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## Commentary

# The AMD3100 story: The path to the discovery of a stem cell mobilizer (Mozobil)

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### ABSTRACT

AMD3100 was found to inhibit HIV-1 and HIV-2 within the 1–10 nM concentration range while not being toxic to the host cells at concentrations up to 500 μM, thus achieving a selectivity index of approximately 100,000. The target of action was initially thought to be the viral envelope glycoprotein gp120. It appeared only to be the indirect target. The direct target of action turned out to be the co-receptor CXCR4 used by T-lymphotropic HIV strains (now referred to as X4 strains) to enter the cells. Initial (phase I) clinical trials undertaken with AMD3100, as a prelude to its development as a candidate anti-HIV drug for the treatment of AIDS, showed an unexpected side effect: an increase in the white blood cell counts. Apparently, AMD3100 specifically increased CD34+ hematopoietic stem cell counts in the peripheral blood. Stromal derived factor 1 (SDF-1), through its interaction with CXCR4, retains the stem cells in the bone marrow (a process referred to as "homing"), and AMD3100 specifically antagonizes this interaction. AMD3100 in combination with granulocyte colony-stimulating factor (G-CSF) resulted in the collection of more progenitor cells than G-CSF alone. At present, the major indication for clinical use of AMD3100 (Mozobil™) is the mobilization of hematopoietic stem cells from the bone marrow into the circulating blood for transplantation in patients with hematological malignancies such as non-Hodgkin's lymphoma or multiple myeloma.

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## 1. The start: an impurity showing anti-HIV activity

When evaluating a number of commercially available cyclam preparations for their potential inhibitory effects on the replication of human immunodeficiency virus (HIV), all these preparations (i.e. JM1498 (Fig. 1)), as expected, did not show marked anti-HIV activity [1]. However, one of these preparations proved quite effective, and, on further exploration, this activity appeared to reside in an impurity, which was characterized as a bicyclam in which the two cyclam rings were tethered by a direct carbon–carbon linkage (i.e. JM1657

(Fig. 1)) [1]. As it did not prove feasible to re-synthesize JM1657, a program was launched to synthesize a bicyclam derivative with the cyclam rings tethered by an aliphatic bridge, the bicyclam derivative with the propyl bridge (i.e. JM2763) being about as active as JM1657 (Fig. 1).

A 100-fold increase in potency was noted upon replacing the aliphatic (i.e. propyl) bridge by an aromatic [i.e. 1,4-phenylene-bis(methylene)] bridge, as in JM2987 (Fig. 1) [2]. This compound proved inhibitory to the replication of HIV-1 and HIV-2 at an $EC_{50}$ of 0.001–0.007 μg/ml, while not being toxic to the host cells at a concentration of >500 μg/ml, thus achieving a selectivity index of >100,000 (Fig. 1). Surprisingly, we did not

| Compound | Structure | EC$_{50}$ ($\mu$M) | | CC$_{50}$ ($\mu$M) |
| --- | --- | --- | --- | --- |
| | | HIV-1(III$_B$) | HIV-2(ROD) | |
| JM1498 | | 399 | 150 | 1248 |
| JM1657 | | 0.144 | 1.01 | 319 |
| JM2763 | | 0.248 | 1.00 | > 622 |
| JM2987 | 8 HBr 2 H$_2$O | 0.005 | 0.010 | > 500 |
| JM3100 | 8 HCl 2 H$_2$O | 0.003 | 0.009 | > 500 |

Fig. 1 – Structures and HIV-inhibitory effects of JM1498, JM1657, JM2763, JM2987 and JM3100.

detect any activity with JM2987 against the simian immuno-deficiency virus (SIV) strains tested, which at that time (1994) was an enigmatic observation [this enigma was resolved, when several years later (1997) we demonstrated that the bicyclams specifically target the CXCR4 co-receptor of the T-lymphotropic X4 strains, while not being active against the M-macrophage tropic R5 strains (SIV strains apparently belong to this category)]. Being equipotent as the bromide salt (JM2987), the chloride salt (JM3100) (Fig. 1) was then used in all further experiments. The ''JM'' (for Johnson Matthey) designation was replaced by ''AMD'' (for AnorMED) when the further development of JM3100 was transferred from Johnson Matthey to AnorMED. From the beginning it was clear that the bicyclam derivatives (including AMD3100) interfered with an early process (viral entry) of the HIV replication cycle that had to be situated after the virus had been adsorbed to the cells but before the (reverse) transcription of the RNA genome [1,2]. It

proved difficult to generate HIV strains resistant to AMD3100, and, on further analysis, these bicyclam-resistant HIV strains carried multiple mutations in the viral glycoprotein (gp120), pointing to gp120 as the putative target for the antiviral activity of AMD3100 [3]. As it turned out, the viral glycoprotein gp120 was only an indirect target, the direct target being CXCR4, the receptor for the CXC chemokine SDF-1 (stromal derived factor), which also functions as the co-receptor (the principal receptor being CD4 (''CD'' standing for ''cluster of differentiation'')) for the T-tropic X4 HIV strains.

