HIV chemokine receptor inhibitors as novel anti-HIV drugs

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Abstract

The chemokine receptors CXCR4 and CCR5 are the main coreceptors used by the T-cell-tropic (CXCR4-using, X4) and macrophage-tropic (CCR5-using, R5) HIV-1 strains, respectively, for entering their CD4+ target cells. In this review, we focus on the function of these chemokine receptors in HIV infection and their role as novel targets for viral inhibition. Besides some modified chemokines with antiviral activity, several low-molecular weight CCR5 and CXCR4 antagonistic compounds have been described with potent antiviral activity. The best CXCR4 antagonists described are the bicyclam derivatives, which consistently block X4 but also R5/X4 viral replication in PBMCs. We believe that chemokine receptor antagonists will become important new antiviral drugs to combat AIDS. Both CXCR4 and CCR5 chemokine receptor inhibitors will be needed in combination and even in combinations of antiviral drugs that also target other aspects of the HIV replication cycle to obtain optimum antiviral therapeutic effects.

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1. Introduction

The human immunodeficiency virus (HIV), that causes acquired immunodeficiency syndrome (AIDS), was first identified 20 years ago by Barre´-Sinousi and colleagues in 1983 [1,2]. Since its discovery as the etiological agent of AIDS, the disease has spread in successive waves in various regions around the world. At present, up to 40 million people are living with HIV/AIDS and already more than 20 million people have been killed by the global HIV/AIDS epidemic (UNAIDS/WHO Report, 2003). Tremendous efforts are made already to fully understand the pandemic of the virus and in consequence, to develop an effective therapy to control the spread of the virus. This led to the development of about 20 effective antiretroviral drugs approved by the Food and Drug Administration (FDA) for treating HIV-infected individuals. These drugs have been developed to target important and vulnerable steps in the virus replication cycle. The majority of them are reverse transcriptase and protease inhibitors, and a more recently approved drug is an HIV-1 fusion inhibitor [3]. Eventually, due to resistance caused by mutations, virus strains already became insensitive to most of these drugs. To overcome this tremendous problem, researchers started to test combination therapy of these single therapeutics and new derivatives are in development, active against these resistant viruses. In regions were these antiviral drugs are available, they already led to a decline of mortality due to HIV disease (UNAIDS/WHO Report, 2003).
The viral core contains two single strands of HIV RNA and multiple reverse transcriptase molecules (p51), the nucleocapsid proteins p6 and p7, the protease p11 and the integrase p32. The HIV genome exists of nine different genes whereof three (gag, pol and env) are common in all retroviruses [6]. Gag is the gene coding for the viral core proteins, pol codes for the viral enzymes reverse transcriptase, integrase and protease and env codes for the envelope glycoproteins. The other genes (tat, rev, vpr, nef, vif and vpu) are responsible for the organisation of the virus life cycle.

To ensure the effective production of new virions by its host cells the viral genome is flanked at each site by long terminal repeat (LTR) sequences that can bind cellular proteins to activate transcription under control of viral signals.

2.2. HIV replication cycle

HIV infection starts with adsorption of a HIV virion to the cell membrane [6,7]. First, the viral envelope protein gp120 binds to the cellular CD4 receptor that is expressed mainly on T-cells and monocyte/macrophages. This binding causes a conformational change in the gp120 uncovering the coreceptor binding site and subsequently the hydrophobic amino-terminal domain of gp41. Binding of the virion to its coreceptor, one of the chemokine receptors CCR5 or CXCR4, is followed by insertion of the N-terminal end of gp41 (‘fusion peptide’) into the cellular membrane causing fusion of the viral with the cellular membrane which admits virus entry into the target cell (see Section 4.3). Thereafter, the virus is uncoated, and the genetic material of the virus is released into the cell cytoplasm. The single-stranded RNA is immediately transcribed to double-stranded DNA by the viral reverse transcriptase enzyme. This “proviral DNA” then enters the cell nucleus and becomes integrated in the host cell DNA under catalyzation of the viral enzyme integrase. After integration, HIV can persist latently for many years [8–10]. By reactivation of the host cell, transcription from DNA into messenger RNA (mRNA) is started including the inserted viral DNA, which is subsequently translated into viral proteins. After migration of the viral RNA and viral proteins out of the cell nucleus and post-translational modification of viral proteins by the viral enzyme protease, these virus elements assemble at the cell membrane into a new virion. During a process that is called ‘budding’, the new virion is released from the cell surface using the host cells’ surface bilayer to form its outer shell.

3. Antiviral therapy

The widespread use of currently approved drugs, reverse transcriptase and protease inhibitors, has already resulted in a significant decrease of mortality of HIV-infected persons in the developed world. Introduction of highly active antiretroviral therapy (HAART), which uses combinations of three or more reverse transcriptase and protease inhibitors, showed already a decrease of viral load to below detectable levels but still cannot eliminate HIV completely in infected individuals. The virus remains in viral reservoirs, from where it rebounds after therapy is stopped [8–10]. Moreover, the efficacy of these products is limited by the emergence of drug-resistant HIV strains [3]. Furthermore, these AIDS-slowing drugs are unaffordable in countries of the less developed world [11]. In addition to the efforts made to improve these currently available drugs to overcome these problems, investigational agents are in development in various classes, each class targeted at another intervention point in the viral life cycle. Table 1 gives an overview of the different classes of inhibitors and the currently available or new potential agents in those distinct classes.

The development of new and improved antiretroviral drugs has to deal with issues of long-term toxicity, oral availability, and drug-resistance and cross-resistance. Besides the well-known reverse transcriptase and protease inhibitors, which are already relatively numerous, another
class of inhibitors, designated entry inhibitors is under investigation, which as their name indicates, inhibit penetration of the HIV virion through the host cell membrane. These entry inhibitors can be subdivided in three different classes, each inhibiting another step of viral entry. The first class of compounds, the adhesion inhibitors, is targeted at the gp120-CD4 binding. Secondly, the coreceptor antagonists inhibit the binding of HIV-1 to the chemokine receptors CCR5 and CXCR4, the major coreceptors for HIV-1. The third class is that of the fusion inhibitors, which bind to different components of gp41, and in this way prevent fusion of the virus with the cellular membrane. The first entry/fusion inhibitor T-20 or enfuvirtide (FuzeonTM) has recently been approved by the FDA. This agent is not bioavailable and one report already showed rapid emergence of clinical resistance to this novel class of compounds [12].

