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Peripheral Blood Stem Cell Mobilization: a Look Ahead

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Abstract

Purpose of Review Mobilized peripheral blood is the predominant source of stem and progenitor cells for hematologic transplantation. Successful transplant requires sufficient stem cells of high enough quality to recapitulate lifelong hematopoiesis, but in some patients and normal donors, reaching critical threshold stem cell numbers is difficult to achieve. Novel strategies, particularly those offering rapid mobilization and reduced costs, remain an area of interest. This review summarizes critical scientific underpinnings in understanding the process of stem cell mobilization, with a focus on new or improved strategies for their efficient collection and engraftment.

Recent Findings Studies are described that provide new insights into the complexity of stem cell mobilization. Agents that target new pathways such HSC egress identify strategies to collect more potent competing HSC, and new methods to optimize stem cell collection and engraftment are being evaluated.

Summary Agents and more effective strategies that directly address the current shortcomings of hematopoietic stem cell mobilization and transplantation and offer the potential to facilitate collection and expand use of mobilized stem cells have been identified.

Keywords Peripheral blood stem cell mobilization · Hematopoietic stem cells · Stem cell collection · HSC egress · High-engrafting stem cells · Hypoxic collection

Introduction

Hematopoietic cell transplantation (HCT) has been used for over 50 years to successfully treat hematologic disease. The use of autologous and allogeneic hematopoietic stem cells (HSC) for HCT has expanded beyond hematological malignancies and bone marrow failure syndromes to non-malignant hematologic disorders and immunological diseases. With the reemergence of HSC-based gene therapy strategies and the use of less myelotoxic preparative regimens, HCT is positioned to expand even further. Successful transplantation requires HSC in sufficient quantity and quality to recapitulate lifelong hematopoiesis. There are three potential sources of HSC for clinical utility: bone marrow, mobilized peripheral blood, and umbilical cord blood (see [1] for a historical perspective). Each source varies in cellular characteristics with potential advantages and disadvantages for clinical use.

Currently, the predominant source of HSC for transplant is peripheral blood collected by apheresis after a multi-day regimen of granulocyte colony-stimulating factor (G-CSF), a process termed peripheral blood stem cell mobilization (PBSCM), [2, 3].While highly successful, G-CSF regimens can be associated with lifestyle disruptive and stressful morbidities [4, 5] and, in some cases, more serious life-threatening toxicities [6]. In high-risk individuals, myocardial infarction and cerebral ischemia can result from the thrombophilic effects of G-CSF.

The dose of CD34+ cells infused in a mobilized peripheral blood stem cell transplant (PBSCT) is an important predictor of neutrophil and platelet recovery and serves as a biomarker of potential stem cell engraftment. An optimal autologous mobilized PBSC graft requires a minimum of 2×10^6 CD34+ cells per kilogram patient body weight to provide for rapid and sustained multi-lineage engraftment, with 5×10^6 being optimal. For allogeneic transplant, a CD34+ cell dose of ~ 4.5×10^6/kg is associated with improved survival without

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increased incidence of acute or chronic graft versus host disease. Despite its success for most patients, poor mobilization rates as high as 40% are observed [7•] and often require multiple apheresis, resulting in increased patient stress, added clinical resources, and higher costs [8, 9].

Recently, the small molecule AMD3100 (plerixafor), a CXCR4 antagonist, shown to mobilize alone and with G-CSF [10–12] was clinically validated [13, 14] and approved by the FDA specifically for use in combination with G-CSF for patients who fail to mobilize a minimum CD34+ cell graft using G-CSF alone. However, addition of plerixafor to the multi-day G-CSF regimen adds significant cost and has restricted its universal use. Based on the potential benefit of a single-day mobilization and apheresis procedure, administration of plerixafor as a stand-alone agent has been explored clinically; however, the level of mobilization was not clinically effective, being significantly lower than G-CSF [15, 16, 17•]. Moreover, a significant number of donors fail to mobilize sufficient cells even after multiple apheresis sessions or dose escalation and infusion [17•]. Thus, the development of novel alternative strategies, particularly those that offer rapid mobilization and reduced costs remains an area of interest. Better understanding of mechanisms of mobilization may lead to more effective strategies and is an area of significant investigation.

Paradigmatic Mobilization Mechanisms?

