Antiviral Chemistry and Chemotherapy
2019, Vol. 27: 1–8

DOI: 10.1177/2040206619829382
journals.sagepub.com/home/avc
SAGE

# Mozobil® (Plerixafor, AMD3100), 10 years after its approval by the US Food and Drug Administration

**Erik De Clercq**

**Abstract**
AMD3100 (plerixafor, Mozobil®) was first identified as an anti-HIV agent specifically active against the T4-lymphotropic HIV strains, as it selectively blocked the CXCR4 receptor. Through interference with the interaction of CXCR4 with its natural ligand, SDF-1 (also named CXCL12), it also mobilized the $CD34^+$ stem cells from the bone marrow into the peripheral blood stream. In December 2008, AMD3100 was formally approved by the US FDA for autologous transplantation in patients with Non-Hodgkin's Lymphoma or multiple myeloma. It may be beneficially used in various other malignant diseases as well as hereditary immunological disorders such as WHIM syndrome, and physiopathological processes such as hepatopulmonary syndrome.

**Keywords**
CXCR4, Mozobil®, AMD3100, stem cells, NHL, MM, WHIM

Date received: 18 October 2018; accepted: 2 January 2019

## Introduction

Just a decade ago, Mozobil® (also known as plerixafor, and AMD3100) was approved by the US Food and Drug Administration (FDA) for the autologous transplantation of bone marrow (BM) cells in patients with Non-Hodgkin's lymphoma (NHL) or multiple myeloma (MM). The bicyclam AMD3100 was originally tailored after a predecessor called JM1657 that had been identified as an impurity in a commercial (mono)cyclam preparation, intended to design a new lead compound for anti-HIV agents. The synthesis of JM1657 (JM standing for Johnson Matthey company), whereby the two cyclam rings are directly linked together, could not be repeated, but JM2763, whereby the cyclam moieties are tethered by a propyl bridge, proved to be a potent and selective inhibitor of both HIV-1 and HIV-2 replication.[1]

When the propyl bridge tethering the two cyclam rings was replaced by an aromatic bridge, as in JM3100, later renamed AMD3100 (AMD standing for AnorMED that had been created as a spin-off of Johnson Matthey), a dramatic increase in anti-HIV potency was noted.[2] In the subsequent years, AMD3100 was discovered to be a specific inhibitor of CXCR4, the co-receptor of T-lymphotropic HIV strains, to enter the target cells.[3,4]

As a prerequisite to the clinical development of AMD3100 as an anti-HIV drug, Craig Hendrix and his colleagues at Johns Hopkins University with the collaboration of the AnorMED investigators examined the safety profile of AMD3100 in human volunteers,[5] and found an increase in the white blood cell (WBC) counts peaking at about 8–10 h after (subcutaneous) injection of AMD3100. At closer inspection, these WBCs were primarily hematopoietic stem cells (HSCs) carrying the CD34 marker.[6] The first proof-of-principle that AMD3100 could mobilize hematopoietic stem cells was provided by Broxmeyer et al.,[7] and so was born the concept that AMD3100 (now also called plerixafor or Mozobil®) could function as a mobilizer of HSCs. The history of the bicyclam

Rega Institute for Medical Research, Leuven, Belgium

**Corresponding author:**
Erik De Clercq, Rega Institute for Medical Research, Herestraat 49, B-3000 Leuven, Belgium.
Email: erik.declercq@kuleuven.be

AMD3100 story has been told in previous review articles.[8–11] How this story evolved in the past few years, until 2018, will be the subject of the present review.

## Mobilization

The minimum threshold for autologous transplantation of peripheral blood stem cells is $\geq 2 \times 10^6$ CD34/kg, which may not always be achieved using optimal doses of granulocyte-colony stimulating factor (G-CSF).[12] Mobilization failures may range from 8% (MM) to 25% (NHL). However, addition of plerixafor to G-CSF was found to dramatically reduce the mobilization failure rates, from 75% to 27%.[13,14]

Plerixafor mobilizes hematopoietic stem cells to the peripheral blood by antagonizing the CXCR4 receptor,[15] thus interfering with the CXCR4/SDF-1 (CXCL12) axis,[16–18] tethering stem cells to the BM.

The BM is a reservoir of progenitor cells, i.e. hematopoietic progenitor cells (HPCs), fibrocytes, mesenchymal stem cells (MSCs) and endothelial progenitor cells (EPCs).[19] Plerixafor would specifically mobilize the $CD34^+$ HPCs, when used alone or as an adjunct to G-CSF.[20] The doses used would be 160 μg/kg × 1 on day 5 for plerixafor, and 10 μg/kg on days 0, 1, 2, 3 and 4 for G-CSF, or 240 μg/kg for plerixafor if used alone. A single dose of plerixafor at 240 μg/kg (subcutaneously) may provide a more rapid and possibly less toxic and cumbersome alternative to traditional G-CSF-based mobilization.[21] Yet, the combination of G-CSF (10 μg/kg subcutaneously daily for up to eight days, together with plerixafor, beginning on the evening of day 4 and continuing daily for up to four days, subcutaneously at a (daily) dose of 240 μg/kg, has been recommended for autologous stem cell mobilization and transplantation for patients with NHL.[22]

