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

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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

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.

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. 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.

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, 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. The first proof-of-principle that AMD3100 could mobilize hematopoietic stem cells was provided by Broxmeyer et al., 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...
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). 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%. Plerixafor mobilizes hematopoietic stem cells to the peripheral blood by antagonizing the CXCR4 receptor, thus interfering with the CXCR4/SDF-1 (CXCL12) axis, 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). Plerixafor would specifically mobilize the CD34$^+$ HPCs, when used alone or as an adjunct to G-CSF. The doses used would be 160 $\mu$g/kg x 1 on day 5 for plerixafor, and 10 $\mu$g/kg on days 0, 1, 2, 3 and 4 for G-CSF, or 240 $\mu$g/kg for plerixafor if used alone. A single dose of plerixafor at 240 $\mu$g/kg (subcutaneously) may provide a more rapid and possibly less toxic and cumbersome alternative to traditional G-CSF-based mobilization. Yet, the combination of G-CSF (10 $\mu$g/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 $\mu$g/kg, has been recommended for autologous stem cell mobilization and transplantation for patients with NHL.

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: 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. That plerixafor seemed to be more effective in MM patients than in NHL patients was also suggested by Bilgin and de Greef. While 25% of patients treated with G-CSF alone still failed mobilization, upon the addition of plerixafor, the failure rate would drop to 4%.

The conventional dose of plerixafor is 240 $\mu$g/kg, but this dose could be safely increased (in healthy donors) to 480 $\mu$g/kg. Figure 1 illustrates the CD34$^+$ cell counts obtained over time following (subcutaneous) injection of plerixafor at doses of 240 and 480 $\mu$g/kg.

Figure 1. CD34$^+$ cell counts in the blood over time following (subcutaneous) injection of plerixafor at doses of 240 and 480 $\mu$g/kg.

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. This makes the MM cells also more sensitive to therapy with cytotoxic agents such as doxorubicin. This sensitization to cytotoxic chemotherapy has also been noted with plerixafor in acute myeloid leukemia.

CXCR4 could be a promising therapeutic target for hilar cholangiocarcinoma (CCA), thus necessitating
the evaluation of plerixafor. The rate of hilar CCA has significantly risen over the past several decades. Nowadays, it is becoming the most common reason for hepatic tumor-induced death.

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. 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.

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. Likewise, AMD3100 has been suggested as a novel approach to offset the effects of obesity on prostate cancer progression (in mice).

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. As CXCR4 and CXCL12 are overexpressed in several cancers, including ovarian tumors, it is logical that AMD3100 has been recommended as a possible (complimentary) treatment of advanced disseminated epithelial high-grade serous ovarian cancer patients. Also, Mao et al. 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.

As to breast cancer, poor prognosis has been noted for the so-called triple-negative breast cancer (TNBC). 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. Similarly, locally advanced cervical cancer may profit from the combination of radiation and AMD3100 treatment.

Among the chemokine receptors, CXCR4 is the most involved in cancer, as it is expressed in at least 23 different types of cancers. Inhibition of CXCR4, i.e. with plerixafor, will impair the development of lung metastases. 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.

CXCR4 and CXCR7 mediate osteosarcoma growth and metastasis towards the lungs. AMD3100 blocks this process via the JNK and Akt pathways. AMD3100 was also found to inhibit brain-specific metastasis in lung cancer via suppressing the CXCR4/SDF-1 axis. And, likewise, blocking the CXCR4 receptor by AMD3100 may be a successful approach to reduce the metastatic spread of colorectal cancer to the liver.

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. 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. In a proof-of-concept clinical trial in HIV-infected patients harboring X4 virus, 4/9 patients had a greater than 1 log10 reduction in X4 viral level. 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. AMD11070 could be credited as the first orally available small molecule antagonist of CXCR4 to enter the clinic.
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-1β results in the enhancement of ischemic angiogenesis and blood perfusion. AMD3100 can also rapidly mobilize EPCs, but long-term administration of AMD3100 may exacerbate cardiac dysfunction and remodeling after myocardial infarction. Danshensu [3-(3,4-Dihydroxyphenyl)-2-hydroxypropanoic acid], through the SDF-1/CXCR4 axis, accelerates angiogenesis after myocardial infarction in rats, and this effect is counteracted by AMD3100. 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 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. 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.

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.

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.

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). HPS is a serious complication of chronic liver disease characterized by arterial hypoxemia and an abnormal alveolar-arterial oxygen gradient. The prevalence of HPS in cirrhotic patients ranges from 5% to 32% according to various threshold values for arterial deoxygenation and no effective medical treatment for HPS exists beyond liver transplantation.

**WHIM syndrome**

WHIM stands for warts, hypogammaglobulinemia, infections and myelokathexis. Myelokathexis refers to retention of mature neutrophils in the BM, resulting in neutropenia (granulocytopenia). It was first described by Zuelzer et al. and Krill et al.
identified as an immunological disorder by Wetzler et al. That the myelokathexis was part of an autosomal dominant disorder, WHIM syndrome, was characterized by Gorlin et al. 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. When expressed in cell lines lacking endogenous CXCR4, the mutated CXCR4 exhibits about two-fold enhanced signaling on exposure to its ligand CXCL12 (also known as stromal cell-derived factor-1).

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. McDermott et al. and Dale et al. 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.

McDermott et al. 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.

Plerixafor clearly holds great promise for the therapy of WHIM syndrome. If CXCR4-specific nanobodies hold potential as possible therapeutics for CXCR4-associated diseases such as WHIM syndrome, 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. 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.

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.

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, 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, and that could be considered as potential drug candidates, i.e. KRH-1636 (Figure 3), and CX0714 (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 as an anti-HIV agent; and 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**

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