and enfuvirtide have suggested synergy in the inhibition of HIV replication. As a disadvantage, PRO-542 cannot be orally prescribed.

**TNX-355** is a non-immunosuppressive monoclonal antibody directed against the CD4 receptor. It competes with HIV gp120 for CD4 binding. Early in vitro studies reported that the antibody binding site in the CD4 receptor is different from the site involved in the interaction with HIV gp120. Thus, TNX-355

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**Figure 1.** HIV entry process. (a) CD4–gp120 binding, (b) gp120-co-receptor interaction and (c) viral and cellular membrane fusion.

**Table 1.** HIV entry inhibitors: mechanisms of action and resistance pathways

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*aThe clinical development of aplaviroc was halted in October 2005 after recognition of severe hepatic damage in some patients.

*bApproved for clinical use in 2003 by the FDA.*
Resistance to CD4–gp120 inhibitors

Several in vitro models have tried to describe the mechanism of action of all these inhibitors, which still remains unclear. Because all these molecules act in different ways, it is expected that their mechanisms of action will differ as well. As a consequence, resistance may develop in any of the different pathways and no cross-resistance should be expected among these compounds.

In vitro studies conducted with BMS-806 and related compounds (BMS-155) have shown that gp120 amino acids involved in resistance are those surrounding the Phe-43 cavity and a water-filled channel that extends from this cavity to the inner domain. Several changes in gp120 residues Trp-112, Thr-257, Ser-375, Phe-382, Met-426, Met-434 and Met-475 result in the escape of HIV strains from BMS-806 and BMS-155 inhibitors.7,20,21 It is interesting to note that the degree of sequence conservation in the nearby V1/V2 variable loops indirectly influences the susceptibility to these drugs. Even though V1/V2 regions are not absolutely required for BMS-806 or BMS-155 binding to gp120, its deletion may alter the susceptibility of some HIV strains to these inhibitors.7 Thus, natural gp120 variability among different HIV-1 subtypes may account for differences in baseline susceptibility to these compounds. Preliminary data suggest that BMS-806 activity might be compromised in some non-B subtypes, particularly in subtypes C and CRF01_AE, which seem to be naturally resistant to BMS-806.26

gp120–co-receptor interaction

In addition to binding to the CD4 cell receptor, HIV needs to bind to a chemokine co-receptor to enter the cells. The main co-receptors involved in HIV entry are by far CCR5 and CXCR4. The formation of the CD4–gp120 complex elicits conformational changes in the viral envelope allowing it to interact with CCR5 or CXCR4.

CCR5 and CXCR4 belong to the seven transmembrane G protein-coupled receptor family. They have an α-helix structure composed of four transmembrane domains, three extracellular loops and one N-terminal domain. The CD4–gp120 complex binds to any co-receptor through the V3 region although other HIV gp120 regions such as V1/V2 and C4 may also be involved in this interaction.27 V3 amino acid sequences determine the co-receptor use.28

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CCR5 antagonists and their mechanism of action

CCR5 and CXCR4 antagonists are divided into three groups depending on their size. Large molecules, such as PRO-140, or molecules with a medium size, as Met-RANTES and AOP-RANTES, which are modified CCR5 natural ligands, make CCR5 inaccessible. Finally, several small-molecule inhibitors directed against CCR5 (TAK-779, SCH-C, SCH-D, UK-427857 and GW-873140) or CXCR4 (AMD3100 and KRI-1636) have been developed.

Most CCR5 antagonists are small molecules which block the gp120–CCR5 interaction after binding to the co-receptor. These
molecules mimic chemokines, which are the natural ligands of the co-receptor, inhibiting their effect. **TAK-779** was the first non-peptide molecule that blocked the *in vitro* replication of R5 strains by interfering in their interaction with the CCR5 co-receptor. The binding site is localized in a CCR5 transmembrane cavity formed by the 1, 2, 3 and 7 co-receptor transmembrane regions. **TAK-779** has little oral bioavailability and its clinical development was discontinued due to local reactions at injection sites which made its management difficult. However, further studies based on TAK-779 have led to the identification of TAK-220. This compound blocks very effectively R5 strains replication and it is orally bioavailable. Phase II clinical trials are currently ongoing.