The integrase inhibitors are another new class of antiretroviral compounds that interfere with one or more catalytic functions of the viral integrase enzyme. In addition, also the maturation (assembly) inhibitors are a new class of HIV inhibitors, which prevent assembly of new virus particles.

4. Chemokine receptors as HIV coreceptors

Almost a decade ago now, the chemokine receptors CCR5 and CXCR4 were identified as the major coreceptors for HIV-1 entry, besides the cellular CD4 receptor [13–17]. The observation that the natural ligands of these receptors (RANTES/CCL5, MIP-1α/CCL3, LD78β/CCL3L1, MIP-1β/CCL4 SDF-1/CXCL12) and also some specific monoclonal antibodies against certain epitopes of these receptors possess anti-HIV-1 activity, made these chemokine receptors attractive novel targets for future anti-HIV therapy [18]. This idea was further supported by the fact that people with a homozygous 32 basepair (bp) deletion in the CCR5 gene (CCR5 Δ32/Δ32), that is decoded in a receptor protein that remains intracellular, show a complete normal phenotype and are relatively resistant against HIV-1 infection [19–21].

4.1. Chemokine receptors

The migration and activation of leukocytes during normal and inflammatory processes is controlled by chemotactic cytokines or chemokines [22]. Chemokines mediate their biological activities by binding to their specific chemokine receptors. To date, 6 CXC- (CXCR1–6), and 10 CC-chemokine receptors (CCR1–10), 1 XC- and 1 CX3C-chemokine receptor are identified [23]. Chemokine receptors are members of the rhodopsin or serpentine receptor superfamily. These are G protein-coupled seven transmembrane (7TM) receptors (GPCR), containing an acidic extracellular N-terminal domain, 7TM regions and an intracellular cytoplasmatic tail. The N-terminal domain is believed to be essential for ligand binding, whereas the

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### Table 1
Overview of HIV chemokine receptor inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Characteristics</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Modified chemokines</td>
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<tr>
<td>Met-RANTES</td>
<td>Aminoterminal addition of methionine residue</td>
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</tr>
<tr>
<td>RANTES(9–68)</td>
<td>Synthetic truncated form of RANTES</td>
<td>[100]</td>
</tr>
<tr>
<td>RANTES(3–68)</td>
<td>Processed by CD26; two N-terminal amino acids removed</td>
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<tr>
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<td>Aminooxypentane-RANTES</td>
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<td>NNY-RANTES</td>
<td>N-nonanoyl-RANTES</td>
<td>[87]</td>
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<tr>
<td>Met-SDF-1</td>
<td>Aminoterminal addition of methionine residue</td>
<td>[105]</td>
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<tr>
<td>AOP-LD78β</td>
<td>Aminooxypentane-LD78β</td>
<td>[104]</td>
</tr>
<tr>
<td>PSC-RANTES</td>
<td>Substitution of first three N-terminal amino acids for a nonanoyl group, a thioproline, and a cyclohexylglycine</td>
<td>[103]</td>
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<th>CXCR4 antagonists</th>
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<tbody>
<tr>
<td>AMD3100</td>
<td>Small-molecule bicyclam</td>
<td>[114]</td>
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<tr>
<td>ALX40-4C</td>
<td>9 β-Amino acid polycationic peptide</td>
<td>[124]</td>
</tr>
<tr>
<td>T22</td>
<td>18 Amino acid peptide; polyphemusin</td>
<td>[121]</td>
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<tr>
<td>T140</td>
<td>14 Amino acid peptide</td>
<td>[123]</td>
</tr>
<tr>
<td>CGP64222</td>
<td>9 Amino acid basic peptide</td>
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<td>SCH-C (SCH 351125)</td>
<td>Small-molecule oxime–piperidine compound</td>
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<td>SCH-D (SCH 417690)</td>
<td>Derivative of SCH-C</td>
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<tr>
<td>PRO 140</td>
<td>Anti-CCR5 mAb</td>
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<td>Spiroketopiperazine-based molecule</td>
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</tr>
<tr>
<td>UK-427,857</td>
<td>Low molecular weight molecule</td>
<td>[140]</td>
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C-terminus is important in G protein activation. The receptors contain N-glycosylation sites in the N-terminal and extracellular regions. The intracellular C-terminus contains several serine and threonine residues, which function as phosphorylation sites, important for desensitization of the receptor. The receptors are typically 340–370 amino acids in length with 25–80% amino acid homology. Chemokine receptors are expressed on different types of leukocytes.

Some are restricted to certain cells while others are spread over various cell types. Only few are expressed constitutively, mostly their expression is induced by other factors (i.e. interleukines, growth factors, cell activation, etc.). In addition, they are also expressed on non-hematopoietic cells like neurons, astrocytes and endothelial cells [24]. Their distinct expression pattern already suggests that the chemokine system has other functions of chemokines besides their role in leukocyte chemotaxis and inflammation. Most chemokine receptors bind more than one chemokine. However, CC and CXC receptors have similar primary, secondary and tertiary structures, CC and CXC receptors only specifically bind CC- and CXC-chemokines, respectively, due to their different quaternary structures [25].

In addition to these specific receptors, other non-signaling molecules are reported that can bind chemokines. One of them is the Duffy antigen receptor for chemokines (DARC) [26]. This receptor is a 7TM receptor, expressed on erythrocytes and endothelial cells, which is known as determinant of the Duffy blood group. It functions as the receptor for the malarial parasite Plasmodium vivax. It is structurally related to chemokine receptors but in contrast does not support chemokine-induced calcium responses. Other non-signaling receptors described are the CC-chemokine receptor D6 [27] and CCX-CKR [28]. Furthermore, negatively charged heparan sulfate proteoglycans (glycosaminoglycans) in the extracellular matrix and on endothelial cells can bind both CC- and CXC-chemokines [29,30]. In addition, it is reported that such immobilisation of chemokines on cellular or extracellular matrix is a selective proces, since specific chemokines bind different types of glycosaminoglycans with divergent affinities [31]. Binding of chemokines to glycosaminoglycans induces polymerization of chemokines at a certain site, resulting in higher local chemokine concentrations or gradient formation. This causes migration of leukocytes up to the chemokine gradient and the relevant site of inflammation or disease [32].

