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Review Article

HIV gp120 envelope as a therapeutic target

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CONTENTS

Abstract

The human immunodeficiency virus type 1 (HIV-1) gp120 and gp41 envelope proteins play essential roles in orchestrating the sequential, multitiered viral entry process. This review discusses antiviral agents that target several key functional areas of gp120: the CD4 and co-receptor binding sites, the V3 loop and specific carbohydrate moieties. These regions represent promising antiviral targets, and significant progress towards the development of novel entry inhibitors has been made in recent years. Importantly, an orally available, small-molecule attachment inhibitor (BMS-488043) and a fusion protein (PRO-542), both targeting the conserved CD4 binding pocket of gp120, have demonstrated clinical efficacy in humans, which validated gp120 as a viable antiviral target. The development of microbicides targeting gp120 to prevent sexual HIV transmission is also discussed.

Introduction

HIV-1 infection remains a major medical problem with approximately 40 million people worldwide currently living with the virus, about 5 million people newly infected and 3.1 million fatalities due to AIDS (acquired immunodeficiency syndrome) (1). Despite the availability of 4 classes and 24 approved antiretroviral agents (nucleoside/nucleotide and non-nucleoside reverse transcriptase inhibitors, protease inhibitors and the fusion inhibitor enfuvirtide), treatment failure continues to occur due to the emergence of drug-resistant strains, inadequate exposure and/or poor adherence, frequently caused by drug-associated toxicity or side effects. Transmission of HIV-resistant viruses in newly diagnosed HIV infections has also been frequently documented (2, 3) and is expected to increase over time. This trend further contributes to an increased demand for new classes of antiretroviral drugs. Mucosal microbicides, topical agents for blocking HIV-1 infection, are also urgently needed to prevent sexual transmission.

Prevention of viral entry is the first line of defense against HIV infection. The entry process, mediated by HIV envelope glycoproteins, provides multiple new targets for intervention and drug discovery. HIV entry to host cells begins with the attachment of the envelope protein gp120 to cellular CD4 receptors. This high-affinity interaction initiates conformational changes in gp120 that result in sequential binding to a co-receptor (CCR5 or CXCR4), insertion of a viral gp41 fusion peptide into the host cell membrane, and the fusion of viral and cell membranes (for review, see 4).

The gp160 viral envelope precursor (~845-870 amino acids) is synthesized in the rough endoplasmic reticulum. The glycosylated gp160 trimers are proteolytically cleaved in the Golgi apparatus to an exterior gp120 and a transmembrane gp41 glycoprotein. About half of the gp120 molecular weight is provided by carbohydrates. Of the 24 asparagine (*N*)-linked oligosaccharides found on its surface, 11 contain a high mannose content. Sequence analysis of HIV isolates identified 5 variable (V1 through V5) regions interspersed with 5 conserved regions (C1 through C5) in gp120 (5). Intramolecular disulfide bonding of V1 to V4 results in loop formation and C1 to C5 fold into a gp120 core. This structural design allows genetically diverse HIV isolates to retain the vital mechanism of “viral entry” using the conserved core, and to simultaneously evade the host immune system via loop variation, steric occlusion of conserved areas, conformational changes and a carbohydrate camouflage (6).

The crystal structure of the HIV gp120 core (lacking V1-V2, V3 loops, *N*- and *C*-termini) in complex with a

2-domain fragment of CD4 and the Fab fragment of 17b, a monoclonal antibody (MAb) that recognizes the CCR5 co-receptor binding region of gp120, has been reported (7). This CD4-bound structure is composed of an inner and an outer domain, as well as a bridging sheet, which all contribute to interactions with CD4. Recently, the structure of a fully glycosylated simian immunodeficiency virus (SIV) gp120 core (excluding V1-V2, V3 loops and parts of *N*- and *C*-termini) in an unliganded conformation was solved (8, 9). It exemplifies the structure of gp120 before CD4 binding, yielding critical information on how gp120 rearranges itself while engaging the receptor. CD4 binds in a conserved recessed pocket of the gp120 core, which includes a shallow and a deep cavity. The opening of the deep cavity is occupied by the phenylalanine 43 (F43) residue of CD4, which contributes to 23% of all CD4 interatomic contacts with gp120 (7, 10). Extensive CD4 contacts (26) in this highly conserved gp120 pocket create an excellent opportunity for therapeutic intervention. The large bonding energy generated by gp120-CD4 binding is believed to drive reordering of gp120 V1-V2 loops, the V3 loop and the bridging sheet to form a functional co-receptor binding site (11). Subsequent binding of this site with CCR5 or CXCR4 co-receptors represents another potential antiviral target. The sequence of the gp120 V3 loop determines the choice of co-receptor the virus uses; a critical interaction for viral entry (12). The V3 and V1-V2 loops and *N*-linked carbohydrate on or near these variable loops have been implicated in the neutralization of HIV-1 isolates by antibodies to circumvent immune evasion, and provide additional potential targets (13, 14).