**TAK-652** is a new antagonist from Takeda Chemical Industries. It shows good oral bioavailability and *in vivo* studies have confirmed its high potency against HIV and a good safety profile. Moreover, it shows broad antiviral activity against different HIV subtypes. **PRO-140** is a monoclonal antibody directed against the CCR5 co-receptor, and in this way it blocks the binding of HIV gp120. In addition to the inhibiting the entrance of HIV-1 subtype B, **PRO-140** is effective against A, C, E and F subtypes. Phase I/II clinical trials are currently ongoing.

The safety and tolerability of **SCH-C** (SCH-351,125) was recently evaluated. SCH-C exerts potent *in vitro* antiviral activity against R5 strains. However, high doses of the drug have been associated with prolongations in the QT cardiac interval. On the basis of this finding, the clinical development of SCH-C has been halted in favour of its analogues **vicirovirc** (SCH-417, 690 or SCH-D) and **AD101** (SCH-350,581). These CCR5 antagonists are orally bioavailable and interact directly with the CCR5 transmembrane cavity, inhibiting HIV gp120 binding. Even though a Phase II study with vicirovirc in treatment-naive HIV-infected patients was recently discontinued due to the poor antiviral activity observed in some patients, the Phase II study in treatment-experienced patients is ongoing. Furthermore, promising pharmacokinetic and pharmacodynamic properties of vicirovirc when boosted with 100 mg of ritonavir have awakened much interest.

**Maravirok** (UK-427, 857) is an orally bioavailable CCR5 antagonist developed by Pfizer. Initial results from Phase II trials were very promising. Almost all patients experienced a remarkable reduction in plasma viraemia (mean of 1.42 log) and remained suppressed for at least 10 days post-treatment. **Maravirok** binds to the transmembrane co-receptor cavity, within the 2, 3, 6 and 7 helix, which is different than the region targeted by TAK-779. The drug is currently in advanced steps of clinical development and is expected to be approved in the near future.

Finally, **apilavirc** (GW-873140) showed significant *in vitro* and *in vivo* antiviral activities, with mean declines in plasma viraemia of 2 logs. However, in October 2005, GlaxoSmithKline announced the discontinuation of the clinical development of the drug due to the appearance of unexpected serious hepatotoxicity. Studies performed with apilavirc and other CCR5 antagonists (SCH-C and TAK-779) showed that apilavirc exerted potent activity against R5 viruses. The drug interacted directly with ECL2 and not with the transmembrane cavity. Due to this different mechanism of action, distinct resistance pathways could be expected and no cross-resistance with other CCR5 antagonists, such as maravirok or vicirovirc, may be assumed.

The CCR5 co-receptor binding site in HIV gp120 is concealed by V1/V2 and V3. Once HIV gp120 binds to CD4 different conformational changes occur and the CCR5 co-receptor binding site is exposed. In the absence of CCR5 antagonists, the CCR5 N-terminus interacts with residues located in the bridging sheet and the V3 stem of HIV gp120, whereas ECL2 interacts with the V3 crown. In the presence of an inhibitor, the conformation of ECL2 is modified and it can no longer interact with the V3 crown, therefore inhibiting viral entry. Although this model was initially developed for AD101 and SCH-C antagonists, it is thought to be the mechanism of action of all small-molecule inhibitors of CCR5. However, TAK-779, SCH-C, vicirovirc and aplaviroc have different molecular structures and bind to CCR5 in different ways.

**CXCR4 antagonists and their mechanism of action**

The potent antiviral activity that AMD3100 shows against X4 strains has been confirmed in different *in vitro* and *in vivo* studies. However, AnorMED, the pharmaceutical company owning this compound, re-orientated the clinical use of AMD3100, now termed Mozobil™, towards stem cell mobilization for transplantation of stem cells in cancer patients (non-Hodgkin lymphoma and multiple myeloma), after recognizing abnormal cardiac activity in two patients recruited in Phase Ia/Iib clinical trials. Moreover, AMD3100 did not show the expected antiviral activity at the doses tested. Subsequent studies have identified derivatives which show potent antiviral activity. One of these compounds AMD070 shows good oral bioavailability and seems to be well tolerated. In March of 2005, AnorMED announced the start of Phase Ib/IIa clinical trials with AMD070.

**KRH-1636** is another CXCR4 antagonist, which shows antiviral activity similar to that of AMD3100. Studies conducted in rats showed that this drug appears to be duodenally absorbable and thus is expected to be orally bioavailable. **KRH-2731** is a new CXCR4 antagonist that binds to the second and third extra-cellular loops (ECL2 and ECL3) of CXCR4. *In vitro* studies have confirmed its potent antiviral activity against X4 and R5X4 HIV strains, which could be 10-fold higher than that for AMD070. It shows good oral bioavailability. Phase II trials are currently ongoing.