On 15 December 2008, the US FDA approved plerixafor for use in combination with G-CSF to mobilize HSCs to the peripheral blood for collection and subsequent autologous transplantation in patients with NHL or MM[23]: 59% of NHL patients mobilized with G-CSF and plerixafor had peripheral blood HSC collections of $\geq 5 \times 10^6$ $CD34^+$ cells/kg in 4 or fewer apheresis sessions, compared with 20% of NHL patients mobilized with G-CSF without plerixafor; in MM patients, the corresponding data were 72% and 34%, respectively.[23] That plerixafor seemed to be more effective in MM patients than in NHL patients was also suggested by Bilgin and de Greef.[24] While 25% of patients treated with G-CSF alone still failed mobilization, upon the addition of plerixafor, the failure rate would drop to 4%.[25]

The conventional dose of plerixafor is 240 μg/kg, but this dose could be safely increased (in healthy donors) to 480 μg/kg.[26] Figure 1 illustrates the $CD34^+$ cell counts obtained over time following (subcutaneous) injection of plerixafor at doses of 480 μg/kg and 240 μg/kg. Increasing the dosage of plerixafor may obviously adjust the recommendations formulated by Giralt et al.[27] and D'Souza et al.[28] However, a major breakthrough in stem cell mobilization was recently reported by Hoggatt et al.[29] They announced that a single injection of both the CXCR2 agonist, GROß, and plerixafor, in mice resulted in stem cell mobilization peaking within 15 min that was equivalent in magnitude to a standard multi-day regimen of G-CSF.[29] This observation, illustrated in Figure 2, may obviously revolutionize the future of stem cell mobilization. Martin et al.[30] had previously shown that both CXCR2 and CXCR4 control the release of neutrophils from the BM, and as neutrophils age, they upregulate expression of CXCR4 and acquire the ability to migrate toward SDF-1α. These senescent neutrophils preferentially home to the BM in a CXCR4-dependent manner.[30]

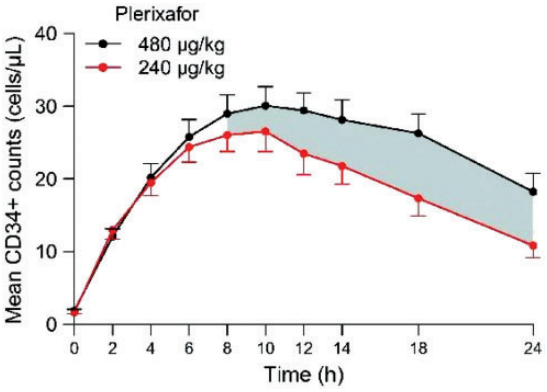


**Figure 1.** CD34+ cell counts in the blood over time following (subcutaneous) injection of plerixafor at doses of 240 and 480 μg/kg.[26]

## Antitumor activity

AMD3100 has been specifically approved for autologous transplantation in patients with NHL and MM. Yet, it offers attractive potential for the treatment of various other cancers.

SDF-1/CXCR4 is a critical regulator of homing of MM cells, and AMD3100 (plerixafor) inhibits the homing of MM cells to the BM niches.[31] This makes the MM cells also more sensitive to therapy with cytotoxic agents such as doxorubicin.[32] This sensitization to cytotoxic chemotherapy has also been noted with plerixafor in acute myeloid leukemia.[33]

CXCR4 could be a promising therapeutic target for hilar cholangiocarcinoma (CCA),[34] thus necessitating

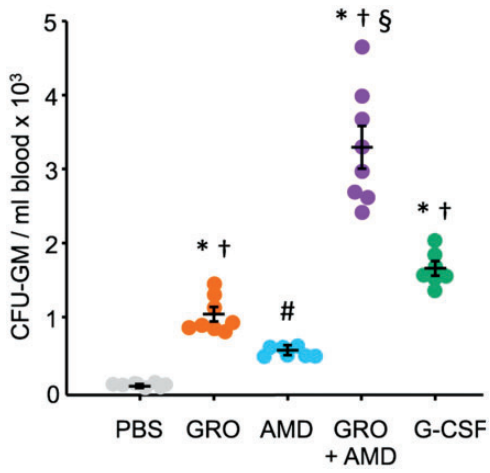


**Figure 2.** Mobilization of hematopoietic stem cells in mice, measured CFU-GM/mL blood at 15 min post GROß, 60 min post-AMD3100 and 15 min post GROß plus AMD3100, compared to mice treated with G-CSF twice daily (bid) for four days.[29] $^{\#}p < 0.05$ compared to control. $^{*}p < 0.001$ compared to control. $^{\dagger}p < 0.001$ compared to AMD3100. $^{\S}p < 0.001$ compared to GROß. Ns: not significant versus GROß or G-CSF.

the evaluation of plerixafor. The rate of hilar CCA has significantly risen over the past several decades.[35] Nowadays, it is becoming the most common reason for hepatic tumor-induced death.[36]

Medullary thyroid carcinoma (MTC) is a rare endocrine malignancy which accounts for about 5% of all thyroid carcinomas; it is derived from the calcitonin-secreting parafollicular C-cells of the thyroid gland.[37] As the CXCR4/CXCR7/CXCR12 axis plays an important role in MTC, the CXCR4 receptor may be a potential therapeutic target for CXCR4 receptor antagonists such as plerixafor in the treatment of advanced MTC.[38]