## 2. CXCR4 as the direct target for the action of AMD3100

That the bicyclam AMD3100 interacted with CXCR4 as its direct target was unequivocally shown in a series of papers
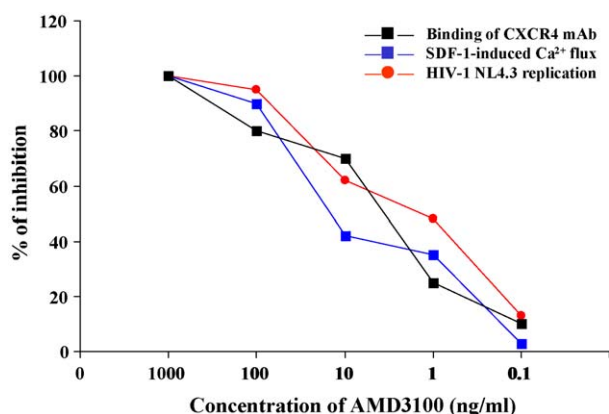
**Fig. 2 – Correlation between inhibitory effects of AMD3100 on HIV-1 replication, CXCR4 mAb binding and SDF-1-mediated signal transduction. According to De Clercq [7].**

published in 1997–1998 [4–6]. More specifically, AMD3100 was demonstrated by Schols et al. [5] and Donzella et al. [6] to inhibit T-tropic HIV strains by selective antagonization of the SDF-1 chemokine receptor CXCR4. In fact, a nice correlation was found between the inhibitory effects of AMD3100 on (i) HIV-1 replication, (ii) binding of CXCR4 monoclonal antibody and (iii) SDF-1-mediated signal transduction (SDF-1-induced $Ca^{2+}$ flux) (Fig. 2), as reviewed by De Clercq [7].

Inhibition of SDF-1-induced $Ca^{2+}$ flux actually allows a very rapid (within 1–2 min) measurement of the blockade of CXCR4 by AMD3100 [8]. Thus, within the HIV-1 replicative cycle AMD3100 interferes with the binding of the HIV gp120 to the CXCR co-receptor after it has first been bound to the CD4 receptor, and before the HIV gp41 initiates the fusion of the viral envelope membrane with the cell membrane (Fig. 3) [9,10].

As reviewed previously [11], AMD3100, akin to SDF-1, specifically blocks those (T-tropic) virus strains using CXCR4 as the co-receptor, whereas neither AMD3100 nor SDF-1 exhibit any activity against the M-tropic virus strains using CCR5 as the co-receptor (Table 1) [5]. *Vice versa*, RANTES (the natural ligand of CCR5) effectively inhibited the M-tropic R5 virus strains, while not being active against the T-tropic R4 virus strains. AMD3100 is a highly specific CXCR4 antagonist inhibiting SDF-1-mediated $Ca^{2+}$ flux in a number of cells expressing CXCR4, but has no inhibitory effect on chemokine-induced signalling from CXCR1, CXCR2, CXCR3, CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8 or CCR9 [12]. The principal interaction points of AMD3100 with CXCR4 may be the aspartic acid residues (particularly at positions 171 and 262) located at the extracellular side of CXCR4 (Fig. 4) [13]. Thus, AMD3100 is a specific antagonist of CXCR4, is not cross-reactive with other chemokine receptors, and is not an agonist of CXCR4 [14].

AMD3100 has shown antiviral activity (as measured by p24 production) in SCID-hu Thy/Liv mice infected with a CXCR4-using clinical HIV isolate (reduction of viral load by 0.9 $\log_{10}$ HIV RNA copies/ml) [15], and proof of concept (POC) that AMD3100 is also effective in a patient infected with an X4 HIV-1 strain has been provided [16]. This was the only patient in this study that had a purely CXCR4-using virus. Overall, the average change in viral load across all patients was +0.03 $\log_{10}$ [17]. AMD3100 has the ability to suppress both X4-tropic and dual (X4 and R5) tropic variants that effectively use CXCR4 to enter the cells [18].