The binding site for CXCR4 antagonists is located in the ECL2 of the CXCR4 co-receptor. Due to the highly negative charge that CXCR4 exhibits on the surface, it is thought that the interactions with the HIV gp120 V3 loop are mainly achieved by means of electrostatic forces.

**Resistance to CCR5 and CXCR4 antagonists**

Two main resistance pathways are theoretically possible for CCR5 and CXCR4 antagonists. The first is a shift in co-receptor usage and the second results from changes in HIV envelope genomic regions which allow the interaction between gp120 and the co-receptor despite the presence of the inhibitor.

Data available so far suggest that most CCR5 antagonist-resistant strains continue the use of the CCR5 co-receptor rather than shifting to CXCR4. Furthermore, multiple mutations within different regions of HIV gp120 (V3, C2, V2, C4) account for the drug-resistant phenotype. Most resistance mutations are
specific for each of the different compounds, which may hopefully limit cross-resistance. However, large clinical studies are needed to prove this concept. Preliminary findings with HIV isolates resistant to maraviroc have demonstrated that they remain susceptible to SCH-C, vicriviroc and aplaviroc. In contrast, vicriviroc-resistant strains show cross-resistance to SCH-C, AD101 and RANTES derivatives, most probably because they share their interaction site with the CCR5 co-receptor. In any case, CCR5 antagonist-resistant strains do not show cross-resistance with the current approved antiretrovirals, RT and protease inhibitors. Nor are they cross-resistant to other entry blockers, such as CD4–gp120 binding inhibitors and enfuvirtide.

Resistance to CXCR4 antagonists is less well documented than resistance to CCR5 antagonists. Mutations in the HIV gp120 V3 domain seem to account for the loss of susceptibility to many of these compounds. However, mutations in other HIV gp120 regions (V1, V2 and V4) have also been associated with resistance to CXCR4 antagonists, including a five amino acid deletion [codons 364–368 (FNSTW)] within the V4 domain.

Although preliminary results have not identified a shift in co-receptor use as the main resistance pathway for evading CCR5 antagonists, it will be important to closely monitor this, particularly in patients with a mixed population of R5 and X4 viruses at baseline. In a Phase IIa clinical study involving the R5 inhibitor maraviroc, one patient with an R5/X4 mixture viral population was inadvertently enrolled. Changes in circulating viruses were analysed during and after the maraviroc treatment. Although R5 variants were suppressed during maraviroc treatment, they again became the dominant population upon treatment cessation. However, another patient enrolled in a clinical trial...
with aplaviroc experienced a shift in the viral population from R5 to R5/X4 on day 10 of the treatment, suggesting that R5/X4 or X4 viruses could be present as minor quasispecies in some individuals and become predominant following initiation of therapy with CCR5 antagonists. The demonstration of a shift in co-receptor use from CCR5 towards CXCR4 using CCR5 antagonists could have dreadful consequences in HIV disease progression, since X4 isolates tend to be more virulent than R5 viruses. On the other hand, the converse could happen as well with the use of CXCR4 antagonists, in which case a shift to R5 viruses occurs. The results from ongoing larger clinical trials with these compounds are eagerly awaited and will answer these critical questions.

Fusion inhibitors and their mechanism of action

Following the interaction between the gp120–CD4 complex and the chemokine receptor CCR5 or CXCR4, additional conformational changes take place in the viral envelope that cause a shift from a non-fusogenic to a fusogenic state of the HIV gp41, which ultimately drive the fusion process. The N-terminal domain of gp41 is exposed and inserted through the fusion peptide (FP) into the cellular membrane. Later, gp41 experiences a structural reorganization that provokes the interaction between the heptad repeat regions HR1 and HR2, forming a thermostable, six-helix bundle structure, which is critical for the viral and cellular membrane fusion. The change in free energy associated with the formation of the six-helix bundle provides the force necessary for the fusion pore formation, and the viral capsid enters the target cell through this process.