As the CXCR4/SDF-1 pathway is also involved in the local invasiveness of malignant pleural mesothelioma (MPM), co-administration of photon irradiation and AMD3100 (plerixafor) has been advocated as a possible strategy to reduce the risk of local recurrence of MPM.[39] Likewise, AMD3100 has been suggested as a novel approach to offset the effects of obesity on prostate cancer progression (in mice).[40]

Ovarian cancer is the fifth most common cause of cancer deaths in women in western countries, more than 90% of the malignant ovarian tumors being of epithelial origin.[41,42] As CXCR4 and CXCL12 are overexpressed in several cancers, including ovarian tumors,[43] it is logical that AMD3100 has been recommended as a possible (complimentary) treatment of advanced disseminated epithelial high-grade serous ovarian cancer patients.[44] Also, Mao et al.[45] recommended targeting the CXCR4/CXCL12 axis in using AMD3100 for treating epithelial ovarian cancer. To this end, AMD3100 could be combined with (low-dose) Taxol to limit ovarian cancer cell growth.[46]

As to breast cancer, poor prognosis has been noted for the so-called triple-negative breast cancer (TNBC).[47] In TNBC, the tumors do not express estrogen receptor, progesterone receptor or human epidermal growth factor receptor 2; TNBC has remained a major therapeutic challenge, currently limited to surgery, chemotherapy and radiotherapy. Yet, AMD3100 has been reported to significantly enhance the response of TNBC cells to ionizing radiation.[48] Similarly, locally advanced cervical cancer may profit from the combination of radiation and AMD3100 treatment.[49]

Among the chemokine receptors, CXCR4 is the most involved in cancer, as it is expressed in at least 23 different types of cancers.[50] Inhibition of CXCR4, i.e. with plerixafor, will impair the development of lung metastases.[51] In fact, the CXCR4/SDF-1 axis has become the hallmark of several metastatic cancers, thus justifying attempts, i.e. by CXCR4 antagonists, to stop metastases.[52]

CXCR4 and CXCR7 mediate osteosarcoma growth and metastasis towards the lungs.[53–55] AMD3100 blocks this process via the JNK and Akt pathways.[56]

AMD3100 was also found to inhibit brain-specific metastasis in lung cancer via suppressing the CXCR4/SDF-1 axis.[57] And, likewise, blocking the CXCR4 receptor by AMD3100 may be a successful approach to reduce the metastatic spread of colorectal cancer to the liver.[58]

## Pleiotropic effects

Wherever the CXCR4/SDF-1 axis is involved, the antagonistic effects of AMD3100 towards CXCR4 may be exploited in a wide spectrum of pathophysiological processes, varying from treating cancer, to preserving cardiac function and combating arthritis.[8,59] And what happened with the original purpose for the clinical development of AMD3100, that is therapeutic use for the treatment of HIV infections? It was immediately realized that to this end, the compound had to be orally bioavailable, and this aim was achieved with AMD11070. In clinical trials in healthy volunteers, this compound (Figure 3) was found to be well tolerated and orally bioavailable.[60] In a proof-of-concept clinical trial in HIV-infected patients harboring X4 virus, 4/9 patients had a greater than 1 $\log_{10}$ reduction in X4 viral level.[61] AMD11070 was well tolerated, with no serious safety concerns, but the compound was put on clinical hold because of histologic changes of the liver observed in long-term animal studies.[61] AMD11070 could be credited as the first orally available small molecule antagonist of CXCR4 to enter the clinic.[62]

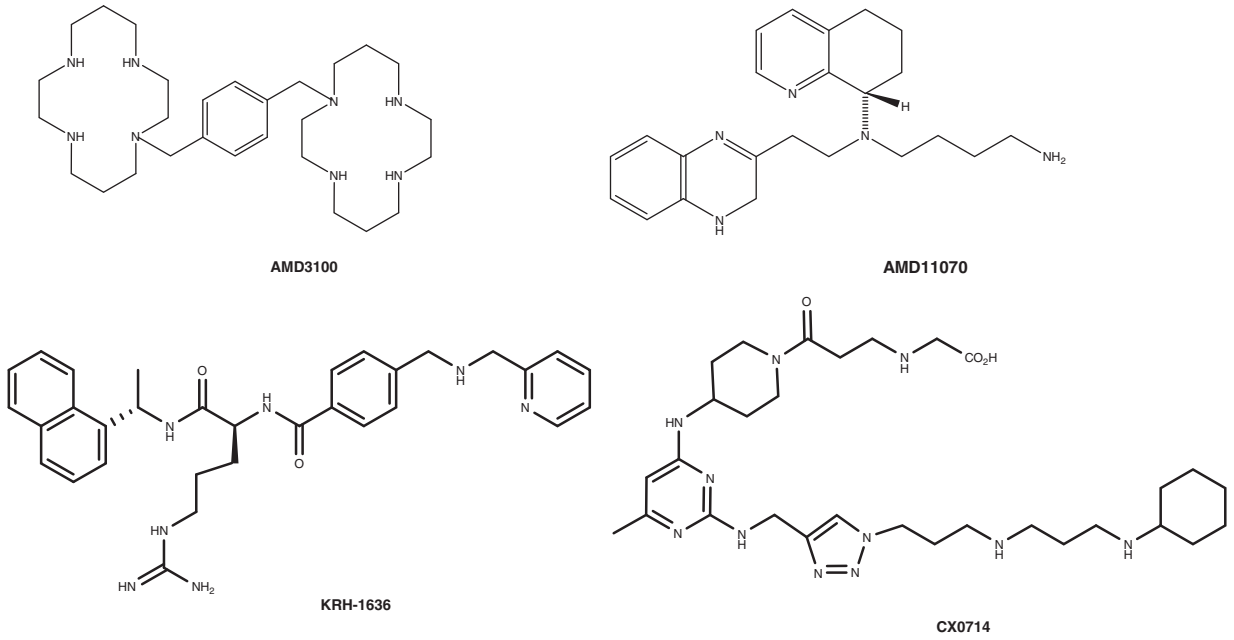


**Figure 3.** CXCR4 antagonists: AMD3100[8]; AMD11070[62]; KRH-1636[94]; and CX0714[95].

After AnorMed was acquired by Genzyme they chose not to pursue the HIV indication.

