DBPR215

Development of Stem Cell Mobilizing Agents DBPR215 Targeting CXCR4 Receptors for Peripheral Blood Stem Cell Transplantation

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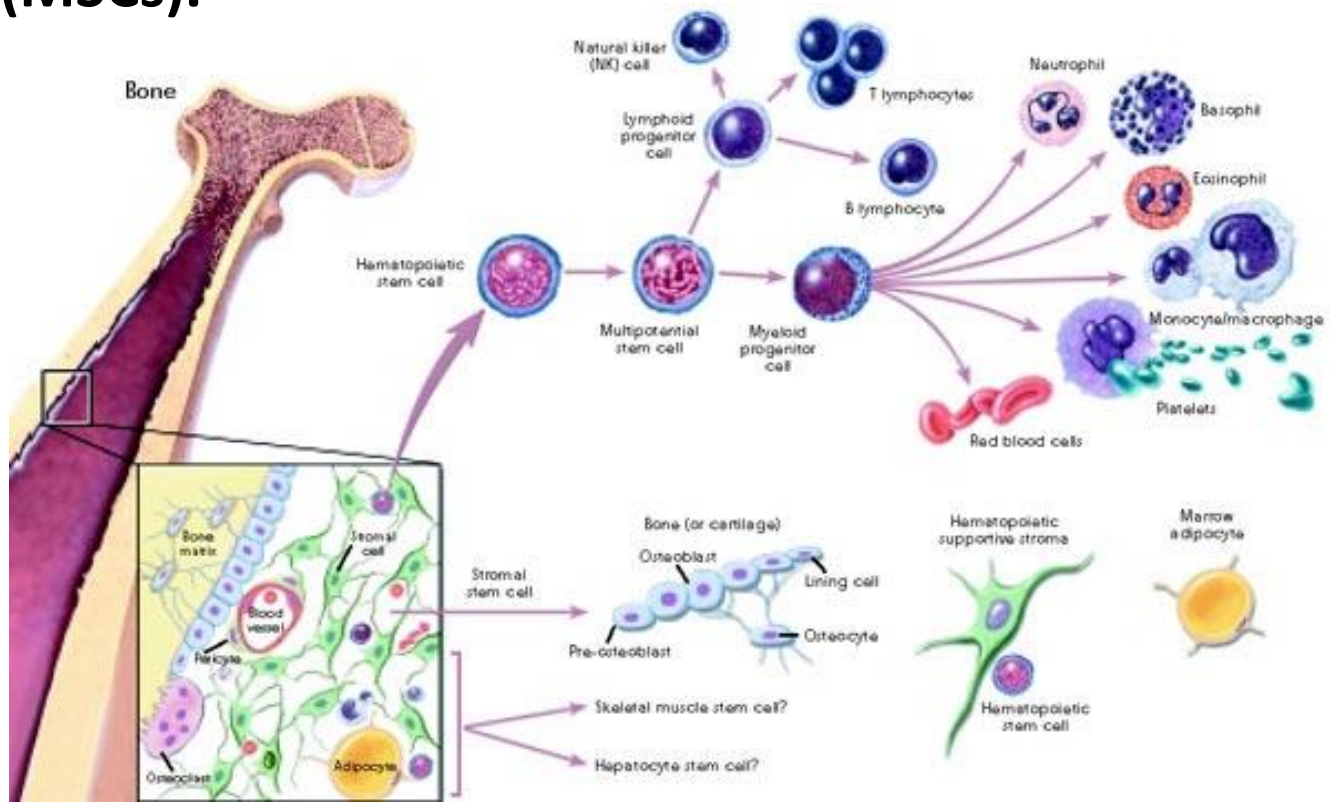
Stem Cell Mobilization

The interaction between CXCL12 and CXCR4 can regulate the trafficking of many different cell types, such as hematopoietic stem cells (HSCs), endothelial progenitor cells (EPCs) and mesenchymal stem cells (MSCs).