4.2. Identification of chemokine receptors as ‘cofactors’ for HIV-infection

In 1984, it was discovered that interaction with CD4 is essential for HIV-1 to enter its host cells [33–35]. However, CD4 alone appeared to be insufficient to permit efficient HIV-1 infection. Two related phenomena led to this conclusion. First, expression of human CD4 on the surface of murine cells did not confer susceptibility to HIV infection, although CD4-positive murine cells are fully competent for binding the viral envelope protein gp120 [36–38]. The second phenomenon concerned the distinct tropisms of different HIV-1 isolates for various CD4+ human target cell types in vitro. Some virus strains, adapted for growth in transformed T-cells, could only replicate in transformed T-cell lines and activated primary T-cells, whereas HIV-1 strains, adapted in peripheral blood mononuclear cells (PBMCs), only replicated in cells from the macrophage/monocyte lineage and activated primary T-cells [39,40]. These viruses were respectively designated T- and M-tropic and not only showed a different infection pattern but also have distinct significance for the spread of HIV-1 and disease course [40,41]. In fact, the viral isolates obtained from HIV-1-infected persons in an early stage of infection are predominantly M-tropic, while those found at a later stage of disease progression towards AIDS are mostly T-tropic. All these data suggested the presence of distinct human cofactors, probably differentially expressed on the HIV-1 target cells, and making them susceptible for entry by either M- or T-tropic HIV-1 strains. Finally, an orphan GPCR was identified as a cofactor for HIV-1 [39]. This coreceptor, designated ‘fusin’ because of its activity in env-mediated cell fusion, acted selectively for T-tropic isolates [14,42]. In addition, it was demonstrated that fusin had strong sequence homology with the peptidergic chemokine receptors. This provided also a direction for the identification of the cofactor for M-tropic isolates. Moreover, an earlier study already demonstrated that CD87 T-cells released some soluble HIV-1 suppressor factors, which were identified as the CC-chemokines RANTES, MIP-1α and MIP-1β [18].

Based on the current knowledge, the process of HIV-1 entry into host cells can be divided into three discrete steps: gp120-CD4 binding, gp120-coreceptor binding and membrane fusion (Fig. 1). The process is initiated by the attachment of the viral envelope protein gp120 to the CD4 receptor. The CD4 molecule is mainly expressed on T-lymphocytes, macrophages and dendritic cells (DC). The CD4 binding site is located at the base of the gp120 core, which is a relatively acidic area that corresponds with the basic domain of the N-terminus of CD4 [48].

However, CD4 independent attachment has also been reported [49]. Namely, rectal and vaginal mucosal epithe-
fusion, the viral contents are expelled into the cell. Following membrane fusion, the viral contents are expelled into the cell (modified from Doms [57]).

Fig. 1. Schematic presentation of the HIV-1 entry process. The entry process is initiated by the attachment of the viral envelope protein gp120 to the CD4 receptor, which induces conformational changes in the gp120 subunit setting free the coreceptor binding site on gp120. After binding of the glycoprotein with the chemokine/coreceptor, HIV-1 gp41 ‘unfolds’ by a hinge mechanism followed by insertion of the fusion peptide into the cell membrane, anchoring the virus to the cellular membrane. This prehairpin intermediate exposes the distal carboxyterminal anchoring the virus to the cellular membrane. This fusion can take place. Following membrane fusion, the viral contents are expelled into the cell (modified from Doms [57]).

After the identification of the chemokine receptors CXCR4 and CCR5 as the major coreceptors of HIV-1, a simple model was used to elucidate the tropism of HIV-1 strains. It can be explained by two considerations: the ability of the viral envelope to use CXCR4 and/or CCR5, and the expression of the chemokine receptors on the different CD4+ target cells. T-tropic strains preferentially use CXCR4, the M-tropic strains prefer CCR5 and the dual-tropic strains use both. Additionally, T-cell lines express CXCR4, monocytes/macrophages express CCR5 and primary T-cells express one or both chemokine receptors, CXCR4 or CCR5 [39,57].

Another nomenclature that has been used for a long time to distinguish between different HIV-1 strains was based on the ability of certain primary HIV-1 isolates to induce syncytia or ‘giant cells’ in T-cell lines. In this system, virus strains are termed either ‘syncytium-inducing (SI)’ or ‘non-syncytium-inducing (NSI)’. Herein, the SI and the NSI viruses generally correspond with respectively the T-tropic and the M-tropic virus strains [36,39].

However, several further studies have pointed out shortcomings of the two classification systems, SI/NSI and T-tropic/M-tropic. The relationship between coreceptor expression and permissiveness for entry of particular HIV-1
variants is very complex since a coreceptor can have differential capacity to support HIV-1 entry depending on which cells it is expressed.

For example, monocytes/macrophages (M/M) express CXCR4 in addition to CCR5. Several groups reported infections of primary cells of the M/M lineage by SI/T-tropic virus isolates, while others did not show any replication of T-tropic virus strains [58,59]. This can imply the existence of cell-specific CXCR4 or a post-entry replication hindrance [60]. Moreover, it was demonstrated that when CCR5-transfected cells are infected with R5-strains they behave like SI strains. In addition, activated T-cells have been demonstrated to express CCR5, and thus allowing M-tropic strains to replicate [51]. In light of these findings on HIV-1 phenotype and chemokine receptor usage, these nomenclatures, SI/NSI and T/M-tropic, are no longer appropriate. Therefore, the HIV-1 phenotype has been revised to indicate coreceptor usage, rather than the less defined characteristics of target cell tropism and SI-properties. HIV-1 virus strains have now been designated as X4 strains (CXCR4-specific), R5 strains (CCR5-specific) or R5/X4 strains (dual-tropic) (Fig. 2) [61].

4.4.2. ‘Minor coreceptors’ of HIV-1

Studies have shown that, besides CXCR4 and CCR5, several other chemokine receptors can function as coreceptors for HIV-1-infection. Importantly, many of these studies applied coreceptor-transfected cells in vitro and their usage in vivo has not yet been demonstrated. Table 2 gives a short overview of the potential HIV-1 coreceptor repertoire.

4.5. Course of HIV infection in vivo

As mentioned earlier, distinct HIV-1 strains not only show a different infection pattern but they also emerge at different stages of disease progression [39,41]. To be more precise, it was determined that R5 viruses predominate in early asymptomatic stages of infection, while R5/X4 and X4 viruses appear at later stages of HIV-1 infection. Moreover, R5 viruses are responsible for transmission of HIV-1 as evidenced by the high degree of resistance to infection of individuals homozygous for a 32 bp deletion in the gene encoding CCR5, who consequently lack a functional receptor [19,20]. The appearance of X4 viruses is associated with accelerated CD4+ T-cell decline and clinical progression towards AIDS [62–65].