Mechanisms underlying the process of HSPC mobilization have been studied for several decades but still remain unclear. What is clear is that G-CSF does not mobilize hematopoietic stem and progenitor cells (HSPC) by directly acting on them. This is supported by pharmacokinetic studies that indicate a two-compartment model. Since HSPC are held within supportive and regulatory marrow niches through interactions with stromal cells, mechanism studies logically focused on the hematopoietic niche. Early studies demonstrated a need for neutrophils for mobilization with G-CSF or the combination of G-CSF plus the chemokine GROβ [18, 19] and a dramatic reduction in concentration of the chemotactic chemokine stromal cell-derived factor-1 (SDF-1/CXCL12) in bone marrow associated with increased marrow proteases [20–22]. This led to the hypothesis of protease-mediated changes in retention mechanisms and alteration of SDF-1 gradient in favor of migration of untethered cells to the periphery as the primary mechanism of G-CSF-induced PBSC mobilization. Several proteases including neutrophil elastase, cathepsin G, matrix metalloproteases, and plasmin are increased and the endogenous protease inhibitors serpin A1 and A3 are reduced in marrow after mobilization by G-CSF. Later, proteases were shown to cleave other HSPC retention factors including integrins and c-kit. Despite the clear evidence in favor of proteases and proteolysis of retention mechanisms as a potentially important and perhaps common mechanism in HSPC mobilization, at least by G-CSF, the identity of the specific proteases involved and their targets remain poorly defined. Conflicting data on the role of individual proteases has come primarily from studies using knockout mice and selective enzyme inhibitors, but these may result from inherent redundancy in the models used [23–25]. Overall, findings support that G-CSF administration results in a highly proteolytic marrow environment and a role for proteases that interfere with the SDF1/CXCR4 and other retention axes. Exactly which protease(s) is involved, whether disruption of these pathways is necessary in all settings and how this facilitates transit of HSPC out of marrow is not clear.

The SDF-1/CXCR4 axis has been the most widely studied and best characterized retention pathway implicated in HSPC mobilization and plays a central common role in a number of mobilization strategies, e.g., G-CSF, Flt-3 ligand, and SCF. This led to the development of plerixafor, a CXCR4 antagonist, for clinical use in patients who mobilize poorly to G-CSF. Following on from plerixafor, additional CXCR4 antagonists, including POL636 [26–28], BKT140 [29, 30], LY2510924 [31–33], TG-0054 [34], and ALT-1188 [35] are in preclinical and/or clinical development, although what their benefit above plerixafor might be is yet to be determined. NOX-A12 an anti-SDF-1 Spiegelmer, a first in class mirror-image oligonucleotide inhibitor of SDF-1 mobilizes HSPC [36]. In addition, anti-CXCR4 nanobodies have also been shown to mobilize HSPC [37]. These agents have the potential to replace G-CSF or improve current G-CSF-based mobilization strategies. Their potential for routine clinical use remains to be determined.

The bioactive phospholipid sphingosine-1-phospahate (S1P) [38] and the complement cascade [39] have been implicated in HSPC mobilization. Proteins involved in niche interactions can be cleaved by C5-mediated proteolysis in bone marrow and membrane attack complex (MAC)-mediated increase in S1P levels favoring migration to the periphery. Mobilization studies in mice deficient in sphingosine kinase 2 support a role for plasma S1P in HSPC egress [40•]. Moreover, administration of a S1P agonist prior to AMD3100-enhanced mobilization was further increased by G-CSF. Interestingly, S1P agonism was unable to increase mobilization alone or with G-CSF, pointing to a critical role of CXCR4 antagonism for mobilization in this setting [41]. This enforces a central role for the SDF-1/CXCR4 axis in the process of mobilization.

Integrins are transmembrane glycoproteins that mediate cell-cell/matrix interactions. The α4β1 integrin VLA4 and counter ligand VCAM-1 pair serve as a HSPC retention mechanism. Interruption of this axis by antibodies or genetic manipulation leads to HSPC mobilization (see [42]). A selective VLA4 inhibitor BIO5192 has been developed and shown to mobilize HSPC and in combination with G-CSF and plerixafor [43]. However, it is unclear whether this

mobilization strategy is being developed and or if combinations of these agents for mobilization is economically efficient and viable.