Taken together, the unique structure of gp120 offers many new antiviral targets, including the CD4 and co-receptor binding sites, the V3 loop, and even the carbohydrate shield. However, the inherent gp120 sequence diversity may pose challenges to entry inhibitor development, including limited viral strain coverage and the rapid emergence of resistance. This review summarizes various gp120 inhibitors according to target sites and provides information on their developmental status. Enfuvirtide, CCR5 and CXCR4 blockers are excluded herein due to their gp41 or cellular target origins. Moreover, since entry inhibitors are being exploited as favored topical agents for blocking HIV-1 infection, studies assessing the potential of some gp120 antagonists as microbicides are discussed.

gp120 inhibitors

Targeting the CD4 binding site

Orally available, small-molecule inhibitors

Novel, small-molecule HIV-1 attachment inhibitors, exemplified by BMS-378806 (Table I) and its analogue BMS-488043, that block viral attachment to CD4 receptors were identified at Bristol-Myers Squibb. The compounds possess potent antiviral activity in cell culture, good oral bioavailability in animal species, and clean safety profiles in initial animal toxicology studies (15-17). Mechanism of action studies showed that attachment inhibitors blocked soluble CD4 (sCD4) binding to all 11 distinct HIV envelope gp120 proteins surveyed. They bind specifically and in an equimolar ratio to gp120 monomers. Binding of the compound and CD4 was mutually exclusive (15, 18). Attachment inhibitors also prevent virion envelope trimers from binding to sCD4 (19). Resistance mapping confirmed the inhibitor interaction sites and showed that selected substitutions span the CD4 binding pocket and other regions of the envelope. Finally, multiple gp120 variants with CD4 binding pocket substitutions were severely defective in compound binding (17, 18). Therefore, in contrast to a previous report (20), our combined data indicate that attachment inhibitor binding primarily disrupts gp120-CD4 interactions in wild-type HIV-1. A potential compound binding site was recently modeled on the SIV unliganded gp120 structure (8).

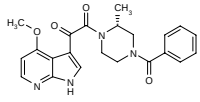
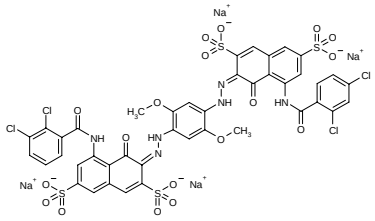
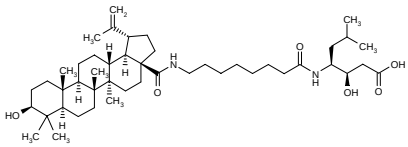
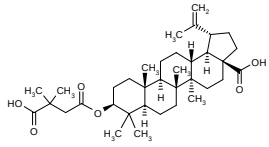
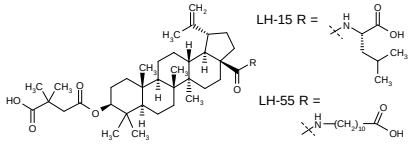
Several attachment inhibitors are currently being evaluated in clinical trials to select an optimal candidate. The antiviral activity, safety and tolerability of BMS-488043 have been investigated in a multiple-dose study in infected adults. Mean maximal changes in plasma HIV-1 RNA of up to -1.2 $\log_{10}$ (21). This compound was well tolerated and no serious adverse events were observed. Therefore, proof-of-concept has been established for this new class of orally bioavailable antiretrovirals. Since gp120 is validated as a viable target, further development of this series of attachment inhibitors is warranted.