## 3. Stem cell mobilization by AMD3100

When AMD3100 was submitted to phase I clinical trials in normal volunteers (before embarking on the phase II clinical trials to evaluate its antiviral activity in HIV-infected patients), an unexpected side effect was noted: a rapid increase in white blood cell (WBC) counts peaking at 6 h following the intravenous infusion of AMD3100 [19] (Fig. 5). The WBC response was clearly dose-dependent over the dosage range used (10, 20, 40 and 80 μg/kg) (Fig. 5B). These results were later confirmed by Lack et al. [20] over a dosage range of 40, 80, 160 and 240 μg/kg (Fig. 6B). On closer inspection, the white blood cells mobilized by AMD3100 appeared to carry the marker CD34, and thus could be characterized as hematopoietic stem cells [21]. The kinetics of mobilization of CD34^{+} cells into the peripheral blood (Fig. 7) [21] with a nadir at 6–9 h following intravenous administration of AMD3100 was almost identical to that noted for the total white blood cell counts (Fig. 6B).

Circulating CD34^{+} cells increased 5-fold after administration of AMD3100 at 80 μg/kg and 15.5-fold after administration of AMD3100 at 240 μg/kg, both at 9 h after injection. Myeloid progenitor cells-colony forming unit granulocyte-macrophage (CFU-GM); CFU-granulocyte, eosinophil, monocyte, megakaryocyte (CFU-GEMM); and burst forming units-erythroid showed similar increases in mobilization to the blood with increasing doses of AMD3100 [22].

AMD3100 (administered at 160 μg/kg on day 5) was then found to act synergistically with granulocyte-colony stimulating factor (G-CSF administered at 10 μg/(kg day) on days 1–4) [23]. Addition of AMD3100 (to G-CSF) resulted in a tripling of circulating CD34^{+} cells within 10 h after administration (2.7-fold increase, range: 1.1- to 6.9-fold) while no mobilization occurred of B cells, tumor cells, or natural killer T-cell subsets such as CD2, CD3, CD4 or CD8 [24].

For the collection of CD34^{+} cells to be used for autologous transplantation, the target number of CD34^{+} cells is $4.0 \times 10^6 \, kg^{-1}$. With G-CSF (10 μg/(kg day) for 5 days) the number of CD34^{+} cells collected was $3.73 \times 10^6 \, kg^{-1}$; with AMD3100 (240 μg/kg on day 5), the number of CD34^{+} cells collected was $3.02 \times 10^6 \, kg^{-1}$; with both G-CSF (10 μg/(kg day) for 5 days) and AMD3100 (160 μg/kg on day 5) combined, the number of CD34^{+} cells collected was $9.88 \times 10^6 \, kg^{-1}$ [23]. Broxmeyer et al. [25] confirmed that AMD3100 induced a rapid mobilization of hematopoietic progenitor cells (HPCs) and synergistically augmented G-CSF-induced mobilization of HPCs. Flomenberg et al. [26] further ascertained that the combination of AMD3100 plus G-CSF is generally safe, effective, and superior to G-CSF alone for autologous HPC mobilization.

Furthermore, the CD34^{+} peripheral blood progenitor cells (PBPCs) mobilized by AMD3100 in combination with G-CSF express significantly higher amounts of genes that potentially promote superior engraftment after myeloablative therapy than G-CSF-mobilized CD34^{+} PBPCs [27]. Indeed, AMD3100
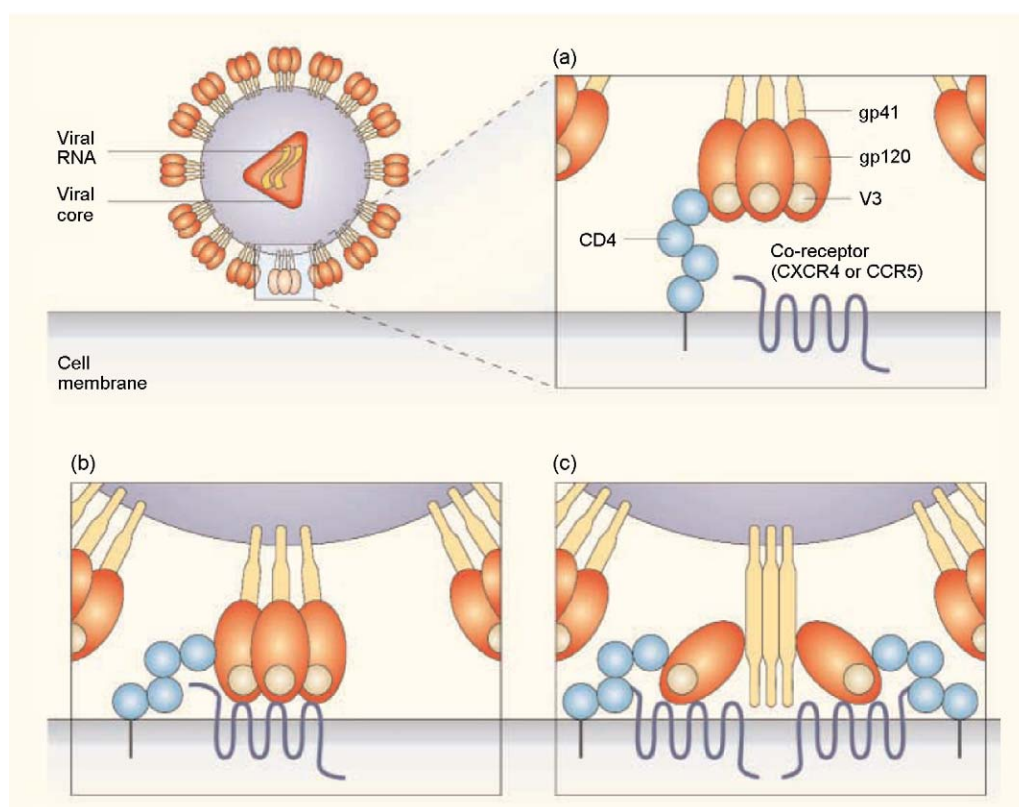
**Fig. 3 – Mechanism of action of bicyclams: inhibiting viral entry by blocking the CXCR4 receptor. During the viral adsorption process, (a) the viral envelope glycoprotein gp120 interacts with the CD4 receptor at the cell membrane. *(b)* Subsequently, gp120 interacts with the co-receptor CXCR4 for T-tropic (X4) HIV strains, whereupon (c) the viral glycoprotein gp41 anchors into the cell membrane. The bicyclams block the interaction between gp120 and CXCR4. According to De Clercq [9].**