A number of natural and synthetic polysaccharides are able to mobilize HSPC, including sulfated polysaccharides and modified glycosaminoglycans (reviewed in [44]). Of particular note, the synthetic octasaccharide EP80031 mobilizes HSPC alone and in combination with G-CSF and/or AMD3100 [45] and uridine diphosphate glucose (UDP-Glc) mobilizes high-engrafting HSC when used in combination with G-CSF [46•]. Advances in oligosaccharide synthesis and development of more potent compounds may lead to therapeutic utility of this class of compounds.

Proteasome inhibitors have been shown to be particularly effective in the treatment of patients with multiple myeloma (MM). In preclinical studies, combining the proteasome inhibitor bortezomib with G-CSF or AMD3100 was more effective in mobilizing HSPC than either agent alone. In a recent phase II trial, combination of bortezomib with cyclophosphamide and G-CSF resulted in enhanced CD34+ cell yield allowing 85% of MM patients to mobilize a sufficient PBSC graft in one apheresis [47].

Prostaglandin E2 (PGE2) signaling through its EP4 receptor has been shown to enforce retention of HSPC in bone marrow, and inhibition of PGE2 synthesis has been linked to HSPC mobilization alone and in combination with G-CSF. In particular, the non-steroidal anti-inflammatory drug (NSAID) meloxicam has been shown to mobilize HSPC in mice, monkeys, and man [48••]. Moreover, the meloxicam mobilized graft led to faster neutrophil and platelet recovery compared to a graft mobilized without NSAID. Since NSAID-enhanced G-CSF mobilization occurred in CXCR4 knockout mice, it appears to be independent of the changes in the SDF-1/CXCR4 axis induced by G-CSF [48••]. In a single-center clinical study, addition of meloxicam to chemotherapy/G-CSF mobilization in poorly mobilizing patients with MM increased peripheral hematopoietic $CD34^+$ cell levels and reduced the need for plerixafor rescue, and significantly lowering the overall mobilization costs [49].

It has been known for some time that stresses such as exercise and ACTH can mobilize HPC [50]. Recently, a link was made between neurotransmitters and osteoblasts, cells known to support HSPC retention and to be reduced in activity following administration of G-CSF and egress of HSPC [51]. Osteoblasts do not express G-CSF receptors, rather these receptors are expressed on sympathetic neurons that innervate bone marrow. While G-CSF administration does not increase norepinephrine, it does prevent its reuptake leading to higher tissue level [52•]. Mobilization in mice occurs following norepinephrine administration where it binds to stromal cells resulting in reduction in niche retention mechanisms, including SDF-1, SCF and VCAM [51, 53, 54]. The potential role of adrenergic receptor agonists as clinical mobilizers remains to be tested.

New Experimental Pathways

The pathways described above serve to place the state of the field in perspective. It is not our intent to exhaustively review the field of peripheral blood stem cell mobilization or to exhaustively present the numerous pathways, mechanisms, and agents that have shown activity to mobilize hematopoietic stem and/or progenitor cells; these have been recently extensively reviewed in several excellent publications [55–59]. Rather, we will discuss several new perhaps non-paradigmatic experimental pathways that may lead to new or improved strategies for HSPC mobilization.

Neuropeptide Y

One protease of interest not discussed above is dipeptidyl peptidase 4 (DPP4/CD26), a serine exopeptidase that cleaves N-terminal dipeptides with alanine or proline in the penultimate position. DPP4 exists both as a membrane bound protease as well as in soluble form. Reduced mobilization response to G-CSF is observed in CD26 knockout mice or mice treated with a selective pharmacologic DPP4 inhibitor [60, 61]. Since DPP4 is expressed on HSPC and can cleave and inactivate SDF-1, and as described, reduced marrow SDF-1 is a hallmark observed after administration of G-CSF, it was hypothesized that cleavage of SDF-1 by CD26 on HSPC plays an essential role in HPC trafficking, likely through cleavage of SDF-1, thereby reducing bone marrow retention [62]. However, evidence showing a direct association between CD26 and disruption of SDF-1 signaling in vivo during G-CSF administration was lacking, as was definitive studies on repopulating HSC.