Following infection, an initial burst of viremia is observed which results in a decrease in CD4+ T-cells. Within weeks after infection, an immune response can be observed. This phenomenon causes a plasma viral load drop and a CD4+ T-cell count increase, although not reaching pre-infection levels. Then, a steady state, also known as clinical latency, is observed for an undetermined period of time [66,67]. Eventually, the asymptomatic steady state is lost when viral replication and resulting cellular destruction exceed the capacity of the immune response system [68]. Subsequently, the viral load rises again, the CD4+ T-cell count declines enormously, resulting in a condition in which the immune system cannot defend itself, and opportunistic infections can occur. The latter symptomatic period of HIV-1 pathogenesis (AIDS) corresponds with the appearance of

<table>
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<th>Chemokine ligands</th>
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<tr>
<td>CXCL16</td>
<td>[150,151]</td>
</tr>
<tr>
<td>Not known</td>
<td>[148,152]</td>
</tr>
<tr>
<td>Not known</td>
<td>[153,154]</td>
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Fig. 2. Simple model of HIV-1 coreceptor usage and HIV-1 tropism. X4 strains (previously called T-tropic or SI strains) specifically infect cells expressing the chemokine receptor CXCR4, while R5 strains (previously called M-tropic or NSI strains) specifically infect cells expressing the chemokine receptor CCR5. Dual tropic or R5/X4 strains can use both CXCR4 and CCR5 to enter their target cells (modified from De Clercq and Schols [61]).
X4 viruses in the plasma of HIV-1-infected persons [69–72]. To date, many research groups have been studying this coreceptor ‘shift’ extensively although still many questions remain.

In the most recent reports, it is hypothesized that certain mutations in the V3 loop of the viral envelope glycoprotein are strongly associated with the shift from R5 viruses to X4 viruses. In particular, basic amino acids at the V3 loop positions 11 and 25 very frequently distinguish X4 from R5 viruses [73–75]. The actual mutational pathway is as yet unexplored. In addition, it is known that dual-tropic R5/X4 viruses also emerge around the time of R5 to X4 transition, but also their evolutionary role is not certain [69,76]. Some groups demonstrated that progression from R5 to X4 occurred via an intermediate that has dual-tropic (R5/X4) [77] or even multi-tropic coreceptor usage such as CCR5, CCR3, CCR2b and CXCR4 [78]. It is believed that cellular and humoral components of the immune system cause selective pressure that results in diversification in env and alterations in coreceptor usage, but this remains largely unexplored.

5. Chemokine receptor inhibitors

The connection of the HIV and the chemokine field first began with the observation that HIV entry into cells could be blocked by certain chemokines (CC-chemokines) [18]. Since then, chemokine receptors constitute an important target for the development of anti-HIV therapies. It has been reported that rapid and extensive internalisation of CCR5 or CXCR4 is responsible for the anti-HIV-1 activity of their natural chemokine ligands [79,80]. However, the concept of using chemokines as antiretroviral therapeutics is restrained because of their short half-life (<10 min) and potential inflammatory side effects. Thereby, chemokines do not invariably act as HIV-suppressive agents. For instance, SDF-1 has been demonstrated to increase the infectivity of R5 strains at the transcriptional level, while blocking the infection of X4 strains at the entry level [81]. It has been reported that higher levels of CC-chemokines (RANTES and MIP-1α) are associated with a slower progression of disease or even a HIV-free status [82,83]. However, it has also been observed that CC-chemokines can enhance HIV-1 infection in vitro in some systems, probably due to chemokine-induced cell activation [84–86]. Moreover, CC-chemokines might drive the evolution of less pathogenic R5 strains to the more pathogenic X4 isolates [87,88]. To overcome these limitations, new chemokine inhibitors have been designed, derived from the natural CCR5 and CXCR4 ligands. These modified chemokines should interact with the receptor and prevent HIV-1 infection by blocking relevant epitopes and/or inducing receptor internalisation without inducing signaling. In addition, new classes of antagonistic compounds are designed to effectively block HIV-1 virus entry, i.e. small-molecule compounds, peptides and monoclonal antibodies.

The strategy to block chemokine receptors has several advantages. First, blocking CCR5 and CXCR4 prevents viral entry rather than limit virus production by cells that have already become infected. In that way, CCR5 antagonists can prevent transmission of the virus while CXCR4 viruses can block the onset of disease progression towards AIDS. Second, CCR5 and CXCR4 inhibitors represent important additions to weapons now used to combat HIV and thus could complement existing antiretroviral drug strategies. Third, if they are antagonists that do not trigger any signals themselves through their target receptor, these agents are less likely to evoke immunological side effects, making them good candidates for prolonged maintenance treatment.

Although the use of coreceptor antagonists seems a very good approach to effectively inhibit HIV-1 entry into its host cells, some concerns raised with regard to the clinical use for long-term treatment of HIV-1 infections. Since people with a homozygous 32 bp deletion in the CCR5 gene (CCR5 Δ32/Δ32), consequently lacking functional CCR5 receptors on their cells, show a completely normal phenotype and are relatively resistant against R5 HIV-1 infection, blocking the CCR5 receptor should not be expected to raise any problems [19,20]. However, some groups reported that in few persons with a homozygous 32 bp deletion that did get infected with HIV-1, progression to death is more rapid [89], which is probably due to the outgrowth of X4 viruses [90]. Moreover, a recent study has shown that there are significant interindividual and interpopulation differences in the copy number of a segmental duplication of the gene encoding for the CCR5 chemokine LD78β. Possession of a LD78β copy number lower than the population average is related with markedly enhanced HIV susceptibility. This susceptibility is even greater in individuals who also possess disease-accelerating CCR5 genotypes [91]. In addition, studies with CXCR4 knockout mice revealed defects in B-cell lymphopoiesis and bone-marrow myelopoiesis. Moreover, mice lacking CXCR4 exhibit hematopoietic and cardiac defects identical to those of SDF-1-deficient mice and die before birth [92–94]. However, all these deficits are developmental and it is not known if SDF-1 and CXCR4 are essential for normal physiological processes after birth. If they are not, blocking CXCR4 to inhibit HIV entry would certainly be a very valuable approach. Indeed, Phase I/II clinical trials with several CXCR4 antagonists proved that blocking the SDF-1/CXCR4 axis is safe and feasible (see further).