mobilizes a population of hematopoietic stem cells with intrinsic characteristics different from those hematopoietic stem cells mobilized with G-CSF, suggesting that the mechanism of AMD3100-mediated hematopoietic stem cell mobilization is fundamentally different from G-CSF-mediated hematopoietic stem cell mobilization [28].

The ability of AMD3100 to mobilize hematopoietic progenitor stem cells from the bone marrow has been demonstrated in a number of experimental model systems i.e. both autologous and allogeneic peripheral blood mononuclear cells (PBMCs) in dogs [29]; hematopoietic progenitor stem cells (from the femoral bone marrow) in mice and humans [30]; and hematopoietic stem cells in Fanconi anemia knockout mice [31].

Holtan and colleagues reported that AMD3100 not only increases the autograft absolute lymphocyte counts

| Table 1 – Anti-HIV activity profile of AMD3100 correlated with co-receptor use. | | | | |
|---|---|---|---|---|
| Strain | Co-receptor used | $EC_{50}$ (ng/ml) | | |
| | | AMD3100 | SDF-1$\alpha$ | RANTES |
| *T-tropic* | | | | |
| HIV-1 IIIB | CXCR4 | 2 | 20 | >1000 |
| HIV-1 RF | CXCR4 | 5 | 50 | >1000 |
| HIV-1 NL4-3 | CXCR4 | 3 | 100 | >1000 |
| HIV-2 ROD | CXCR4 | 7 | 55 | >1000 |
| *M-tropic* | | | | |
| HIV-1 BaL | CCR5 | >25,000 | >1000 | 25 |
| HIV-1 SF-162 | CCR5 | >25,000 | >1000 | 5 |
| HIV-1 ADA | CCR5 (CCR2b, CCR3) | >25,000 | >1000 | 10 |
| HIV-1 JR-FL | CCR5 (CCR2b, CCR3) | >25,000 | >1000 | 4 |
| According to Schols et al. [5]. | | | | |
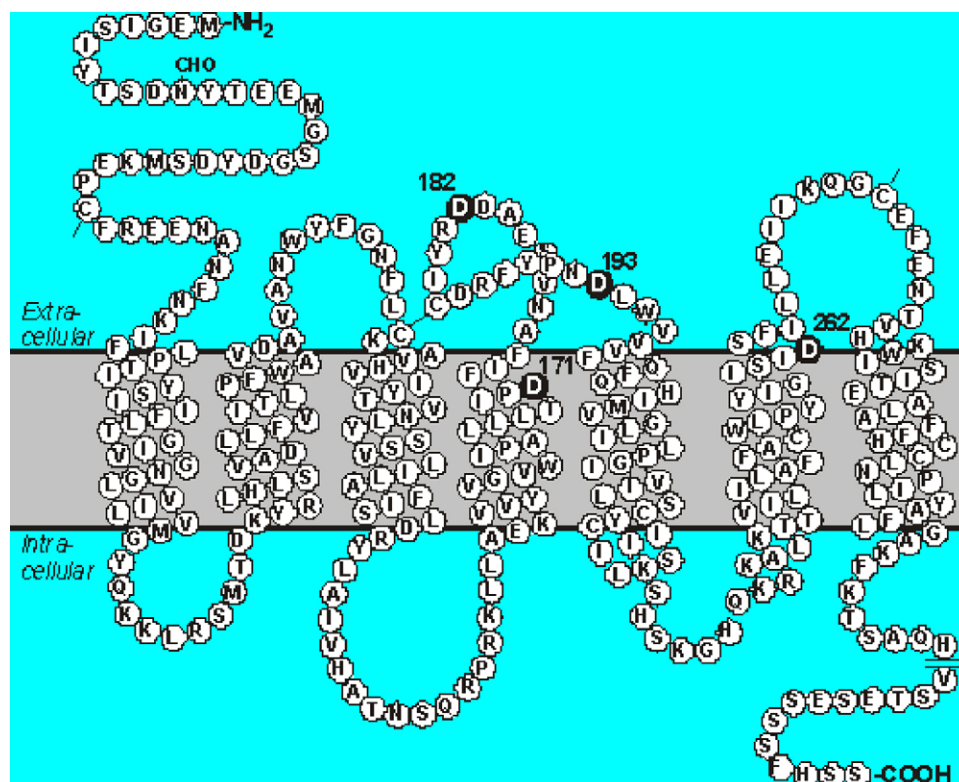
**Fig. 4 – Amino acid sequence and membrane organization of the chemokine receptor CXCR4. According to Hatse et al. [13].**