Recently, a proof was provided that mobilization of repopulating HSC by G-CSF is in fact reduced by inhibition of DPP4/CD26; however, using chimeric mice created by transplanting bone marrow from wild-type or CD26 knockout mice into syngeneic wild-type or CD26 knockout recipient mice, it was found that HSPC-intrinsic CD26 expression was not required for HSPC egress in response to G-CSF, but rather, mobilization was dependent on CD26 expression on stromal cells [63••]. Moreover, G-CSF-associated degradation of SDF-1 occurred equally in wild-type and CD26 knockout mice or mice treated with a DPP4 enzyme inhibitor, as determined by mass spectrometry. Following G-CSF administration, CD26 was only increased on a subpopulation of sinusoidal endothelial cells (EC) that form the mechanical barrier between the peripheral blood and marrow and regulate hematopoietic trafficking [64]. Since HSPC must transmigrate across the EC barrier to enter the peripheral circulation whether EC CD26 regulated HSPC, egress was evaluated. In monolayer EC transmigration models, G-CSF increased EC CD26 expression and activity leading to enhanced HSPC transmigration, but blocking DPP4 activity prevented transmigration.

Since optimal mobilization was dependent on CD26 but not mediated through cleavage of SDF-1, protein databases were searched for proteins involved in leukocyte trafficking and possessing a putative CD26 cleavage site. This search identified the neurotransmitter neuropeptide Y (NPY), a ligand with cognate receptors on marrow stromal cells including EC and which has been reported to regulate immune cell and bone homeostasis and be produced by both nerve fibers and endothelium [65–68]. Mass spectrometry confirmed that CD26 cleaved full length NPY into a NPY_{3-36} truncated form. NPY interacts with several G protein-coupled receptors (NPYR1-5), preferentially binding NPYR1, while NPY_{3-36} preferentially binds NPYR2 and NPYR5. Each of these receptors was found to be expressed by sinusoidal EC [63••]. In the monolayer EC transmigration model, HSPC transmigration that is blocked by inhibiting DPP4 activity was reversed by addition of NPY_{3-36}. Administration of NPY_{3-36} restored normal HSPC mobilization in CD26 knockout mice or mice treated with a DPP4 inhibitor, and this restoration of response was blocked by selective antagonists of the NPY2 and NPY5 receptors. Mice genetically deficient in NPY also showed poor mobilization to G-CSF that could be restored by administration of NPY_{3-36}. Since NPY receptors are known to regulate vascular integrity, bone marrow sinusoidal permeability was evaluated. Using live animal imaging, G-CSF enhanced sinusoidal permeability that could be blocked by a DPP4 inhibitor that was reversed by NPY_{3-36}. Truncated NPY augmented endothelial barrier permeability by downregulating adherence junction molecules VE-cadherin and CD31 that widened the gap between vascular ECs. This resulted in greater HSPC transmigration.

These studies provide new insights into the complexity of stem cell mobilization. Alteration of retention axes represents only one part of the mobilization process but activation of additional steps are required for optimal activity. These studies now show that ECs act as gatekeepers regulating HSPC egress and that enzymatic regulation of NPY by CD26 acts as the open/close signal. The ability to target NPY receptors with ligands and antagonists in vivo make them an attractive new target for regulating HSPC trafficking. Treatment of mice with NPY_{3-36} but not full-length NPY significantly enhanced HSPC mobilization by AMD3100 which mobilizes independently of CD26 [63••], supporting the concept of regulation of vascular permeability as a common feature associated with HSPC marrow egress and a potential broadly applicable strategy for HSPC mobilization.

GROβ plus AMD3100

With the goal of developing a safe, rapid single-day mobilization regimen, combination mobilization with the CXCR4 antagonist AMD3100/plerixafor and the CXCR2 ligand GROβ, previously shown to mobilize HSPC in mice and rhesus monkeys [18, 69, 70••] and, recently, also in man [70••], was explored. While the CXCR4 signaling axis has been a focus of mechanism of HSPC mobilization, particularly associated with the action of G-CSF, the chemokine ligands of the CXCR2 receptor, notably GROβ and IL8, induce rapid HSPC mobilization. The mechanism of action of these chemokines has not been linked to the SDF-1/CXCR4 axis, but instead to metalloprotease-9 (MMP-9), which has the potential to non-selectively degrade many types of cell-stromal-matrix interactions. Genetic models and antibody neutralization studies indicate that rapid mobilization by these ligands is dependent on MMP-9 [18, 69, 71] mediated through the CXCR2 receptor expressed on neutrophils but not expressed on HSPC.