5.1. Modified chemokines

The chemokine LD78β, a non-allelic isoform of MIP-1α, which only differs from LD78α in 3 amino acids, proved very effective in suppressing R5 HIV-1 viruses in PBMCs [95] and monocytes/macrophages (M/M) [96]. LD78β is the most active natural CCR5 agonist that is described to date and the most potent chemokine to suppress R5 HIV-1 infection [91,95,96].
In contrast, intact RANTES actually has no anti-HIV-1 activity but only becomes antivirally active when it is truncated at the aminoterminal end by dipeptidyl peptidase IV (DPP IV), also called CD26. CD26 plays an important role in natural chemokine processing because of its posttranslational modification function [97]. RANTES(3–68) is such a processed form of RANTES that lacks two N-terminal residues [98]. By this truncation the chemokine loses its agonistic activity, but shows the ability to potently block R5 viruses in an antagonistic manner [98,99]. A synthetic truncated form of RANTES, i.e. RANTES(9–68), lacking eight amino acids at its N-terminus, also was antagonistic but less potently inhibited R5 HIV-1 strains than RANTES(3–68) [98–100].

Several derivatives of RANTES that bind to CCR5 and inhibit infection of lymphocytes and cells of the macrophage lineage with R5 viruses have been identified. Aminoxypentane (AOP)-RANTES was created by chemical modification of the aminoterminus. This derivative has been found to decrease HIV-1 infectivity in many cell types and showed reduced capacity to induce chemotaxis. In addition, like intact RANTES it induced down-modulation of surface CCR5 to early endosomes. However, AOP-RANTES also prevented the recycling of CCR5 to the cell surface resulting in a long-lasting depletion of CCR5 [80]. Comparable results were obtained with the N-nonanoyl (NNY)-RANTES derivative that also reduced proinflammatory signaling through its interaction with CCR5 [101].

Extension of human RANTES by a single residue at the amino terminus also proved sufficient to produce a potent and selective antagonist. Methionylated RANTES (Met-RANTES) had no effect on IL-8- or MCP-1-induced calcium mobilisation and chemotaxis assays with the monocytic cell line THP-1 and antagonized the RANTES- and MIP-1α-induced chemotaxis in these cells and in primary T-cells. Its antagonistic effect was selective since Met-RANTES had no effect on IL-8- or MCP-1-induced responses in these cells [102]. Another RANTES analog, by changing the first three aminoterminus amino acids of the native protein with a nonanoyl, thioproline and cyclohexylglycine, called PSC-RANTES, showed potent anti-HIV activity against R5 viruses in vitro and was also capable of preventing vaginal SHIV transmission in rhesus macaques [103]. All the RANTES analogs showed internalization and down-modulation of the CCR5 receptor, which may also explain their potent anti-HIV activity [103]. In addition it was reported that an aminoxypentane-linked variant of LD78β, termed AOP-LD78β, is about 10-fold more active than AOP-RANTES at inhibiting HIV entry, making it the most effective chemokine-based inhibitor of HIV entry through CCR5 described to date [104].

In addition, some attempts have been made to generate an optimized CXCR4 antagonist by the addition of an aminoterminus methionine residue to the chemokine (Met-SDF-1). This derivative showed enhanced X4 HIV-1 inhibition, which was correlated with prolonged down-regulation of CXCR4 compared to unmodified SDF-1 [105]. Moreover, in vitro studies with Met-SDF-1 demonstrated that it induced a more pronounced intracellular calcium signaling [105].

All these data suggest a positive role for chemokines and their derivatives in controlling HIV-1 infection. However, because these derivatives, like the chemokines they are derived of, also are predicted to have inflammatory side-effects when used therapeutically, new classes of antagonistic compounds were designed to effectively block HIV-1 infection, i.e. small-molecule compounds, peptides and monoclonal antibodies.

5.2. Chemokine receptor antagonists

The primary mechanism of coreceptor antagonist function does not rely on receptor down-modulation, but on receptor occupancy. As attempted with the design of modified chemokines, such inhibitors are unable to induce signaling and therefore implausible to indirectly augment virus replication or to induce inflammation. Several important coreceptor antagonists have been described so far: small-molecule inhibitors, peptidic inhibitors and also some monoclonal antibodies with specific anti-HIV-1 activity.

5.2.1. CXCR4 antagonists

5.2.1.1. The bicyclams. Shortly after the discovery that HIV is the cause of AIDS, the most extensively studied anti-HIV drugs were then the reverse transcriptase inhibitors. However, these earlier compounds had to deal with high toxicity and a fast rate of virus resistance development.

In the search for new anti-HIV agents with better characteristics than the existing drugs, a novel class of compounds was discovered with potent and selective anti-HIV activity, namely the bicyclams [106]. The prototype compound used for the development of these new agents was the monocyclam AMD1498 (1,4,8,11-tetraazacyclotetradecane), which itself was active at concentrations up to 400 M, with a selectivity index of >5 (Fig. 3). AMD1498 was part of a project aimed at making new anti-HIV compounds that would gain anti-HIV activity by the formation of metal complexes using organic molecules, possible by the presence of four nitrogens in the centre of the cyclam ring. The bicyclams exist of two such macrocyclic rings, containing 12–14 members each, linked in various ways [107]. Two compounds, designated AMD1657 and AMD2763, were found active against HIV-1 and HIV-2 at a concentration of 0.14–1.4 M, with a selectivity index of >1000–10,000. This antiviral activity was observed in different cell lines including PBMCs and with several HIV-1 and HIV-2 strains. In AMD1657 the cyclam moieties were linked with a direct carbon-carbon bridge creating two chiral centres, in AMD2763 via an aliphatic (propylene) bridge (Fig. 3). To examine at which stage the bicyclams interact with the viral life cycle, time-of-addition experiments were
carried out, in which compounds are added at different time intervals after virus infection. Addition of AMD1657 and AMD2763 could only be delayed for 1–2 h without loss of activity. Thus, it appeared that the compounds interacted with an early process in the replication cycle following virus adsorption but preceding reverse transcription, i.e. virus–cell fusion or uncoating [106].