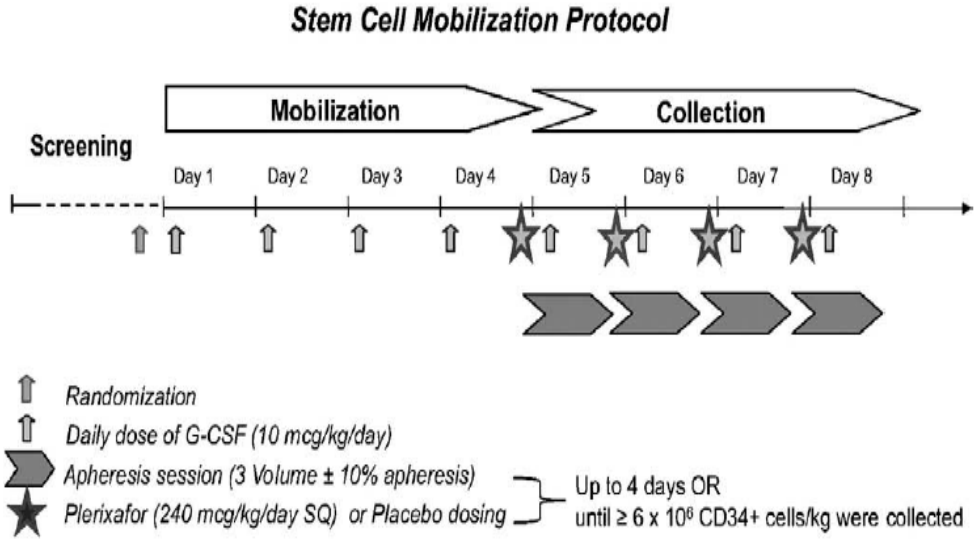


Development of CXCR4 Antagonist (DBPR215) as Stem Cell Mobilizer for PBSCT

- **AMD3100 (plerixafor, Mozobil™) has been approved by US/FDA in 2008 as a stem cell mobilizer, which in combination with the granulocyte colony-stimulating factor (G-CSF) can mobilize HSCs efficiently from bone marrow into peripheral circulation to help cancer patients suffering from non-Hodgkin's lymphoma or multiple myeloma restore their immune system after chemo- or radiotherapy through a medical procedure called peripheral blood stem cell transplantation (PBSCT).**
- **A highly specific and potent CXCR4 antagonist, named DBPR215, has been identified as a drug candidate for PBSCT. This newly developed chemical entity not only exhibited better stem cell-mobilizing ability to release HSCs from bone marrow, but also a much higher maximum tolerated dose (MTD) than marketed AMD3100 following subcutaneous administration in mice.**

Protocol of PBSCT

Clinically, the mobilizing regimen consists of an 8-day treatment period during which patients receive a daily dose of G-CSF for four consecutive days to stimulate stem cell production. Beginning on day 5, a stem cell mobilizer (AMD3100) is co-injected with G-CSF daily and patients undergo up to four consecutive apheresis by which CD34+, a HSCs marker, stem cells are harvested and combined for subsequent autologous transplantation. In general, the effective dose of CD34+ cells required for transplantation is considered more than 2×10^6 cells/kg with an optimal dose up to 6×10^6 cells/kg.



Net Sale of Mozobil

Year	Total (€ million)	Western Europe	United States	Emerging Markets	Rest of the World
2012	96	30	56	7	3
2013	101	32	56	10	3
2014	111	34	62	12	3
2015	143	38	83	15	7
2016	152	42	95	7	8