($4.16 \times 10^9$ lymphocytes/kg *versus* $0.288 \times 10^9$ lymphocytes/kg), but also that with a median follow-up of 20 months, no relapses occurred in the AMD3100 group (compared with 15 of 29 in the control group) of non-Hodgkin's lymphoma patients after autologous stem cell transplantation [32]. Calandra et al. [33] found that AMD3100 when given with G-CSF mobilized a sufficient number of CD34+ cells in non-Hodgkin's lymphoma, multiple myeloma, and Hodgkin's disease patients who could not deliver sufficient cells for autologous transplant following other mobilization regimens [33]. With one dose of AMD3100 (240 μg/kg) by subcutaneous injection, two-thirds of the donors collected an allograft with a number of CD34+ cells

sufficient for transplantation [34], and, in this sense, AMD3100 may provide a more rapid and possibly less toxic and less cumbersome alternative to the traditional G-CSF-based CD34+ cell mobilization in normal donors.

Thus, in conclusion, AMD3100 is a rapid and efficient stem cell-mobilizing agent [35]; once in the circulating blood, stem cells can be collected for use in autologous stem cell transplantation in patients with haematological malignancies such as multiple myeloma or non-Hodgkin's lymphoma [36]. There is no increased risk that in the patients with multiple myeloma or non-Hodgkin's lymphoma AMD3100 may itself mobilize tumor cells [37–39].
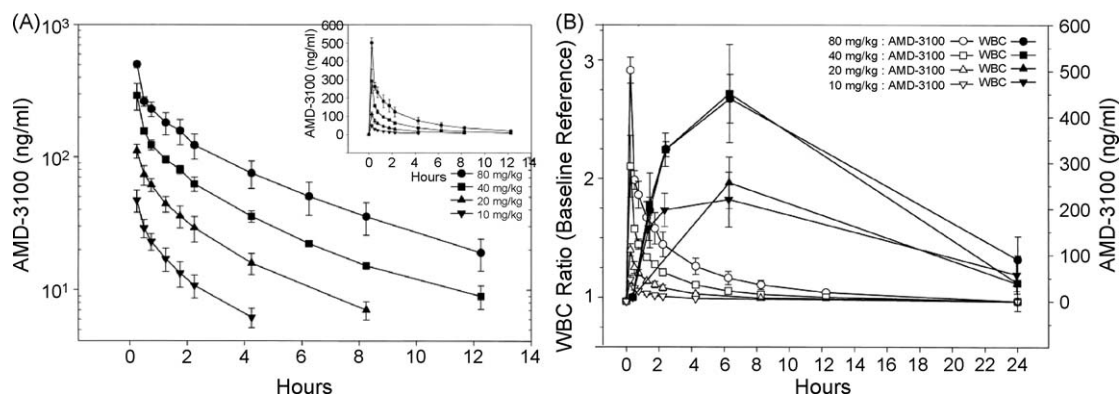