Further studies pointed out that bicyclam derivatives in which the two monocylam rings are connected by an aromatic linker, in stead of an aliphatic linker, inhibit HIV replication at concentrations of 1 to 10 ng/ml, which is about 100-fold lower than the concentration required for AMD2763 to inhibit HIV replication and about 100,000 times lower than the cytotoxic concentration (>500 μg/ml) [108]. The most potent bicyclam of these series and also the prototype is AMD3100, previously called JM3100 or SID791, in which the two cyclam moieties are tethered by a 1,4-phenylenebis(methylene)-bridge (Fig. 3) [108]. AMD3100 inhibited HIV-1 and HIV-2 replication with a 50% effective concentration of 1–10 nM and provided complete protection of monocytes and lymphocytes at 10–30 ng/ml. The compound also inhibited syncytium formation between cocultures of persistently infected HUT-78 cells (with the X4 HIV-1 strain IIIB) and uninfected MOLT-4 cells, albeit at higher concentrations (1–5 μM). Structure-activity relationship studies demonstrated that the antiviral activity of the bicyclam analogues is dependent on the number of members (i.e. 12–14) in the two macrocyclic rings. Moreover, the length of the linker between the two rings and specific substitutions on the phenylenebis(methylene) linker are also important for their potency [109,110]. In addition, in line with the results of the time-of-addition experiments, which revealed that the bicyclams interact at a stage following virus adsorption but preceding reverse transcription, additional studies demonstrated that capsid proteins remained associated and virus did not have the possibility to uncoat in presence of AMD3100. Studies with AMD3100- and AMD2763-resistant viruses pointed to gp120 as the possible target molecule for the bicyclams because a number of mutations accumulate in the V3–V4 region of gp120, in viruses rendered resistant to the bicyclams [111]. Moreover, the molecular clones HIV-1 IIIB and HIV-1 NL4.3 remained sensitive to AMD3100 during up to 49–105 days [108,111]. More exactly, it took more than 60 passages in cell culture for the X4 HIV-1 strain, clone NL4.3, to become 300–400-fold resistant to AMD3100 [111–113].

At this time, the V3 loop was discovered to be very important in the viral fusion process and M- and T-tropic strains were found to interact respectively with the chemokine receptors CCR5 and fusin, now designated CXCR4 [14,15,17,42,45]. Soon thereafter, it was shown by our group

Fig. 3. Chemical structures of several small molecule CXCR4 antagonists: AMD1498, AMD1657, AMD2763 and AMD3100 (AnorMED) and KRH-1636 (Kureha Chemical Industry).
that the bicyclam derivatives exhibit their strong and selective antiviral efficacy through their interaction with CXCR4 [114]. Indeed, AMD3100 showed activity against a wide variety of X4 and even R5/X4 HIV strains in PBMCs but not against R5 strains [61, 71, 115–117]. Moreover, further studies showed that AMD3100 potently inhibits the intracellular calcium signaling induced by SDF-1, the natural ligand of CXCR4, in many cell types (Fig. 4). Furthermore, also the SDF-1-induced chemotaxis and internalisation could be dose-dependently blocked by AMD3100 [115, 116, 118]. Additionally, the chemokine receptor inhibition by AMD3100 is strictly confined to its interaction with CXCR4 and not with any
other chemokine receptor [118]. As shown in Fig. 5, AMD3100 is able to block the SDF-1-induced Ca²⁺ flux in purified monocytes, but not the calcium signaling induced by MIP-1β, MCP-1, MIP-1α, MCP-3 and RANTES.

The first human study of AMD3100 evaluated the safety, bioavailability, and single dose pharmacokinetics of progressively higher doses of AMD3100, from 10 to 80 μg/kg, administered intravenously over 15 min in successive cohorts of three to five healthy volunteers [119]. Five volunteers also received a single subcutaneous injection (40 or 80 μg/kg) and three volunteers also received oral doses (80 or 160 μg/kg). AMD3100 was well tolerated in all patients by all routes of administration. Six of the 12 subjects (50%) had mild, transient symptoms, primarily gastrointestinal in nature. Most patients experienced a transient, dose-dependent increase in white blood cell count 1.5–3 times baseline values within 6 h of the infusion, which returned nearly to baseline by 24 h after dosing. The pharmacokinetic profiles were dose proportional with an estimated half-life of 3.6 h. Absorption following subcutaneous administration was very good (bioavailability 87%), but no drug was detectable in the blood following oral dosing.

In the next study safety, pharmacokinetics and antiviral activity of AMD3100 was evaluated in HIV-infected persons [120]. AMD3100 was administered for 10 days by continuous intravenous infusion in an open-label, dose escalation study from 2.5 up to 160 μg/kg/h. Forty HIV-infected patients with viral load >5000 copies/ml, either on stable antiretroviral regimens or off therapy were enrolled. At the time of the clinical study, NSI/SI phenotype was determined in an MT-2 cell assay. The HIV phenotype was SI (30%), NSI (45%), or not tested (25%). One patient (5 μg/kg/h) had serious and possibly drug-related thrombocytopenia. Two patients (40 and 160 μg/kg/h) had unexpected, though not serious, premature ventricular contractions. Most patients in the 80 and 160 μg/kg/h cohorts had paresthesias. Only one patient, the patient whose virus was confirmed to use purely CXCR4, and who received the highest dose studied (160 μg/kg/h) had a significant 0.9 log₁₀ copies/ml HIV RNA drop at day 11. In conclusion, AMD3100 was the first CXCR4 antagonist to demonstrate a clinical anti-HIV effect and warrants the development of orally bioavailable CXCR4 antagonists for HIV treatment.

5.2.1.2. Other CXCR4 antagonists. Several other molecules have been described as anti-HIV agents owing their antiviral activity to their specific interaction with CXCR4. For example, some peptidic agents are described with potent antiretroviral activity. A disadvantage of such peptidic compounds is their complex synthesis, which will contribute considerably to a high cost of therapy. Moreover, no orally bioavailable peptidic agents have been described to date so if they were to move into the clinic they must be administered by injection.

For example, T22, [Tyr⁵¹², Lys⁷]–polyphemusin, is a cationic 18-amino acid peptide, derived from horseshoe crab blood cells. It was shown to inhibit replication of both
laboratory strains and primary isolates of HIV-1 by specific binding to the N-terminus and two extracellular loops of CXCR4 [121]. T22 did not induce signaling or receptor down modulation at concentrations required for inhibition of infection (200 nM). Studies with a derivative of T22, called T134, demonstrated that this compound efficiently inhibits the replication of an AMD3100-resistant virus strain, suggesting that the binding sites for AMD3100 and T22 only partially overlap [122], although they both block the binding of the CXCR4-specific mAb 12G5 and the natural ligand SDF-1 to CXCR4. Tamamura et al. also reported on a second analog of T22, the 14-residue peptide called T140, which showed stronger inhibitory activity against HIV-1 entry [123].