Cited by Sanofi reports

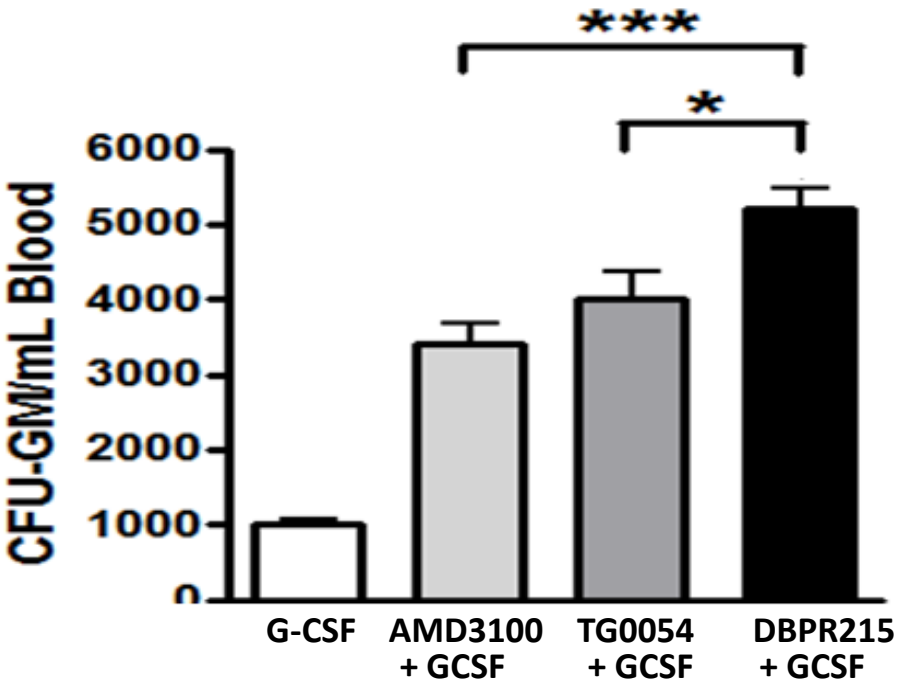
Biological Profiles of DBPR215

Study items	DBPR215 (NHRI)	AMD3100/ Plerixafor (Sanofi)	TG0054/ Burixafor (TaiGen)
IC_{50} (Human CXCR4 binding assay)	34.2 nM	213.1 nM	43.4 nM
EC_{50} (Chemotaxis assay)	13.7 nM	65.8 nM	21.1 nM
MTD (mg/Kg, SC, C57BL/6j)	75	25	50 (iv)
$CD34^+$ Minimum effect dose (mg/Kg, SC, C57BL/6)	3	1	25 (iv)
Therapeutic index (MTD/MED, SC, C57BL/6)	25	25	2 (iv)
Plateau dose for $CD34^+$ (mg/Kg, SC, C57BL/6)	35	6	50 (iv)
$CD34^+$ fold at Plateau dose (antagonist /control)	3-5 fold	2.5-3 fold	3-5 fold
CFU-GM fold at Plateau dose (antagonist + G-CSF)/G-CSF	3-5 fold	2-3 fold	3-5 fold
CFU-GM comparison ratio (antagonist +G-CSF)/(TG0054+ G-CSF)	1.1-1.5	0.8	1.0

Biological Profiles of DBPR215

Study items	DBPR215 (NHRI)	AMD3100/ Plerixafor (Sanofi)	TG0054/ Burixafor (TaiGen)
$[C]_{max}$ of PK profile (ng/mL), (6 mpk, SC)	16,400	6,200	17,833 (iv)
[AUC] of PK profile (ng/mL · hr), (6 mpk, SC)	13,515	7,152	9,430 (iv)
CYP450 inhibition at 10 μM (1A2, 2C9, 2C19, 2D6, 2E1, 3A4)	No inhibition	NA	NA
Metabolic stabilities in liver microsomes (mouse, rat, dog, and human)	stable	NA	NA
Inhibition > 50% at 10 μM in 68 Off-target profiling	2 items	NA	NA
Counter screening: selectivity index (CCR2, CCR4, CCR5, CXCR2)	> 290	NA	NA
IC_{50} (hERG Patch clamp assay)	>100 μM	NA	NA
14-day repeated dose toxicology study (non-GLP)	clean	NA	NA

In Vivo Efficacy Comparison in Colony-Forming Assay



n = 8-12;
D1-D5: G-CSF: 100 μg/kg
D5: co-injection
DBPR215 (35 mg/kg, SC);
AMD3100 (6 mg/kg, SC);
TG0054 (50 mg/kg, IV);

- **DBPR215 has demonstrated superior *in vivo* efficacy (vs. AMD3100 and TG0054) in the critical CFU-GM assay**

Toxicology Study for DBPR215

Table: 14-Day non-GLP Repeated Dose Toxicology (SD Rats, 50 mg/kg, SC)

Study items	Result
Survival rate for 5 Rats	100%
Body weight	Normal
Organ weight analysis (17 items)	0/17
Hematology analysis (20 items)	0/20
serum chemistry analysis (7 items)	1/7

Note: slightly increased creatinine level was noted in serum chemistry analysis

DBPR215 Patent Status

Country	Title	Priority date	Filing number	Published version
US	Heterocyclic compounds and use thereof	September 21, 2014	14/860,033	US/2016/0083369A1
PCT	Heterocyclic compounds and use thereof	September 21, 2014	PCT/US15/51143	WO/2016/048861A2
ROC	雜環化合物及其用途	September 21, 2014	104131241	

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(19) **United States**

(12) **Patent Application Publication**

Shia et al.

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(54) **HETEROCYCLIC COMPOUNDS AND USE THEREOF**

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Publication Classification

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(57) **ABSTRACT**

Heterocyclic compounds of Formula (I) shown herein. Also disclosed are pharmaceutical compositions containing the heterocyclic compounds and methods of using the heterocyclic compounds to mobilize hematopoietic stem cells and endothelial progenitor cells into the peripheral circulation. Further provided are methods for treating tissue injury, cancer, inflammatory disease, and autoimmune disease with the heterocyclic compounds.

Major Advantages and Differentiation of DBPR215

- Potent and selective CXCR4 antagonist with potent IC_{50} and EC_{50} values *in vitro*
- Demonstration of superior efficacy (stem cell mobilization in mice CFU-GM assay) in head-to-head studies against the leading product (AMD3100) and other major competitor (TG0054)
- Large therapeutic window (25) with higher MTD/dose tolerance (up to 75 mpk) and clean toxicology profile as compared to AMD3100.
- Good overall ADME and pharmaceutical properties for clinical development (SC administration)
- Stable and crystalline di-phosphate salt has been identified for clinical formulation and development use
- Potential “Best-in-Class” CXCR4 antagonist for PBSCT with potential additional usage toward other indications (ischemic stroke, preliminary *in vivo* POC studies completed)