Endothelial progenitor cells (EPCs) are quietly retained within their niche in the BM, as secured by the SDF-1/CXCR4 axis, but disruption of the SDF-1/CXCR4 axis, i.e. by P2G, a mutant protein of SDF-1ß results in the enhancement of ischemic angiogenesis and blood perfusion.[63] AMD3100 can also rapidly mobilize EPCs,[64] but long-term administration of AMD3100 may exacerbate cardiac dysfunction and remodeling after myocardial infarction.[65] Danshensu [3–(3,4-Dihydroxyphenyl)-2-hydroxypropanoic acid], through the SDF-1α/CXCR4 axis, accelerates angiogenesis after myocardial infarction in rats, and this effect is counteracted by AMD3100.[66]

Autologous $CD34^+$ stem cells (as mobilized by G-CSF and/or AMD3100) can be safely delivered intra-arterially into the infarct territory in patients with acute ischemic stroke[67] and future studies should further address the eligibility criteria, dosage and timing before undertaking larger clinical trials.

AMD3100 may accelerate re-endothelialization of neointima in rabbit saccular aneurysm after FD (flow diverter) treatment.[68] This procedure may ultimately promote the repair of saccular aneurysms.

AMD3100 may also elicit analgesic effects and restore the GlyRα3 expression against neuropathic pain, in rats.[69]

The SDF-1/CXCR4 axis plays an important role in alveolar bone metabolism during orthodontic tooth movement (OTM) and here, again, AMD3100 may acquire a therapeutic application in bone remodeling and bone fracture healing.[70]

Antibody-secreting cells (ASCs) including short-lived plasmablasts and long-lived memory plasma cells (LLPCs) contribute to autoimmune pathology. AMD3100 efficiently depleted ASCs, including LLPCs. Combination with the proteasome inhibitor bortezomib significantly enhanced the depletion effect of AMD3100. This combination holds great promise in the treatment of lupus as indicated by its efficacy in the NZB/W murine preclinical lupus model.[71]

Finally, AMD3100 has been shown to attenuate pulmonary angiogenesis, by reducing the C-kit (+- cells and its pro-angiogenic activity in CBDL (common bile duct ligation) rat lungs, an experimental model for hepatopulmonary syndrome (HPS).[72] HPS is a serious complication of chronic liver disease characterized by arterial hypoxemia and an abnormal alveolar-arterial oxygen gradient.[73] The prevalence of HPS in cirrhotic patients ranges from 5% to 32% according to various threshold values for arterial deoxygenation,[74] and no effective medical treatment for HPS exists beyond liver transplantation.[75]

## WHIM syndrome

WHIM stands for warts, hypogammaglobulinemia, infections and myelokathexis.[76] Myelokathexis refers to retention of mature neutrophils in the BM, resulting in neutropenia (granulocytopenia). It was first described by Zuelzer et al.[77] and Krill et al.[78] and

identified as an immunological disorder by Wetzler et al.[79] That the myelokathexis was part of an autosomal dominant disorder, WHIM syndrome, was characterized by Gorlin et al.[76] The cause of almost all cases of WHIM syndrome is the inheritance of carboxyterminal truncation mutations that remove 10–19 amino acids from the chemokine receptor CXCR4.[80] When expressed in cell lines lacking endogenous CXCR4, the mutated $CXCR4^{R343X}$ exhibits about two-fold enhanced signaling on exposure to its ligand CXCL12 (also known as stromal cell-derived factor-1.[81]

The CXCR4 antagonist plerixafor (AMD3100) has been approved by the US FDA for mobilizing hematopoietic stem cells (HSCs) from BM for use in autologous transplantation in patients with NHL or MM.[22,82] McDermott et al.[83] and Dale et al.[84] found plerixafor to be of potential value to correct the panleukopenia (myelokathexis) in WHIM syndrome. Long-term treatment with plerixafor (for six months, subcutaneously twice daily at a dose of 0.01 to 0.02 mg/kg (4% to 8% of the FDA-approved dose) was then found efficacious and safe in the mechanism-based therapy of WHIM syndrome.[85]

McDermott et al.[86] also reported the spontaneous cure of WHIM syndrome by chromothripsis, whereby the chromosomes undergo massive deletion and rearrangement. The significance and impact of this curious observation remains to be assessed. Also, a mouse model for WHIM syndrome has been developed.[87]

Plerixafor clearly holds great promise for the therapy of WHIM syndrome.[88] If CXCR4-specific nanobodies hold potential as possible therapeutics for CXCR4-associated diseases such as WHIM syndrome,[89] it would seem imperative to evaluate their efficacy in comparison and/or conjunction with plerixafor.