ALX40-4C (N-α-acetyl-nona-ω-arginine (Arg) amide) is a (poly)peptide of nine Arg residues stabilized by terminal protection and inclusion of ε-amino acids [124]. Initially it was characterized as an inhibitor of the HIV-1 Tat-trans-activation response element (TAR) interaction [125]. ALX40-4C inhibits HIV-1 NL-4-3 in the nanomolar range (IC\textsubscript{50} of 3 nM) in the HUT-78 T-cell line and in PBMCs. In addition, it was demonstrated that ALX40-4C inhibited entry of X4, but not R5 HIV-1 strains. ALX40-4C also inhibited primary R5/X4 virus isolates, but only when cells expressed CXCR4 alone, while infection of CCR5\textsuperscript{*}/CXCR4\textsuperscript{*} double positive cells by R5/X4 virus strains was not inhibited by ALX40-4C. Moreover, addition of ALX40-4C to cells expressing CXCR4 prevented SDF-1-induced changes in intracellular calcium and prevented binding of an anti-CXCR4 mAb, clone 12G5. The epitope recognized by the 12G5 mAb resides in the first and second extracellular loops, the same region of CXCR4 that is used by both dual- and T-tropic HIV-1 strains and that overlaps with the activation site of SDF-1. In addition, Doranz et al. described that ALX40-4C was well tolerated in phase I/II clinical trials in humans, but no significant reductions in viral load were noted [126]. Furthermore, ALX40-4C was shown to be an antagonist to APJ, a GPCR that could serve as an alternative coreceptor for HIV-1 in the central nervous system [127].

CGP64222 is a basic peptoid oligomer of nine residues that inhibits the replication of a wide range of laboratory strains of HIV-1 and HIV-2 in MT-4 cells [128]. Besides its activity against Tat/TAR binding [129], the compound was also shown to inhibit HIV infection through a selective interaction with the CXCR4 receptor. This was demonstrated by the fact that CGP64222 proved inactive in MT-4 cells against HIV-1 strains that are resistant to the bicyclams and the compound inhibited SDF-1-induced calcium signaling [128].

KRH-1636 (Kureha Chemical Industries) is a small-molecule CXCR4 antagonist that has a potent anti-HIV activity both in vivo and in vitro (Fig. 3). The compound selectively inhibited infection of X4 virus strains including several clinical isolates without affecting R5 HIV-1. It also inhibited binding of the CXC chemokine, SDF-1, to CXCR4 specifically and subsequent signal transduction. KRH-1636 prevented monoclonal antibodies from binding to CXCR4 without down-modulation of the coreceptor. Moreover, KRH-1636 showed potent antiviral activity in the human peripheral blood lymphocytes/severe combined immunodeficiency (hu-PBL-SCID) mouse model. Furthermore, this compound was absorbed into the blood after intraduodenal administration as judged by anti-HIV-1 activity and liquid chromatography in the plasma of rats [130].

AMD070 (AnorMED) is a novel orally bioavailable CXCR4 antagonist that potently inhibited X4 viruses at EC\textsubscript{50} varying between 1 and 20 nM in T cell lines, CXCR4-transfected cell lines and PBMCs [131]. A Phase Ib/Ila trial to evaluate the potential of AMD070 as an anti-HIV drug in HIV-infected patients is just recently initiated.

5.2.2. CCR5/CXCR4 antagonist

Recently our group presented a CCR5/CXCR4 antagonist, called AMD3451 as the first low-molecular-weight anti-HIV agent with selective HIV coreceptor, CCR5 and CXCR4 interaction. AMD3451 is an N-pyridinylmethyl cyclam analog (Fig. 6A), which shows antiviral activity against a wide variety of R5, R5/X4 and X4 strains of HIV-1 and HIV-2 (IC\textsubscript{50} ranging from 1.2 to 26.5 μM) in various T-cell lines, CCR5- or CXCR4-transfected cells, PBMCs and monocytes/macrophages [132]. AMD3451 also inhibited R5, R5/X4 and X4 HIV-1 primary clinical isolates in PBMCs (IC\textsubscript{50} 1.8–7.3 μM). A PCR-based viral entry assay revealed that AMD3451 blocks R5 and X4 HIV-1 infection at the virus entry stage. AMD3451 dose-dependently inhibited the intracellular Ca\textsuperscript{2+} signaling induced by the CXCR4 ligand SDF-1 in CXCR4-transfected cells, as well as the RANTES-induced Ca\textsuperscript{2+} flux in CXCR4-transfected cells. The compound did not interfere with any other chemokine receptor, nor did it induce intracellular Ca\textsuperscript{2+} signaling by itself. AMD3451 also inhibited the SDF-1 and MIP-1β-induced chemotaxis in a dose-dependent manner and was able to block the SDF-1- and LD78β-induced endocytosis in CXCR4- and CCR5-transfected cells. Moreover, studies showed that the compound interacts in a different manner with CXCR4 than the specific CXCR4 antagonist AMD3100 since AMD3451 did not inhibit but enhanced the binding of anti-CXCR4 mAbs (such as clone 12G5) at the cell surface [132]. The precise interaction sites of AMD3451 with CCR5 and CXCR4 have yet to be elucidated, however this study demonstrates that it is possible to develop compounds that interact with both HIV-1 coreceptors. Also because of their dual interaction with both CXCR4 and CCR5 and, consequently, their potential to block cellular infection of R5, R5/X4 and X4 viruses, these compounds can be important for the development of an effective anti-HIV microbicide.

5.2.3. CCR5 antagonists

The first low molecular weight CCR5 antagonist with antiviral activity that was described was TAK-779 (N,N-
dimethyl-N-[4-[[2-(4-methylphenyl)-6,7-dihydro-5H-benzocyclohepten-8-yl]carbonyl]amino]benzyl]tetrahydro-2H-pyran-4-ammonium chloride) (Takeda Chemicals) (Fig. 6B) [133]. It was shown to inhibit R5, but not X4, virus replication with laboratory-adapted strains and clinical isolates without activating or downregulating CCR5. The compound did not inhibit the binding of RANTES, eotaxin, TARC or SDF-1 to respectively CCR1-, CCR3-, CCR4- or CXCR4-transfected cells. However, TAK-779 inhibited the binding of MCP-1- to CCR2b-transfected cells. It was further demonstrated that the binding of TAK-779 and interaction with CCR5 can be assigned to a cavity formed between transmembrane helices 1–3, and 7 near the extracellular surface of the receptor [134].