CD4-IgG fusion protein PRO-542

The truncated form of sCD4 exhibited good antiviral activity against laboratory-adapted HIV-1 isolates but failed as a therapeutic anti-HIV agent due to its lack of activity against patient isolates and a short serum half-life (22, 23). PRO-542 (Progenics) is a fusion protein comprised of human IgG_2 in which the Fv portions of both heavy and light chains have been replaced with 4 copies of the HIV binding region of the CD4 receptor (domains 1 and 2). Due to its increased valency and conformational flexibility, PRO-542 broadly and potently neutralizes diverse primary HIV-1 isolates (24, 25). A single intravenous infusion of 10 (26) or 25 mg/kg (27) of PRO-542 to treatment-experienced HIV-1 subjects provided viral load reductions of about 0.5 $\log_{10}$, which persisted for up to 4-6 weeks post-treatment. Administration of 4 doses (10 mg/kg) of PRO-542 weekly to infected children generated a similar viral load reduction (> 0.7 $\log_{10}$) (28). PRO-542 appeared to be well tolerated in these studies, with no serious adverse events. However, intravenous administration and cost of protein drug may be obstacles to wider clinical use.

PRO-542 was also evaluated for its microbicidal properties. Sexual transmission of HIV-1 in women is primarily through mucosal infection of the cervical and vaginal

Table I: Profiles of selected inhibitors.

Name	Structure	Target	Development stage	Ref.
BMS-378806 and analogues		CD4 binding site on gp120	Phases I and II	15-17, 21
FP-21399		V3 loop of gp120	Phase II	45-56
IC-9564		Entry	Preclinical	68-70
PA-457		Budding	Phase II	72
LH-15 and LH-55		Entry and budding	Preclinical	73

tissues. Using human cervical mucosal tissues *in vitro*, PRO-542 was shown to block both localized HIV-1 infection and viral dissemination pathways (29), suggesting its potential application as a microbicide.

Chimeric protein sCD4-17b

To improve potency and viral strain coverage over neutralizing MAbs, a novel single-chain sCD4-17b neutralizing agent was designed. It contains sCD4 attached via a flexible polypeptide linker to a single-chain variable region of the 17b MAb (30). Individually, sCD4 and 17b proteins have minimal neutralizing abilities. However, when combined into a bifunctional protein with greater affinity for gp120, sCD4-17b potently neutralizes multiple primary HIV-1 isolates and exhibits better inhibitory activity than the neutralizing antibodies IgGb12, 2G12 (gp120 MAbs) and 2F5 (a gp41 MAb) (30). sCD4-17b is now being developed as a topical microbicide either as a purified protein or by expression in *Lactobacillus*, the major component of the microflora colonizing the healthy human vaginal tract (31).

CD4M9 and CD4M33 peptides

Inhibition of the CD4-gp120 interaction has also been attempted with CD4 mimetics. A 33-residue peptide inhibitor was constituted by replacing a loop of the scorpion toxin charybdotoxin with an equivalent of the gp120-binding CDR2-like loop from CD4, which interacts directly with gp120. This miniprotein competitively inhibited the gp120-CD4 interaction and elicited antibodies specifically recognizing CD4 (32). A derivative of this miniprotein also induced exposure of CD4i epitopes (33). Further optimization provided an enhanced mini-CD4 protein (CD4M9; 28-mer) that could inhibit the replication of both laboratory-adapted and primary HIV-1 isolates, albeit with approximately 100-fold lower potency than a native sCD4 (34). Structural information on the CD4-gp120-17b complex (7) aided the synthesis of CD4M33, a new 27-amino-acid mimic with enhanced gp120 interaction properties. It binds to viral particles and diverse HIV-1 envelopes with affinity similar to native CD4 protein (35). In a sCD4/gp120 competition ELISA, CD4M33 had IC_{50} values of 4.0-7.5 nM compared to values of 1.1-2.0 nM for sCD4. It inhibited the replication of 8 HIV-1 strains with EC_{50}

values close to those of sCD4. Issues associated with the development of this compound class include molecular size, pharmacokinetic properties and drug delivery. To target multiple conserved CD4 binding pockets in the trimeric gp120, bivalent CD4 miniprotein inhibitors that contained 2 CD4M9 moieties tethered by a spacer of varied length were synthesized and evaluated (36). The synthetic bivalent miniproteins showed 5-21-fold enhancement in anti-HIV activity over the monovalent miniprotein, with the most potent molecule displaying an EC_{50} of 120 nM. This compound has a calculated distance of about 52 Å between binding phenylalanines, while the distance between CD4 binding sites on the gp120 trimer is approximately 30-60 Å.

In another approach, a small-molecule (MW 810), water-soluble, proteolytically stable CD4 β-turn mimetic (residues Q40 to T45 of the gp120 binding region of CD4) was reported to have a low micromolar K_d for HIV gp120 and to reduce syncytium formation. A patent application covering CD4-designed mimics has been published (37).