## CXCR4 antagonists

The crystal structure of CXC4 in complex with UMIP-II, a CC chemokine encoded by Kaposi's sarcoma-associated herpesvirus, has been elucidated by Qin et al.[90] CXCR4 is remarkable in its ability to recognize multiple unrelated small molecules, peptides and proteins. The ligands thereby occupy different regions of the binding pocket due to the receptor conformational plasticity.[90]

Engineering of an efficacy switch mutation in CXCR4, F292A in the middle of the transmembrane helix 7, can convert the antagonists AMD3100 and AMD11070 into partial agonists. As agonists on F292A CXCR4, AMD3100 and AMD11070 were less disruptive to CXCR4 signaling while remaining efficient inhibitors of HIV entry.[91]

X4 Pharmaceuticals is developing CXCR4 antagonists (i.e. X4P-001) for the treatment of WHIM syndrome and renal cell carcinoma (RCC), the latter in combination with Inlyta® (personal communication from X4 Pharmaceuticals).

Various agonists and antagonists of the CXCR4 receptor have been identified,[92] and the therapeutic implications of these agonists, that could be blocked by the CXCR4-selective antagonist AMD3100, can only be guessed upon.

Meanwhile, AMD3100 has served as the model for the exploration of novel stem cell mobilizers that target the CXCR4 receptor,[93] and that could be considered as potential drug candidates, i.e. KRH-1636[94] (Figure 3), and CX0714[95] (Figure 3), which may be useful as stem cell-mobilizing agents for the same indications that have so far been considered for AMD3100.

## Conclusion

The AMD3100 story that has led in 2008, now 10 years ago, to the approval of a stem cell mobilizer, Mozobil® (plerixafor) for the autologous transplantation in patients with NHL or MM, can be viewed as a chain of serendipitous events: *first*, the identification of an impurity as an anti-HIV agent; *second*, the recognition of the CXCR4 receptor as the target for the anti-HIV activity of AMD3100; and *third*, the therapeutic use of AMD3100 as a stem cell mobilizer. As the role of the CXCR4 receptor and its ligand, SDF-1 (or CXCL12) in a multitude of physiopathological processes continuously evolves, so do the potential therapeutic applications of AMD3100. This activity spectrum is not limited to the various forms of cancer, but extends to far beyond, such as WHIM syndrome (retention of mature neutrophils in the BM) and hepatopulmonary syndrome (HPS). Meanwhile, new CXCR4 antagonists have been described which, while not structurally related to AMD3100 (for example KRH 1636, and CX0714), may behave in a similar fashion. This keeps the mobilization of stem cells in a continuous flux, not only in terms of therapeutic implications, but also with regard to the diversity of drug candidates. All of this exploration of CXCR4 antagonism for varying indications started with an adventitious impurity in a commercial cyclam preparation evaluated for anti-HIV activity.

### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

## References


1. De Clercq E, et al. Potent and selective inhibition of human immunodeficiency virus (HIV)-1 and HIV-2 replication by a class of bicyclams interacting with a viral uncoating event. *Proc Natl Acad Sci* 1992; 89: 5286–5290.
2. De Clercq E, et al. Highly potent and selective inhibition of human immunodeficiency virus by the bicyclam derivative JM3100. *Antimicrob Agents Chemother* 1994; 38: 668–674.
3. Schols D, et al. Bicyclams, a class of potent anti-HIV agents, are targeted at the HIV coreceptor fusin/CXCR-4. *Antiviral Res* 1997; 35: 147–156.
4. Schols D, et al. Inhibition of T-tropic HIV strains by selective antagonization of the chemokine receptor CXCR4. *J Exp Med* 1997; 186: 1383–1388.
5. Hendrix CW, et al. Pharmacokinetics and safety of AMD-3100, a novel antagonist of the CXCR-4 chemokine receptor, in human volunteers. *Antimicrob Agents Chemother* 2000; 44: 1667–1673.
6. Liles WC, et al. Mobilization of hematopoietic progenitor cells in healthy volunteers by AMD3100, a CXCR4 antagonist. *Blood* 2003; 102: 2728–2730.
7. Broxmeyer HE, et al. Rapid mobilization of murine and human hematopoietic stem and progenitor cells with AMD3100, a CXCR4 antagonist. *J Exp Med* 2005; 201: 1307–1318.
8. De Clercq E. The bicyclam AMD3100 story. *Nat Rev Drug Discov* 2003; 2: 581–587.
9. De Clercq E. The AMD3100 story: the path to the discovery of a stem cell mobilizer (Mozobil). *Biochem Pharmacol* 2009; 77: 1655–1664.
10. De Clercq E. Recent advances on the use of the CXCR4 antagonist plerixafor (AMD3100, Mozobil$^{TM}$) and potential of other CXCR4 antagonists as stem cell mobilizers. *Pharmacol Therap* 2010; 128: 509–518.
11. De Clercq E. AMD3100/CXCR4 inhibitor. *Front Immunol* 2015; 6:1–3.
12. DiPersio JF. New hope for mobilization failures … again. *Biol Blood Marrow Transplant* 2012; 18: 159–160.
13. Pusic I, et al. Impact of mobilization and remobilization strategies on achieving sufficient stem cell yields for autologous transplantation. *Biol Blood Marrow Transplant* 2008; 14: 1045–1056.
14. Attolico I, et al. Plerixafor added to chemotherapy plus G-CSF is safe and allows adequate PBSC collection in predicted poor mobilizer patients with multiple myeloma or lymphoma. *Biol Blood Marrow Transplant* 2011; 18: 241–249.
15. Bachelerie F, et al. International Union of Basic and Clinical Pharmacology. [corrected]. LXXXIX. Update on the extended family of chemokine receptors and introducing a new nomenclature for atypical chemokine receptors. *Pharmacol Rev* 2014; 66: 1–79.
16. Liu X, et al. SDF-1/CXCR4 axis modulates bone marrow mesenchymal stem cell apoptosis, migration and cytokine secretion. *Protein Cell* 2011; 2: 845–854.
17. Wescott MP, et al. Signal transmission through the CXC chemokine receptor 4 (CXCR4) transmembrane helices. *Proc Natl Acad Sci USA* 2016; 113: 9928–9933.
18. Eby JM, et al. Functional and structural consequences of chemokine (C-X-C motif) receptor 4 activation with cognate and non-cognate agonists. *Mol Cell Biochem* 2017; 434: 143–151.
19. Pitchford SC, et al. Differential mobilization of subsets of progenitor cells from the bone marrow. *Cell Stem Cell* 2009; 4: 62–72.
20. Liles WC, et al. Augmented mobilization and collection of CD34+ hematopoietic cells from normal human volunteers stimulated with granulocyte-colony-stimulating factor by single-dose administration of AMD3100, a CXCR4 antagonist. *Transfusion* 2005; 45: 295–300.
21. Devine SM, et al. Rapid mobilization of functional donor hematopoietic cells without G-CSF using AMD3100, an antagonist of the CXCR4/SDF-1 interaction. *Blood* 2008; 112: 990–998.
22. DiPersio JF, et al. Phase III prospective randomized double-blind placebo-controlled trial of plerixafor plus granulocyte colony-stimulating factor compared with placebo plus granulocyte colony-stimulating factor for autologous stem-cell mobilization and transplantation for patients with non-Hodgkin's lymphoma. *J Clin Oncol* 2009; 27: 4767–4773.
23. Brave M, et al. FDA review summary: Mozobil in combination with granulocyte colony-stimulating factor to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation. *Oncology* 2010; 78: 282–288.
24. Bilgin YM and de Greef GE. Plerixafor for stem cell mobilization: the current status. *Curr Opin Hematol* 2016; 23: 67–71.
25. Azar N, et al. Impact of plerixafor (mozobil) on hospital efficiency: a single center experience. *J Clin Apher* 2018; 33: 5–13.
26. Pantin J, et al. Effect of high-dose plerixafor on CD34+ cell mobilization in healthy stem cell donors: results of a randomized crossover trial. *Haematologica* 2017; 102: 600–609.
27. Giralt S, et al. Optimizing autologous stem cell mobilization strategies to improve patient outcomes: consensus guidelines and recommendations. *Biol Blood Marrow Transpl* 2014; 20: 295–308.
28. D'Souza A, et al. Current use and trends in hematopoietic cell transplantation in the United States. *Biol Blood Marrow Transpl* 2017; 23: 1417–1421.
29. Hoggatt J, et al. Rapid mobilization reveals a highly engraftable hematopoietic stem cell. *Cell* 2018; 172: 191–204.
30. Martin C, et al. Chemokines acting via CXCR2 and CXCR4 control the release of neutrophils from the bone marrow and their return following senescence. *Immunity* 2003; 19: 583–593.
31. Alsayed Y, et al. Mechanisms of regulation of CXCR4/SDF-1 (CXCL12)-dependent migration and homing in multiple myeloma. *Blood* 2007; 109: 2708–2717.
32. Azab AK, et al. CXCR4 inhibitor AMD3100 disrupts the interaction of multiple myeloma cells with the bone marrow microenvironment and enhances their sensitivity to therapy. *Blood* 2009; 113: 4341–4351.

