



## REVIEW

# Past, present, and future efforts to enhance the efficacy of cord blood hematopoietic cell transplantation [version 1; peer review: 3 approved]

Xinxin Huang<sup>1\*</sup>, Bin Guo<sup>2\*</sup>, Maegan Capitano<sup>3\*</sup>, Hal E. Broxmeyer <sup>3</sup><sup>1</sup>Xuhui Hospital and Institutes of Biomedical Sciences, Fudan University, Shanghai, China<sup>2</sup>Department of Pathophysiology, Shanghai Jiao Tong University School of Medicine, Shanghai, China<sup>3</sup>Department of Microbiology and Immunology, Indiana University School of Medicine, Indianapolis, IN, 46202-5181, USA

\* Equal contributors

**V1** First published: 31 Oct 2019, 8(F1000 Faculty Rev):1833 (<https://doi.org/10.12688/f1000research.20002.1>)Latest published: 31 Oct 2019, 8(F1000 Faculty Rev):1833 (<https://doi.org/10.12688/f1000research.20002.1>)**Abstract**

Cord blood (CB) has been used as a viable source of hematopoietic stem cells (HSCs) and hematopoietic progenitor cells (HPCs) in over 35,000 clinical hematopoietic cell transplantation (HCT) efforts to treat the same variety of malignant and non-malignant disorders treated by bone marrow (BM) and mobilized peripheral blood (mPB) using HLA-matched or partially HLA-disparate related or unrelated donor cells for adult and children recipients. This review documents the beginning of this clinical effort that started in the 1980's, the pros and cons of CB HCT compared to BM and mPB HCT, and recent experimental and clinical efforts to enhance the efficacy of CB HCT. These efforts include means for increasing HSC numbers in single CB collections, expanding functional HSCs *ex vivo*, and improving CB HSC homing and engraftment, all with the goal of clinical translation. Concluding remarks highlight the need for phase I/II clinical trials to test the experimental procedures that are described, either alone or in combination.

**Keywords**

Cord Blood, Hematopoietic Cell Transplantation; Hematopoietic Stem Cells; Hematopoietic Progenitor Cells; Regulation of Hematopoiesis; Collection/Processing of Cord Blood; Influence of Oxygen Tension; Ex-vivo Expansion; Homing

**Open Peer Review**Reviewer Status 

	Invited Reviewers		
	1	2	3
<b>version 1</b> published 31 Oct 2019			

**F1000 Faculty Reviews** are written by members of the prestigious **F1000 Faculty**. They are commissioned and are peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

- Jonathan Hoggatt**, Harvard University, Cambridge, USA
- Mariusz Ratajczak**, Division of Hematology and Oncology, University of Louisville, Louisville, Kentucky, USA
- Elizabeth J Shpall**, University of Texas MD Anderson Cancer Center, Houston, USA

Any comments on the article can be found at the end of the article.

**Corresponding author:** Hal E. Broxmeyer ([hbroxmey@iupui.edu](mailto:hbroxmey@iupui.edu))

**Author roles:** **Huang X:** Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Guo B:** Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Capitano M:** Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Broxmeyer HE:** Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing

**Competing interests:** HEB was a member of the Medical Scientific Advisory Board of Cord:Use, a cord blood banking company up until 2018. Cord:Use provided cord blood samples for some of the papers from the Broxmeyer Laboratory but had no input into the use of the cord blood samples provided, for any of the work performed, or for anything in the papers published. HEB started in October 2019 as a member of the Scientific Advisory Board of Elixell, a cell therapy company. Elixell had no input into any of the studies shown or in the writing of this review. The other authors have no competing interests to declare.

**Grant information:** The studies reported in this review from the Broxmeyer laboratory were supported by the following US Public Health Service grants to Dr. Broxmeyer: R35 HL139599, R01 DK109188, and U54 DK106846.

*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

**Copyright:** © 2019 Huang X *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**How to cite this article:** Huang X, Guo B, Capitano M and Broxmeyer HE. **Past, present, and future efforts to enhance the efficacy of cord blood hematopoietic cell transplantation [version 1; peer review: 3 approved]** F1000Research 2019, 8(F1000 Faculty Rev):1833 (<https://doi.org/10.12688/f1000research.20002.1>)