A phage display approach modifying the charybdotoxin scaffold resulted in the identification of effective gp120 binders lacking F43 (38). This method is potentially useful in assessing CD4/gp120 structural determinants and may facilitate the design of new attachment inhibitors. However, an alternative attempt to design small-molecule analogues to mimic the crucial features of CD4 F43 and R59 residues was unsuccessful (39).

Neutralizing MAb IgGb12

Eliciting human neutralizing MAbs which are effective against diverse HIV-1 envelopes is fraught with difficulties. Nevertheless, a select few have been identified that are highly potent against a broad spectrum of HIV-1 and possess very long serum half-lives, *i.e.*, 50-100 times longer than those of peptides such as enfuvirtide, a marketed fusion inhibitor. MAb IgGb12 (b12 for short) has a finger-like protrusion that fits precisely into the CD4 binding site of gp120, as depicted by the b12-gp120 structural docking model (40). It broadly neutralizes subtype B HIV-1 but is less active against other subtypes (41, 42). Like PRO-542, b12 was also shown to block both localized HIV-1 infection and viral dissemination *in vitro* in human cervical mucosal tissues (43). However, the development of an MAb as a potential therapeutic agent needs to overcome issues associated with production cost and drug delivery.

Targeting the co-receptor binding site

CCR5 *N*-terminal peptides

Both CCR5 and CXCR4 co-receptors contain negatively charged sulfotyrosines in the *N*-terminal gp120 binding regions that appear essential for function. For the CCR5 receptor, the 9 *N*-terminal amino acids (positions 10-18) and the 2 sulfotyrosines contained within (residues 10 and 14) are believed to be the minimal structure which binds to gp120 (44). As an example, an *N*-terminal peptide (the first 22 amino acids of the CCR5 *N*-terminus with tyrosines 10 and 14 sulfated and cysteine 20 altered to a serine) inhibited R5 virus infection at concentrations of 100-200 μM (45). The same sulfated peptide could also restore function to a CCR5 variant lacking residues 2-17 in the *N*-terminal region, suggesting that the tyrosine-sulfated region of the CCR5 *N*-terminus can act independently to mediate binding of chemokines and the HIV-1 envelope with the remaining domains of CCR5 (46). On the contrary, a full-length peptide reconstructing the entire *N*-terminal region of CCR5 failed to inhibit the entry of R5 viruses even in the sulfated form, and was shown to unexpectedly increase the infectivity of CXCR4 viruses through the upregulation of both CD4 and CXCR4 receptors (47). The seeming discrepancy with earlier data could be attributed to the lower concentrations used in this study (25-50 μM) or the fact that a full-length peptide was used instead of the truncated *N*-terminal region. This approach remains at an early research stage.

CCR5 extracellular loop peptides

Synthetic peptides corresponding to CCR5 extracellular loops 1, 2 or 3 caused concentration-dependent inhibition of fusion and HIV infection, although potencies and specificities varied for different envelopes. Due to the high concentrations (≥ 25 μg/ml) required to achieve ≥ 50% inhibition in sensitive strains, in addition to linear sequence determinants, the ordered structural peptide motifs are likely to be important. Combining suboptimal doses of 3 peptides (15 μg/ml) provided greater inhibition against some strains than after a single peptide (48). In another study, peptide mimics derived from the first extracellular loop of CCR5 bearing nonpeptide spacers in place of Ala-Ala-Ala residues in the CCR5 peptide moiety inhibited HIV-1 replication (49). Future progress in this and the CCR5 *N*-terminal peptide areas will likely entail size reduction, potency improvement and the development of drug-like sulfated tyrosines or isosteric replacements to maintain affinity for gp120.

Neutralizing Fab X5

Screening of human phage display libraries against a gp120-CD4-CCR5 complex to elicit broadly neutralizing MAbs led to X5, a custom-designed Fab (50). The X5 epitope was mapped to the vicinity of I423 and K432 on gp120 by site-directed mutagenesis and crystallography (51), which overlaps the MAb 17b binding site on gp120. The X5 footprint is very close to the CD4 and the co-receptor binding sites on gp120, but does not overlap them (51). This antibody inhibited infection of representative primary HIV-1 isolates from multiple subtypes with an efficiency comparable to that of the broadly neutralizing MAb b12 (50). However, in a separate study, X5 was

shown to neutralize only the sensitive HIV subtype B primary isolates (42). Due to its critical binding site on gp120, X5 can potentially be a useful component of a multi-MAb cocktail.