**Fig. 5 – (A) Single-dose AMD3100 pharmacokinetics following 15-min intravenous infusion (median and range). According to Hendrix et al. [19]. (B) WBC ratio *versus* time compared to AMD3100 concentration *versus* time following single-dose intravenous AMD3100 administration. According to Hendrix et al. [19].**
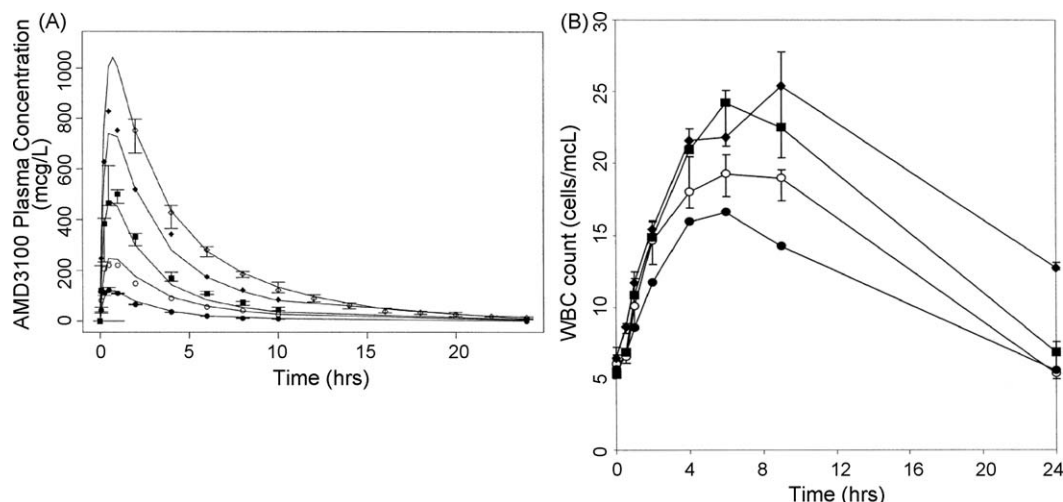
Fig. 6 – (A) AMD3100 plasma concentrations *versus* time in healthy human volunteers. The points represent the experimental data (median). The error bars represent the interquartile range (shown for representative data sets) for 40 μg/kg (●), 80 μg/kg (○), 160 μg/kg (■), 240 μg/kg (◆), and 320 μg/kg (◇). The lines represent the population-predicted concentrations from the pharmacokinetic model. According to Lack et al. [20]. (B). Total white blood cell counts *versus* time. The points represent the experimental data (median). The error bars represent the interquartile range (shown for representative data sets) for 40 μg/kg (●), 80 μg/kg (○), 160 μg/kg (■), and 240 μg/kg (◇). According to Lack et al. [20].

## 4. Any potential of AMD3100 in the treatment of arthritis, ischemia, cancer or virus infections (other than HIV)?

To the extent that in the pathogenesis of any given disease the CXCR4 interaction with SDF-1 plays a critical role, AMD3100, as a potent and selective CXCR4 antagonist, may be expected
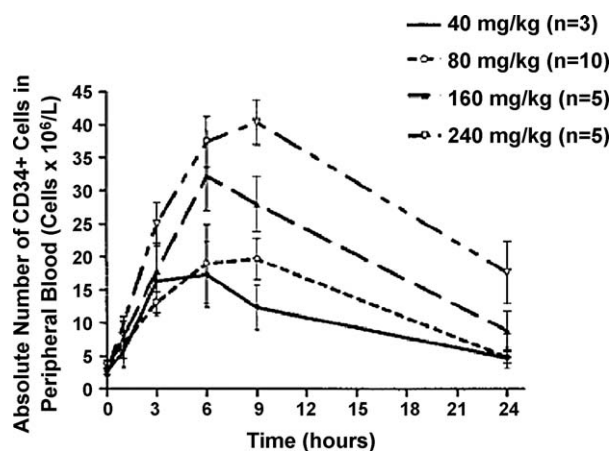


Fig. 7 – Dose–response analysis of AMD3100-induced mobilization of CD34+ cells into peripheral blood. Healthy human volunteers received a single subcutaneous injection of AMD3100 at the following doses: 40 μg/kg (n = 3; solid line); 80 μg/kg (n = 10; ○); 160 μg/kg (n = 5; ▲); and 240 μg/kg (n = 5; ▽). Peripheral venous blood was withdrawn at time intervals after drug administration, and FACS analysis was used to determine the concentration of CD34+ cells. Each value represents the mean SEM. According to Liles et al. [21].

to interfere with the clinical course of this disease. Hence AMD3100 has been found to inhibit collagen-induced arthritis in mice, concomitantly with the inhibition of SDF-1-elicited intracellular $Ca^{2+}$ flux in Mac-1+ cells harvested from the spleens of these mice [40].