Single combined injection of GROβ plus AMD3100 mobilized more HSPC in 15 min than the number of HSPC mobilized by G-CSF in a 4-day regimen in mice [70••]. Extensive biochemical, molecular, and genetic evidence all confirmed cross talk between these neutrophil receptors. Stimulation of release of MMP-9 from neutrophil granules through stimulation of CXCR2 by GROβ was greatly enhanced by antagonizing CXCR4 receptors on the same cells. These studies also identified a negative signaling pathway as a result of antagonism of the CXCR4 receptor, at least on the MMP-9 protease. In this regard, it is possible that the degradation of SDF-1 observed during G-CSF-based regimens may release this negative signal as well, allowing increased MMP-9 release that contributes to mobilization. The rapid and robust kinetics of GROβ plus AMD3100 mobilization was not associated with the histological changes commonly observed following G-CSF mobilization, e.g., osteolineage cell flattening, reduction of adhesion and chemoattractant molecules, and localization of accessory cell populations. When intra vital microscopy was applied, there was an increase in vascular permeability with the GROβ plus AMD3100 combination mobilization within 5 min. Importantly, this increased vascular permeability was completely blocked if mice were treated with an anti-MMP-9 antibody. On histological examination of marrow sections, increased nucleated cells within the sinusoid lumens could also be seen as early as 5 min. These findings strongly suggest an effect of MMP-9 on EC barrier integrity. It remains to be determined how this is accomplished.

Functional comparison of the hematopoietic grafts mobilized by GROβ plus AMD3100 versus G-CSF in transplant studies was quite revealing. The GROβ plus AMD3100 combination mobilized a higher engrafting and competitive HSC population than G-CSF. While both GROβ [72] and AMD3100 [10] alone have shown enhanced engraftment compared to G-CSF, these studies only compared whole peripheral blood mononuclear populations and, although suggestive, are not definitive assessments of HSC function and could be due solely to a graft containing greater numbers of HSC. However, in studies comparing HSC number in the GROβ plus AMD3100 versus G-CSF mobilized grants, the GROβ plus AMD3100 graft actually contained fewer

phenotypically defined HSC. Competitive transplants using highly purified HSC from mice mobilized with GROβ plus AMD3100 or G-CSF and transplanted with the exact same number of HSC showed the HSC from GROβ plus AMD3100 mobilized mice to be twice as competitive as those from mice mobilized with G-CSF and indicated that GROβ plus AMD3100 mobilizes a distinct highly engraftable HSC population (heHSC) with superior competitiveness [70••]. RNA sequencing of these heHSC indicated that they had a distinct transcriptome compared to HSC mobilized by G-CSF. Intriguingly, in gene set enrichment analysis, these cells showed a transcriptome that mirrors young fetal liver HSC.

Other chemokines/chemokine pathways have been explored as HSPC mobilizers. A genetic variant BB10010 of the chemokine macrophage inflammatory protein-1 (MIP-1) mobilized HPC in mice but was without activity in patients [73]. A rationally designed SDF-1 analog that downregulates CXCR4 rapidly mobilized neutrophils and HPC when used alone and synergized with G-CSF [74, 75], but did not mobilize HSC in mice [76]. In addition, an alternate ligand of the CXCR2 receptor GROγ had no activity to mobilize HSPC [76]. Given that plerixafor (AMD3100) is an approved drug and GROβ has already been administered in man, it is expected that clinical testing of combination mobilization with GROβ plus AMD3100 should be forthcoming. Both compounds have shown the same pattern of mobilizing fewer HSPC than G-CSF as stand-alone mobilizers in both mice and man. Since synergistic mobilization of both HPC and repopulating HSC by GROβ plus AMD3100 is seen in the mouse model, this suggests a similar effect which will be seen in man.