Targeting the V3 loop

Neutralizing MAb 447-52D

The MAb 447-52D neutralizes up to 47% of subtype B HIV-1 strains (41, 42) and docks to the conserved GPGR motif at the tip of the V3 loop. This loop is essential for gp120 binding to the HIV co-receptors (12). However, 447-52D does not appear to neutralize virus with the GPGQ motif that is prevalent in non-subtype B isolates (41). Combination with other anti-HIV agents will be needed to attain its potential use.

Neutralizing MAb hNM01

hNM01 is a humanized monoclonal antibody that binds to the V3 loop region (GPGRAF motif) of HIV-1 gp120. This binding leads to the activation of complement, disruption of the viral envelope and neutralization of at least 20 clinical isolates tested (52). An initial phase I dose-escalating study of hNM01 (0.2-5 mg/kg) administered intravenously showed that the antibody was well tolerated, with a mean elimination half-life of 6.4 days (53). However, hNM01 did not exert significant therapeutic effect. Additional studies with higher doses to evaluate efficacy and toxicity are being planned.

FP-21399

FP-21399 (Lexigen Pharmaceuticals) is a bis-azo compound, a member of the naphthalenesulfonic acid family (Table I). It inhibits viral entry to the cell likely by interacting with the gp120 V3 loop, as evidenced by blockade of the interaction between gp120 and antibodies against the V3 loop (54). An FP-21399-resistant virus harbors substitutions in the V3 and V4 regions of gp120, further supporting its molecular target (54, 55). A phase I study evaluated once-weekly intravenous administration of FP-21399 at doses of 1, 2 and 3 mg/kg for 4 consecutive weeks to 34 HIV-infected patients and found to be to well tolerated. CD4+ cell counts improved about 15% in some patients. Viral load reductions from –0.5 $\log_{10}$ to undetectable levels were observed in 4 patients (56). However, FP-21399 is no longer in development due to its compound color (personal communications).

Anionic polymers

Several polyanionic compounds, including dextrin-2-sulfate, cellulose sulfate, carrageenan, PRO-2000, SAMMA (mandelic acid condensation product) and cellulose acetate phthalate, are being evaluated as microbicides and have successfully undergone phase I clinical studies and beyond. A common property of these anionic polymers is their negative charge at neutral pH. Their antiviral activity is mediated by charge-based interactions with the positively charged areas of gp120, mainly in the V3 loop and the co-receptor binding areas. This binding likely impairs the viral entry function of the envelope. Some polyanionic compounds may also strip gp120 from the virus and inactivate it. Although this class of compounds has the advantage of low development cost and a reduced risk of systemic toxicity due to high molecular mass, the main concern is that most cationic V3 loops are specific to X4 viruses, which is not the key virus transmitted sexually (57, 58).

Targeting the carbohydrate moieties

Neutralizing MAb 2G12

The human neutralizing antibody MAb 2G12 recognizes a unique conformational gp120 epitope which is comprised of terminal mannose residues on 3 proximally located *N*-linked glycans to form an antibody footprint (14). The relative conservation of the gp120 glycan structure enables 2G12 to neutralize many subtype B HIV-1 isolates and some isolates from other subtypes (41, 42, 59). Once bound, 2G12 prevents gp120 from functioning during receptor attachment and fusion, probably by impeding gp120 binding to the co-receptor. Recent attempts have been made to determine whether combining 2G12 with the gp41 MAbs 2F5 and 4E10 could improve efficacy and reduce the potential for neutralization escape in humans. The initial phase I study showed that 2G12, 2F5 and 4E10 can be co-administered safely (60). Additional studies are now ongoing to determine if the combination approach can enhance antiviral effects.

Cyanovirin-N protein

Cyanovirin-N (CVN), an 11-kDa protein isolated from a cyanobacterium, exerted broad antiviral activity against diverse strains of HIV-1, HIV-2 and feline and simian immunodeficiency viruses. The protein interacted with high avidity with gp120 in a carbohydrate-dependent manner that occluded or altered the binding sites of MAb 2G12 (61, 62). CVN binding to gp120 led to steric blockage and/or conformational changes of gp120, resulting in the inaccessibility of the co-receptor binding site. Furthermore, CVN was reported to induce gp120 dissociation from target cells. The inhibition mechanism(s) of CVN involves interference with essential interactions between gp120 and cellular receptors (63, 64).