33. Uly GL, et al. A phase 1/2 study of chemosensitization with the CXCR4 antagonist plerixafor in relapsed or refractory acute myeloid leukemia. *Blood* 2012; 119: 3917–3924.
34. Tan X-Y, et al. Silencing of CXCR4 inhibits tumor cell proliferation and neural invasion in human hilar cholangiocarcinoma. *Gut Liver* 2014; 8: 196–204.
35. Shaib Y and El-Serag HB. The epidemiology of cholangiocarcinoma. *Semin Liver Dis* 2004; 24: 115–125.
36. DeOliveira ML, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 2007; 245: 755–762.
37. Ball DW. American Thyroid Association guidelines for management of medullary thyroid cancer: an adult endocrinology perspective. *Thyroid* 2009; 19: 547–550.
38. Werner TA, et al. CXCR4/CXCR7/CXCL12 axis promotes an invasive phenotype in medullary thyroid carcinoma. *Br J Cancer* 2017; 117: 1837–1845.
39. Yamauchi Y, et al. Low-dose photon irradiation induces invasiveness through the SDF-1α/CXCR4 pathway in malignant mesothelioma cells. *Oncotarget* 2017; 8: 68001–68011.
40. Saha A, et al. Proinflammatory CXCL12-CXCR4/CXCR7 signaling axis drives myc-induced prostate cancer in obese mice. *Cancer Res* 2017; 77: 5158–5168.
41. Bowtell DD. The genesis and evolution of high-grade serous ovarian cancer. *Nat Rev Cancer* 2010; 10: 803–808.
42. Vaughan S, et al. Rethinking ovarian cancer: recommendations for improving outcomes. *Nat Rev Cancer* 2011; 11: 719–725.
43. Kryczek I, et al. CXCL12 and vascular endothelial growth factor synergistically induce neoangiogenesis in human ovarian cancers. *Cancer Res* 2005; 65: 465–472.
44. Figueras A, et al. A role for CXCR4 in peritoneal and hematogenous ovarian cancer dissemination. *Mol Cancer Ther* 2018; 17: 532–543.
45. Mao TL, et al. Targeting the CXCR4/CXCL12 axis in treating epithelial ovarian cancer. *Gene Ther* 2017; 24: 621–629.
46. Reeves PM, et al. CXCR4 blockade with AMD3100 enhances Taxol chemotherapy to limit ovarian cancer cell growth. *Anticancer Drugs* 2017; 28: 935–942.
47. Venkitaraman R. Triple-negative/basal-like breast cancer: clinical, pathologic and molecular features. *Expert Rev Anticancer Ther* 2010; 10: 199–207.
48. Zhou KX, et al. CXCR4 antagonist AMD3100 enhances the response of MDA-MB-231 triple-negative breast cancer cells to ionizing radiation. *Cancer Lett* 2018; 418: 196–203.
49. Lecavalier-Barsoum M, et al. Targeting the CXCL12/CXCR4 pathway and myeloid cells to improve radiation treatment of locally advanced cervical cancer. *Int J Cancer* 2018; 143: 1017–1028.
50. Balkwill F. Cancer and the chemokine network. *Nat Rev Cancer* 2004; 4: 540–550.
51. D'Alterio C, et al. Inhibition of stromal CXCR4 impairs development of lung metastases. *Cancer Immunol Immunother* 2012; 61: 1713–1720.
52. Ramsey DM and Mc Alpine SR. Halting metastasis through CXCR4 inhibition. *Bioorg Med Chem Lett* 2013; 23: 20–25.
53. Zhang P, et al. CXCR4-mediated osteosarcoma growth and pulmonary metastasis is promoted by mesenchymal stem cells through VEGF. *Oncol Rep* 2013; 30: 1753–1761.
54. Goguet-Surmenian E, et al. CXCR7-mediated progression of osteosarcoma in the lungs. *Br J Cancer* 2013; 109: 1579–1585.
55. Brennecke P, et al. Expression of the chemokine receptor CXCR7 in CXCR4-expressing human 143B osteosarcoma cells enhances lung metastasis of intratibial xenografts in SCID mice. *PLoS One* 2013; 8: e74045.
56. Liao Y-X, et al. AMD3100 reduces CXCR4-mediated survival and metastasis of osteosarcoma by inhibiting JNK and Akt, but not p38 or Erk1/2, pathways in in vitro and mouse experiments. *Oncol Rep* 2015; 34: 33–42.
57. Li H, et al. AMD3100 inhibits brain-specific metastasis in lung cancer via suppressing the SDF-1/CXCR4 axis and protecting blood-brain barrier. *Am J Transl Res* 2017; 9: 5259–5274.
58. Benedicto A, et al. CXCR4 receptor blockage reduces the contribution of tumor and stromal cells to the metastatic growth in the liver. *Oncol Rep* 2018; 39: 2022–2030.
59. Matthys P, et al. AMD3100, a potent and specific antagonist of the stromal cell-derived factor-1 chemokine receptor CXCR4, inhibits autoimmune joint inflammation in IFN-gamma receptor-deficient mice. *J Immunol* 2001; 167: 4686–4692.
60. Stone ND, et al. Multiple-dose escalation study of the safety, pharmacokinetics, and biologic activity of oral AMD070, a selective CXCR4 receptor inhibitor, in human subjects. *Antimicrob Agents Chemother* 2007; 51: 2351–2358.
61. Moyle G, et al. Proof of activity with AMD11070, an orally bioavailable inhibitor of CXCR4-tropic HIV type 1. *Clin Infect Dis* 2009; 48: 798–805.
62. Mosi RM, et al. The molecular pharmacology of AMD11070: an orally bioavailable CXCR4 HIV entry inhibitor. *Biochem Pharmacol* 2012; 83: 472–479.
63. Yan X, et al. A novel CXCR4 antagonist enhances angiogenesis via modifying the ischaemic tissue environment. *J Cell Mol Med* 2017; 21: 2298–2307.
64. Huang YH, et al. Rapid mobilization of murine hematopoietic stem and progenitor cells with TG-0054, a novel CXCR4 antagonist. *Blood* 2009; 114: 3542.
65. Dai S, et al. Chronic AMD3100 antagonism of SDF-1alpha-CXCR4 exacerbates cardiac dysfunction and remodeling after myocardial infarction. *J Mol Cell Cardiol* 2010; 49: 587–597.
66. Yin Y, et al. Danshensu accelerates angiogenesis after myocardial infarction in rats and promotes the functions of endothelial progenitor cells through SDF-1α/CXCR4 axis. *Eur J Pharmacol* 2017; 814: 274–282.
67. Banerjee S, et al. Intra-arterial immunoselected CD34+ stem cells for acute ischemic stroke. *Stem Cells Transl Med* 2014; 3: 1322–1330.