In terms of quality of mobilized cells, one wonders how the HSC and HPC are organized within the marrow with regard to their capacity to be mobilized. It is known that there is a large store of HPC within the marrow [77], many more than are likely needed in non-stressed conditions, and this may also apply to HSC. There is also a large reserve of marrow polymorphonuclear neutrophils (PMN) that can be characterized as younger or older PMN depending on the timing of their production, such that the older PMN, those which are produced earlier, are the PMN that are first released into the blood [78]. A question is if this concept of first in the marrow (e.g., produced) versus first out to the blood for PMN also may apply to the marrow stores of HSC and/or HPC when these cells are mobilized. If such a first-in, first-out scenario applies to HSC/HPC, are these kinetics different for the different HSPC mobilizing procedures, and is the combination of GRO-β plus AMD3100/plerixafor that appears to mobilize a more potent population of competing HSC reflecting this kinetic hierarchy?

Optimal Collections of HSC

The optimal collection of mouse BM and human cord blood HSC has been underestimated [79, 80••]. Oxygen is an important factor in the stem cell microenvironment. Upon immediate collection of these cells in atmospheric (ambient) air levels of ~21% O_2, there is an induced differentiation of the HSC to HPC. This is due to the ambient air-induced production of reactive oxygen species (ROS) that involves a p53-mitochondrial permeability transition pore opening-cyclophilin *D*-axis and, also, involves hypoxia-inducing factor 1-α and the hypoxamir miR210. If these cells are instead collected and processed at much lower oxygen levels of hypoxia (~3% O_2) or at ambient oxygen levels but in the presence of cyclosporine A [79], or with combinations of anti-oxidants and/or epigenetic enzyme inhibitors [81], one can collect significantly more HSC than if the cells were collected/processed as usually done in ambient air. This increase in collected HSC is at the expense of HPC, but these hypoxia-collected cells are potent engrafting cells. Whether such procedures will enhance the actual numbers of HSC collected after peripheral blood mobilization especially for patients that do not mobilize well remains to be determined as does the engrafting capabilities of these increased numbers of mobilized HSC. Such studies are underway.

Summary

The need for more effective mobilization strategies in hard to mobilize patients, to reduce resources and costs of mobilization regimens and to reduce patient fear of pain and inconvenience of multi-day regimens, lies at the heart of current studies in understanding and targeting mechanisms of HSPC mobilization. Targeting the gateway to HSPC release with agonists of the NPY receptors on EC, rapid mobilization of high-engrafting HSC by the combination of GROβ and plerixafor, and utilization of agents that mitigate oxygen shock are new strategies that can be used alone and in combination or in combination with other procedures to acquire more HSC or better engrafting HSC for transplant.

The benefit of rapid mobilization with safe and stand-alone inexpensive agents and efficacy in hard to mobilize populations is well recognized, and new compounds and strategies in development may ultimately address these issues. Strategies that can enhance HSPC homing and engraftment and mobilize a hematopoietic graft with enhanced engraftment capabilities may reduce the need to attain higher numbers of HSPC.

Several approaches have been taken to enhance homing/engraftment of cord blood HSPC including short-term exposure of the grafts to inhibitors of DPP4 [82••, 83], pulsing with prostaglandin E2 [84, 85], glucocorticoids [86•], inhibiting HDACs [87•], or hyperthermia treatment [88], and some have been successful in clinical testing [89] as has been treatment of recipients of single-cord HCT with the DPP4 inhibitor Januvia® [90, 91]. Enhancing homing and engraftment of mobilized hematopoietic grafts has not been extensively

studied. However, in a recent study, using mobilized PBSC, pulse exposure to PGE2 enhanced homing/engraftment of transduced HSC in patients undergoing gene therapy [92]. Given the strategies outlined above, it will be interesting to see how effective and how far these strategies can push the concept of minimal cell numbers for transplant and expand the use of PBSCT particularly in the area of gene therapy where transduction protocols adversely affect HSC homing and engraftment.

It should be noted that mobilization procedures may also be useful in additional contexts. AMD3100 has been shown to ameliorate cigarette smoke-induced emphysema-like manifestations in mice [93] and use of G-CSF plus AMD3100 in canines with x-linked severe-combined immunodeficiency disease (SCID-X1) has enhanced in vivo gene therapy approaches to treat SCID-X1 [94]. Thus, more mechanistic insight into mobilization processes may be of relevance to more than just that for use of HSPC for HCT.

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Compliance with Ethical Standards

Conflict of Interest Louis M. Pelus and Hal E. Broxmeyer declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects.

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