The broad antiviral activity, minimal cytotoxicity and resistance to physicochemical degradation make CVN an attractive candidate as a microbicide. The *in vivo* efficacy

of CVN gel was demonstrated in vaginal challenge and rectal transmission macaque models using a chimeric SIV/HIV-1 virus (65, 66). However, an efficient protein expression strategy will be required to sustain sufficient CVN concentrations in the vaginal mucosa and to overcome the high development cost of a protein microbicide (67). Potential immunogenicity of protein microbicides is also a concern.

gp120 inhibitors with partially defined mechanisms

Betulinic acid derivatives

The anti-HIV mechanism of betulinic acid derivatives varies widely with structure and the side-chain position. While the mechanism of IC-9564, with side-chains at the C-28 acid position and a free hydroxy group at position 3 (Table I), has not been unambiguously determined, it has been shown to inhibit the entry of both R5 and X4 HIV-1 and to target gp120 (68, 69). Selection with IC-9564 resulted in a T198P mutation mapped to gp120 of a primary isolate, which may cause resistance via an allosteric change in the envelope conformation (70). IC-9564 is in the preclinical stage of development.

Conversely, other betulinic derivatives containing side-chains at the 3 position and an unsubstituted C-28 acid, such as the HIV-1 maturation inhibitor PA-457 (Table I) (71, 72), exert their activities late in the viral life cycle. Recently, compounds with side-chains at both the C-3 and C-28 positions were prepared to assess their potential for blocking both HIV entry and maturation (Table I). Two compounds, LH-15 and LH-55 (Table I), were found to exhibit potency at least 1 log better than PA-457 or IC-9564 in an infectivity assay (73). In addition, these dual side-chain compounds inhibited viruses resistant to betulinic acid derivatives containing only a single side-chain at either position 3 or 28, suggesting that they are indeed able to work by two separate mechanisms.

12p1

A linear peptide, 12p1 (RINNIPWSEAMM) was isolated from a phage display library (74) and found to inhibit the interaction of gp120 with both CD4 and MAb 17b, a CCR5 surrogate, with IC_{50} values of 1.1 and 1.6 μM, respectively (75). 12p1 binds directly to gp120 with a binding stoichiometry of 1:1. Studies demonstrated that the peptide is an allosteric rather than a competitive inhibitor of CD4 binding and likely acts prior to achievement of a CD4-bound conformation of gp120. These results indicated that 12p1 binds to a unique site that may be a new target for novel CD4-gp120 inhibitors.

Conclusions

The HIV-1 gp120 envelope represents a new stage of the viral life cycle that can be effectively inhibited with small-molecule compounds, peptides, proteins and antibodies. Since currently available anti-HIV agents target reverse transcriptase, protease and the gp41-mediated fusion process, gp120 inhibitors are expected to be effective in patients already infected with viruses resistant to marketed drugs, thereby preserving therapeutic options for both treatment-naïve and -experienced patients. It is worth noting that gp120 inhibitors work extracellularly before virus entry and thus do not require cell uptake for antiviral activity. This class of antiretroviral agents may have fewer safety issues compared to co-receptor blockers, since the compounds target virus instead of a host cell target. Furthermore, new therapeutic combinations may be possible, as demonstrated by the synergistic antiviral effect seen *in vitro* when two HIV entry inhibitors are combined (76, 77). The enhanced antiviral effect may result from the interdependence of various entry steps. Although genetic diversity of the gp120 protein affects the viral strain coverage and resistance development rate, chemistry efforts to broaden the antiviral range appear feasible. Inhibitors with improved potency and better pharmacokinetic properties should also increase the viral strain coverage. Finally, co-administration with other anti-HIV agents in patients to reduce viral load threshold should significantly impede resistance development.

Steady efforts to develop approaches against HIV entry have continued since the initial failed attempts to use sCD4 in the clinic. Despite issues with drug delivery and production cost, the biological agent PRO-542, with a broad anti-HIV spectrum, holds promise for those patients failing current therapy. The fact that an orally available, small-molecule inhibitor like BMS-488043 exhibits excellent antiviral potency in infected patients further establishes gp120 as an exciting new antiviral target. Hopefully, various ongoing efforts in developing gp120 inhibitors will reach fruition in a not too distant future. Because an effective vaccine is currently not on the horizon, effective microbicides will be critical for preventing HIV sexual transmission. Since blocking HIV entry is the first line of defense against viral infections, gp120 is considered as a favored target for rational microbicide development and many potentially cost-effective HIV entry inhibitors are now being developed.

In summary, gp120 provides exciting alternative anti-HIV targets for new treatment and prevention measures, and thus may eventually offer more options for patients. Additional studies with this class of inhibitors are also likely to further enhance our understanding of the HIV-1 envelope structure and the viral entry process.

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