Several human breast cancer cell lines have been found to express CXCR4 [41], and it is therefore surprising that the potential of AMD3100 in the treatment of breast cancer has not been further followed up in recent years.

Studies of Rubin et al. [42] have shown that systemic administration of AMD3100 inhibits the growth of intracranial glioblastoma and medulloblastoma xenographs. CXCR4 is apparently critical to the progression of diverse brain malignancies, thus providing a scientific rationale for clinical evaluation of AMD3100 in the treatment of malignant brain tumors [42].

CXCR4 has proven to be essential for the trans-endothelial migration of Waldenstrom macroglobulinemia (WM) cells, and this process is inhibited by AMD3100 [43]. AMD3100 may be useful in future clinical applications in the regulation of trafficking of WM cells and increasing sensitivity to therapeutic agents.

Furthermore, AMD3100 has been shown to effectively reduce tumor growth in nude mice inoculated with anaplastic thyroid carcinoma (ATC) cells and may well represent a novel potential strategy in the treatment of ATC, a rare thyroid cancer with extremely poor prognosis [44].

CXCR4 and SDF-1 are overexpressed in human pituitary adenomas, and as CXCR4 activation may contribute to pituitary cell proliferation, and, possibly, adenoma development as well, AMD3100 could play a role in suppressing the growth of pituitary adenomas in humans [45].

AMD3100 has also been reported to decrease invasion of human colorectal cancer cells *in vitro* [46]. Thus, blocking the interaction of CXCR4 with SDF-1 (CXCL12) may provide a novel
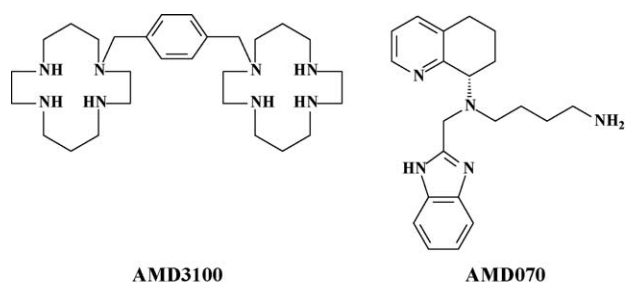
**Fig. 8 – Structures of AMD070 and AMD3100.**

means of preventing the invasion and metastasis of colorectal cancer.

AMD3100 is a potent and rapid mobilizer of angiogenic cells [47], which may stimulate angiogenesis at sites of ischemia through a paracrine mechanism [48], including ischemia in a diabetic environment [49].

Recently, McCandless et al. [50] reported that AMD3100 promoted the entry into the CNS parenchyma of CD8^{+} T-lymphocytes specific for WNV (West Nile virus), reduced viral load within the CNS, and significantly improved survival after WNV infection.

## 5. What about anti-HIV activity of CXCR4 antagonists? From AMD3100 to AMD070

Guided by AMD3100 as the prototype, several small-molecule CXCR4 antagonists (i.e. based on two aromatic amine moieties connected by a *para*-xylylene group) were synthesized, the most effective congener inhibiting the interaction of CXCR4 with SDF-1 at a concentration as low as 1.2 nM [51].

The identification of AMD070 as a potent, orally bioavailable CXCR4 antagonist which strongly inhibits HIV infectivity (at an $EC_{50}$ of 1–10 nM) dates already from more than 5 years ago, but has so far only been communicated in abstract form [52]. AMD070 was found to inhibit X4 HIV replication in five different CD4^{+} T-cell lines, CXCR4-transfected cell lines and peripheral blood mononuclear cells (PBMs). AMD070, akin to AMD3100, had no activity against R5 HIV-1 variants. Unlike AMD3100, AMD070 cannot be considered a bicyclam (Fig. 8). The structure of AMD070 was revealed by Kazmierski et al. in their report [53]. Proof of concept that AMD070 (originally referred to as AMD11070) can selectively inhibit X4-tropic virus in HIV-1-infected patients was provided by Saag et al. [54] and Moyle et al. [55]. Like AMD3100, AMD070 induced a dose-related elevation of the WBC counts, which can be attributed to CXCR4 blockade. Whether AMD070, which, unlike AMD3100 (which has to be given parenterally) can be administered orally, has any future potential as either an anti-HIV agent, or a stem cell-mobilizing agent, or, possibly, an agent inhibitory to any other CXCR4-mediated process, remains subject of further study.

What is for sure, is that if CRIs (co-receptor inhibitors), whether CXCR4 inhibitors or CCR5 inhibitors, are used as anti-HIV agents, they should be used in combination regimens, so as to prevent selection of CXCR4-using T-tropic variants if only

CCR5 inhibitors are used, and to prevent selection of CCR5-using M-tropic variants if only CXCR4 inhibitors are used [56,57].