68. Li Z, et al. AMD3100 accelerates reendothelialization of neointima in rabbit saccular aneurysm after flow diverter treatment. *World Neurosurg* 2017; 107: 416–423.
69. Liu X, et al. CXCR4 antagonist AMD3100 elicits analgesic effect and restores the GlyRα3 expression against neuropathic pain. *J Pain Res* 2017; 10: 2205–2212.
70. Hatano K, et al. The chemokine receptor type 4 antagonist, AMD3100, interrupts experimental tooth movement in rats. *Arch Oral Biol* 2018; 86: 35–39.
71. Cheng Q, et al. CXCR4-CXCL12 interaction is important for plasma cell homing and survival in NZB/W mice. *Eur J Immunol* 2018; 48: 1020–1029.
72. Shen C-C, et al. AMD3100 treatment attenuates pulmonary angiogenesis by reducing the c-kit (+) cells and its pro-angiogenic activity in CBDL rat lungs. *Biochim Biophys Acta Mol Basis Dis* 2018; 1864: 676–684.
73. Rodriguez-Roisin R and Krowka MJ. Hepatopulmonary syndrome – a liver-induced lung vascular disorder. *N Engl J Med* 2008; 358: 2378–2387.
74. Schenk P, et al. Hepatopulmonary syndrome: prevalence and predictive value of various cut offs for arterial oxygenation and their clinical consequences. *Gut* 2002; 51: 853–859.
75. Zhang J, et al. Hepatopulmonary syndrome: update on pathogenesis and clinical features. *Nat Rev Gastroenterol Hepatol* 2012; 9: 539–549.
76. Gorlin RJ, et al. WHIM syndrome, an autosomal dominant disorder: clinical, hematological, and molecular studies. *Am J Med Genet* 2000; 91: 368–376.
77. Zuelzer WW, et al. "Myelokathexis" – a new form of chronic granulocytopenia. Report of a case. *N Engl J Med* 1964; 270: 699–704.
78. Krill CE, et al. Chronic idiopathic granulocytopenia. *N Engl J Med* 1964; 270: 973–979.
79. Wetzler M, et al. A new familial immunodeficiency disorder characterized by severe neutropenia, a defective marrow release mechanism, and hypogammaglobulinemia. *Am J Med* 1990; 89: 663–672.
80. Hernandez PA, et al. Mutations in the chemokine receptor gene CXCR4 are associated with WHIM syndrome, a combined immunodeficiency disease. *Nat Genet* 2003; 34: 70–74.
81. McDermott DH, et al. AMD3100 is a potent antagonist at CXCR4(R334X), a hyperfunctional mutant chemokine receptor and cause of WHIM syndrome. *J Cell Mol Med* 2011; 15: 2071–2081.
82. Dugan MJ, et al. Safety and preliminary efficacy of plerixafor (Mozobil) in combination with chemotherapy and G-CSF: an open-label, multicenter, exploratory trial in patients with multiple myeloma and non-Hodgkin's lymphoma undergoing stem cell mobilization. *Bone Marrow Transplant* 2010; 45: 39–47.
83. McDermott DH, et al. The CXCR4 antagonist plerixafor corrects panleukopenia in patients with WHIM syndrome. *Blood* 2011; 118: 4957–4962.
84. Dale DC, et al. The CXCR4 antagonist plerixafor is a potential therapy for myelokathexis, WHIM syndrome. *Blood* 2011; 118: 4963–4966.
85. McDermott DH, et al. A phase 1 clinical trial of long-term, low-dose treatment of WHIM syndrome with the CXCR4 antagonist plerixafor. *Blood* 2014; 123: 2308–2316.
86. McDermott DH, et al. Chromothriptic cure of WHIM syndrome. *Cell* 2015; 160: 686–699.
87. Balabanian K, et al. Proper desensitization of CXCR4 is required for lymphocyte development and peripheral compartmentalization in mice. *Blood* 2012; 119: 5722–5730.
88. Heusinkveld LE, et al. Pathogenesis, diagnosis and therapeutic strategies in WHIM syndrome immunodeficiency. *Expert Opin Orphan Drugs* 2017; 5: 813–825.
89. de Wit RH, et al. CXCR4-specific nanobodies as potential therapeutics for WHIM syndrome. *J Pharmacol Exp Ther* 2017; 363: 35–44.
90. Qin L, et al. Structural biology. Crystal structure of the chemokine receptor CXCR4 in complex with a viral chemokine. *Science* 2015; 347: 1117–1122.
91. Berg C, et al. Inhibition of HIV fusion by small molecule agonists through efficacy-engineering of CXCR4. *ACS Chem Biol* 2018; 13: 881–886.
92. Mishra RK, et al. Discovery and characterization of novel small-molecule CXCR4 receptor agonists and antagonists. *Sci Rep* 2016; 6: 30155
93. Wu C-H, et al. Discovery of novel stem cell mobilizers that target the CXCR4 receptor. *Chem Med Chem* 2012; 7: 209–212.
94. Zachariassen ZG, et al. Probing the molecular interactions between CXC Chemokine Receptor 4 (CXCR4) and an arginine-based tripeptidomimetic antagonist (KRH-1636). *J Med Chem* 2015; 58: 8141–8153.
95. Wu C-H, et al. Development of stem-cell-mobilizing agents targeting CXCR4 receptor for peripheral blood stem cell transplantation and beyond. *J Med Chem* 2018; 61: 818–833.