SCH-C (Schering-Plough) is the most potent CCR5 antagonist described to date. The compound, also designated SCH-351125, is an oxime–piperidine compound with potent activity against R5 HIV-1 strains in U87.CD4 cells transfected with CCR5, but not against X4 strains in CXCR4-expressing cells (Fig. 6B). As shown by multiple receptor binding and signal transduction assays, SCH-C is a highly specific CCR5 antagonist [135]. In addition, SCH-C was demonstrated to have broad and potent antiviral activity against primary R5 isolates in vitro and showed a favorable pharmacokinetic profile in rodents and primates. Later, SCH-C has shown in vivo antiviral efficacy in clinical studies by reducing the plasma viremia in R5 HIV-1-infected persons [136]. Recently, a derivative of SCH-C, SCH-D or SCH-417690 was presented (Fig. 6B) [137]. This compound is about 10-fold more potent against a panel of primary R5 isolates compared with SCH-C, and is viral genotype independent. SCH-D is currently undergoing phase II clinical trials.

Two other recently described CCR5 antagonists are GW873140, a spiroketopiperazine based agent (Ono Phar-
maceutical/Glaxo Smith Kline) [138,139] and UK-427,857 (Pfizer) [140]. Both compounds exerted potent antiviral activity against a wide spectrum of R5 laboratory strains and primary isolates and revealed favorable oral bioavailability. At this time, both compounds are under clinical investigation (Phase II/III studies) [138–140].

Anti-coreceptor mAbs that inhibit HIV-1 entry represent another class of blocking HIV agents. PRO 140 (Progenics Pharmaceuticals, NY) is an anti-CCR5 mAb that potently inhibits HIV-1 entry at concentrations that do not affect CCR5 chemokine receptor activity and showed to be genetic-subtype-independent [141]. A recent study also showed that PRO140 was able to control HIV-1-infection in the hu-PBL-SCID mouse model [142].

6. Concluding remarks

The crucial role of the cellular CD4 receptor in viral entry of the host cells by the human immunodeficiency virus (HIV) has since long been established. Almost a decade ago, it has been discovered that HIV also requires one of the chemokine receptors, CCR5 or CXCR4, as a coreceptor for successful entry into the target cell. These two G protein-coupled seven transmembrane (7TM) receptors play a prominent role in the transmission of HIV and during disease progression towards AIDS. Macrophage-tropic HIV strains, using CCR5 as their main coreceptor, represent the major virus subtype that is encountered in individuals in the early stages of infection. These R5 viruses are responsible for transmission of the disease via sexual intercourse. These viruses do not severely affect the CD4+ T-cell count of a HIV-infected person. Disease progression towards AIDS is often closely correlated with the emergence of CXCR4-using (X4) virus strains, which rapidly destroy the immune system by depletion of the CD4+ T-lymphocyte population. This review described the development of potent and selective antagonists of both the CCR5 and CXCR4 chemokine receptors, and exploring further their therapeutic potential for the treatment of HIV-infected persons.

A class of chemical compounds, designated the bicyclams, were described in our laboratory as potent anti-HIV agents that were active against a broad range of HIV-1 and HIV-2 strains, but not against any other RNA or DNA virus. The precise mechanism of action of the bicyclams remained unknown, until, following the discovery of the chemokine receptors as cofactors for HIV entry, it was demonstrated that they specifically interact with CXCR4. The bicyclam AMD3100 (1,1-[1,4-phenylenebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane), the most potent compound of this series, showed antiviral activity in the nanomolar concentration range against a wide range of X4 and even dual tropic R5/X4 HIV-1 strains in PBMCs.

By means of mutational analysis studies, it was shown that two aspartate residues at positions 171 (TM IV) and 262 (TM VI) of CXCR4 are crucial for the high-affinity binding of AMD3100 to CXCR4. Elucidation of these molecular interaction sites of AMD3100 revealed new insights for the design of novel CXCR4 inhibitors. As the in vitro results were very promising, the pharmacokinetics, safety and antiviral efficacy of AMD3100 were evaluated in phase I and II clinical trials [143]. These studies demonstrated for the first time that a cellular receptor, CXCR4, is a suitable anti-HIV-1 target in vivo. With this information, further investigation was done to design a novel non-macrocyclic, orally bioavailable CXCR4 antagonist. This led to the development of a new generation of non-cyclic and orally bioavailable CXCR4 antagonists, of whom AMD070 was selected as the new lead compound. AMD070 showed strong and specific antagonistic activity against SDF-1/CXCL12-induced signaling and had potent antiviral activity against various HIV-1 laboratory-adapted and primary X4 isolates. This compound is currently being evaluated in phase I/II clinical studies.

In addition, our studies not only revealed potential and valuable CXCR4 antagonists but also a CCR5/CXCR4 dual antagonist, which shows specific interaction with both HIV-1 coreceptors, as assessed in diverse antagonistic assays. The CCR5/CXCR4 antagonist, designated AMD3451, has antiviral activity against a wide range of HIV strains and primary isolates in many different cell types. Although AMD3451 has less potent antagonistic and antiviral activity compared to the previously described specific CCR5 and CXCR4 antagonists, it is very appealing to study in which way it is able to interact with both receptors, especially since it is assumed that both CCR5 and CXCR4 have to be targeted to effectively inhibit HIV-1 infection.

CCR5 is a particular attractive drug target as CCR5 Δ32/Δ32 homozygote persons exhibit no consequences of being CCR5 negative. Several CCR5 antagonists, such as GW873140 and UK-427,857, proceed or will proceed to clinical phase III studies. However, a concern for the use of CCR5 inhibitors is the possibility for viruses to escape by evolving to use CXCR4, which is associated with disease progression. Studies have shown that R5 viruses can indeed adapt to use CXCR4 to escape CCR5 inhibitors [87].

We conclude from these studies that CXCR4 and CCR5 antagonists will be highly suitable anti-HIV drugs to combat AIDS in the near future. The combination of a CCR5 and a CXCR4 antagonist or a more potent dual antagonist with already existing anti-HIV agents will certainly be a great step forward in anti-HIV drug research.

References