## 6. The immediate future use for AMD3100, now known as Mozobil[TM]: hematopoietic stem cell mobilization

Genzyme Corporation announced on 17 June 2008 that it has submitted marketing applications in both the United States and the European Union for Mozobil[TM] (plerixafor injection) (previously known as AMD3100), a product candidate intended to enhance mobilization of hematopoietic stem cells for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma. On 15 December 2008 Genzyme Corporation announced that the US FDA had granted marketing approval for Mozobil[TM]. European approval is expected in 2009. Additional global applications in up to 60 countries are expected to follow [58].

Genzyme plans to launch Mozobil in the U.S. and Europe in 2009. Upon commercial launch, Mozobil will be marketed and sold by Genzyme's existing Transplant sales force, which has a commercial presence in more than 55 countries worldwide. Approximately 55,000 stem cell transplants are performed each year for multiple myeloma, Hodgkin's and non-Hodgkin's lymphoma, and other conditions in markets where Genzyme has a commercial infrastructure, including the United States, Europe, Latin America and the Asian Pacific countries [59].

Numerous Genzyme and investigator-sponsored trials are planned or underway to study Mozobil's use in other settings such as allogeneic hematopoietic stem cell transplants. Genzyme is also studying the use of Mozobil to improve the efficacy of chemotherapy and/or immunotherapy in various types of hematologic malignancies such as chronic lymphocytic leukemia and acute myelogenous leukemia, and is pursuing preclinical work to explore the role that Mozobil may play in cord blood transplantation, solid organ transplantation, cardiovascular disease, renal ischemic disease, and a variety of additional types of solid tumor malignancies [59].

## 7. Conclusion

The bicyclam AMD3100 represents a typical example of the meandrous path of drug discovery, hopping from one unexpected ("serendipitous") observation to another, ultimately leading to the clinical use for which originally it was neither conceived nor developed. Bicyclam JM1657 (JM standing for Johnson Matthey) was originally identified as an impurity in a (mono)cyclam preparation evaluated for its potential inhibition of the replication of HIV. While most of the commercially available cyclam preparations were virtually inactive against HIV, one particular preparation showed a marked anti-HIV activity, apparently due to an impurity. This impurity was purified and identified as the bicyclam JM1657 (with the 2 cyclam rings tethered through a direct carbon–carbon linkage). While re-synthesis of this compound failed, it

was the onset of a large synthetic effort leading first to the synthesis of JM2763 (with the 2 cyclam rings tethered by an aliphatic bridge), and, then to the synthesis of JM3100 (later designated as AMD3100, AMD standing for AnorMED) (with the 2 cyclam rings tethered by an aromatic bridge). AMD3100 was found to inhibit HIV [both HIV-1 and HIV-2, but not SIV (simian immunodeficiency virus)], within the 1–10 nM concentration range while not being toxic to the host cells at concentrations up to 500 $\mu$M, thus achieving a selectivity index of approximately 100,000. The target of action was initially thought to be the viral envelope glycoprotein gp120. It appeared only to be the indirect target. The direct target of action turned out to be the co-receptor CXCR4 used by T-lymphotropic HIV strains to enter the cells (the primary receptor being CD4). Consequently, the anti-HIV activity of AMD3100 was confined to those HIV strains (now referred to as X4 strains) using CXCR4 as co-receptor [the normal ligand for CXCR4 is the chemokine SDF-1 (stromal derived factor), now also referred to as CXCL12]. Initial (phase I) clinical trials undertaken with AMD3100, as a prelude to its development as a candidate anti-HIV drug for the treatment of AIDS, showed an unexpected side effect: an increase in the white blood cell (WBC) counts. On closer inspection it appeared that AMD3100 specifically increased CD34+ (hematopoietic stem) cell counts in the peripheral blood. SDF-1, through its interaction with CXCR4, retains the stem cells in the bone marrow (a process referred to as ''homing''). One single parenteral injection of AMD3100 (at a dose of 240 $\mu$g/kg) suffices to mobilize the stem cells from the bone marrow into the bloodstream, where they can be collected by leukapheresis. AMD3100 in combination with granulocyte colony-stimulating factor (G-CSF) results in the collection of more progenitor cells than G-CSF alone. AMD3100 is a more rapid mobilizer of hematopoietic stem cells than G-CSF. At present, the major indication for clinical use of AMD3100 (Mozobil[TM]) is the mobilization of hematopoietic stem cells from the bone marrow into the circulating blood, from where the stem cells can be harvested for use in transplantation in patients with hematological malignancies such as non-Hodgkin's lymphoma or multiple myeloma.

## Acknowledgments

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