The antiviral properties of peptides synthesized on the basis of the amino acid sequences of HR1 and HR2 of gp41 were originally recognized in the early 1990s. DP106, which mimicked a fragment of the HR1 amino acid sequence, was the first HIV peptide inhibitor described. In 1993, the in vitro potency of another peptide, DP-108, synthesized on the basis of the amino acid sequence of HR2, was demonstrated. This molecule is currently known as T-20 or enfuvirtide. Enfuvirtide is a synthetic peptide of 36 amino acids that mimics an HR2 fragment of gp41. Its binding to the HR1 region blocks the formation of the six-helix bundle structure, which is critical for the fusion process. The clinical efficacy and safety of enfuvirtide was demonstrated in the TORO 1 and 2 clinical trials, in which the virological and immunological benefits of adding enfuvirtide along with an optimized antiretroviral regimen in multidrug-experienced patients was demonstrated. Enfuvirtide was approved for the treatment of HIV infection in the year 2003.

T-1249 represents a second generation of fusion inhibitors. This molecule is a 39 amino acid peptide synthesized, like enfuvirtide, on the basis of the HR2 sequence. However, it overlaps a different HR1 region. Interestingly, T-1249 was active against HIV-1 enfuvirtide-resistant strains as well as against HIV-2 and SIV. However, the clinical development of this drug was discontinued in January 2004.

Resistance to fusion inhibitors

Early in vitro studies showed that enfuvirtide resistance involves the selection of changes in a three amino acid domain (positions 36–38) within the HR1 region of gp41. Subsequent results obtained in clinical studies have shown that resistance in patients receiving enfuvirtide may also be due to changes expanding from codon 36 to 45 within HR1 (GIVQQQNNLL) (Figure 5). A spectrum of different mutations has been described in this amino acid region (positions 36–45), each one reducing significantly, although to a different extent, the susceptibility to the drug. Overall, enfuvirtide should be considered as a drug with a low genetic barrier for resistance.

A wide range of susceptibility to enfuvirtide in viral isolates has been shown in enfuvirtide-naive patients, as well as in individuals undergoing enfuvirtide therapy and harbouring apparently the same resistance mutations. The determinants of this heterogeneity are unclear, but polymorphisms in the HR2 region of gp41 as well as changes in HR2 selected during enfuvirtide treatment could explain this phenomenon. Several changes in HR2 have been recognized in patients under enfuvirtide therapy.

Figure 5. Schematic representation of the gp41 linear structure. Enfuvirtide and T-1249 sequences mimic HR2. FP, fusion peptide; CC, cysteine-cysteine; TM, transmembrane domain.
although they do not seem to follow a specific pattern. Therefore, it is difficult to conclude that changes in HR2 may influence enfuvirtide susceptibility. However, some authors have identified specific changes in HR2 selected during enfuvirtide therapy (i.e. mutation S138A), which could be secondary and/or compensatory mutations.

There is controversy regarding the impact of HIV co-receptor use on susceptibility to enfuvirtide. While some in vitro studies have shown that R5 strains could be more resistant to enfuvirtide, in vivo studies have not found significant differences in the response to enfuvirtide therapy when comparing patients harbouring R5 strains with those harbouring X4 strains. Besides viral factors, host determinants (i.e. the level of co-receptor expression on target cells) may also influence the susceptibility to enfuvirtide. In this way, the presence of high levels of CCR5 on the cellular surface might result in more rapid HIV fusion, reducing the time during which HIV gp41 could be targeted by enfuvirtide. Accordingly, individuals carrying Δ32–CCR5, who express low levels of CCR5, seem to respond more favourably to enfuvirtide.

Conclusions

Entry inhibitors are a promising therapeutic option for HIV-infected patients carrying drug-resistant viruses. Enfuvirtide is the first fusion inhibitor approved for clinical use, but many other compounds are currently in the advanced stages of clinical development. The knowledge of the mechanisms of action of each of these molecules is crucial to understand and predict the corresponding resistance pathways. While resistance to enfuvirtide is largely dependent on the selection of changes in residues 36–45 within the gp41 HR1 region, the resistance profile for other entry inhibitors is expected to be more complex. The variability of the env gene among the different HIV strains, in conjunction with the different structures and mechanisms of action of the whole family of entry inhibitors, is the major factor responsible for this complexity. Multiple changes in different gp120 domains have been associated with resistance to entry inhibitors. Moreover, it remains to be confirmed whether a shift in co-receptor use might be an alternative pathway for HIV to evade drug pressure in patients exposed to CCR5 or CXCR4 antagonists.

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References

1. Poveda E, Briz V, Soriano V. Enfuvirtide, the first fusion inhibitor to treat HIV infection. AIDS Rev 2005; 7: 139–47.