**First published:** 31 Oct 2019, 8(F1000 Faculty Rev):1833 (<https://doi.org/10.12688/f1000research.20002.1>)

## Background: the beginning of cord blood transplantation

Cord blood (CB) is a clinical source of transplantable hematopoietic stem cells (HSCs) and hematopoietic progenitor cells (HPCs) for hematopoietic cell transplantation (HCT)<sup>1-3</sup>. Until the late 1980's, the cellular source to treat patients with malignant and non-malignant hematopoietic and other disorders by HCT was mainly bone marrow (BM). Mobilized peripheral blood (mPB), where clinicians utilize known agents (e.g. granulocyte colony-stimulating factor<sup>4,5</sup> and/or HSC/HPC retention signal antagonists such as AMD3100<sup>6-8</sup>) to release high numbers of HSCs and HPCs into the bloodstream for easy collection, was only in its early stages. In the 1980's, umbilical CB, usually a discarded material except for routine newborn blood tests, was studied for HSC and HPC biology in a national collaboration<sup>9</sup>. This scientific work was performed at the Indiana University School of Medicine (IUSM). The authors<sup>9</sup> demonstrated that there were likely enough HSCs and HPCs for CB clinical transplantation and the collected cells could be stored for days at room temperature, shipped by overnight express mail to a distant site, and cryopreserved for future CB HCT. The first proof-of-principle CB storage bank for HLA-matched siblings, set up in the Broxmeyer laboratory<sup>9,10</sup>, led to the first CB HCT at the Hôpital St. Louis, Paris, in the transplant center directed by Eliane Gluckman as part of an international study<sup>11</sup>. CB cells were collected and sent from a distant obstetric unit to the Broxmeyer laboratory, where they were tested, cryopreserved, and tested again after thawing of a small separate part of the frozen unit before being hand-delivered to Paris for the clinical HCT. On 6 October 1988, the CB unit was infused into a 6-year-old boy with Fanconi anemia who had been first conditioned by a modified regimen specifically for patients with Fanconi anemia that had been previously developed by Dr. Gluckman, utilizing HLA-matched sibling CB from his sister. This first CB HCT<sup>11</sup> was curative for the hematological manifestations of Fanconi anemia; the recipient is alive and well over 31 years later. A total of six more CB HCTs were done in Paris, Baltimore, and Cincinnati using HLA sibling CB cells cryopreserved in the Broxmeyer laboratory to treat Fanconi anemia<sup>10,12,13</sup> and juvenile chronic myelogenous leukemia (first CB transplant to treat a leukemia)<sup>14</sup>. Additional information on CB HCT has been reported<sup>1-3,15,16</sup> and on the functionality of CB HSCs and HPCs<sup>17-30</sup>. Information presented in the original scientific paper was produced years in advance of the clinical transplant, but the scientific<sup>9</sup> and clinical<sup>11</sup> papers were both published in 1989, as we waited until we knew the first clinical CB HCT<sup>11</sup> was successful before submitting the scientific paper<sup>9</sup>. Cryopreserved CB can be stored for at least 23 and a half years<sup>18,31,32</sup> with little or no loss of HPCs (comparing thawed cells to pre-freeze numbers). CB HCT was extended to partially HLA-disparate and unrelated donors<sup>1-3</sup>. Over 35,000 clinical CB HCT procedures have been performed to date to treat both children and adults with the same malignancies and non-malignancies treated by BM HCT. Advantages of CB HCT are ease of collection and storage of CB without significant risks for the delivering mothers, the ready and quick availability of HLA-typed frozen CB units in public and private CB banks (should such units be rapidly needed for transplantation), and elicitation of relatively

low acute and chronic graft versus host disease (GVHD) in recipients after CB HCT, even with unrelated partially HLA-disparate donor cells, compared to that elicited by BM or mPB. Problems include fewer HSCs and HPCs in CB collections than BM or mPB, in part resulting in delayed engraftment of neutrophils, platelets, and immune cells compared to BM and especially with mPB. While not life-threatening, this delay in engraftment with CB prolongs hospital stays, incurring additional health costs<sup>3,33</sup>.

Efforts to address slower time to donor blood cell recovery have focused on *ex vivo* (in cell culture) expansion of HSCs (with the idea and possibility that increased numbers of HSCs infused will ameliorate slower time to recovery) or enhancing the homing capacity of HSCs to optimize engraftment. Few such efforts have been tested in the clinical setting<sup>34-40</sup> and only in a few selected transplant centers. This review focuses on enhancing the efficacy of "limited" numbers of HSCs and HPCs in CB collections for CB HCT. A clear distinction must be made between phenotypically recognizable and functional HSCs and HPCs. There are rigorous criteria to phenotypically identify human and mouse HSCs and subsets of HPCs by their cell surface proteins, entailing specific antibodies and flow cytometry. However, phenotype does not necessarily recapitulate functional status. For functional analysis, one must perform specific engraftment studies *in vivo* in mice for mouse and human HSCs and colony forming assays *in vitro* for HPCs<sup>41,42</sup>. Recent information on collection, *ex vivo* expansion, and homing of CB HSCs/HPCs for the potential enhancement of CB HCT follows.

## Increasing hematopoietic stem cell numbers in single cord blood collections

Hypoxia is associated with HSC/HPC functions in these cells' *in vivo* microenvironment<sup>43</sup>. A means to enhance the efficacy of HCT is through hypoxic collection and processing of HSCs such that the collected cells are never exposed to ambient air oxygen (~21% oxygen) levels<sup>44,45</sup>. The BM environment, in which HSCs/HPCs reside, has oxygen levels ranging from 1-5%, with some areas possibly being slightly higher or lower depending on proximity to the vasculature<sup>46-49</sup>. Isolating HSCs/HPCs under ambient air (~21% oxygen) exposes these cells to hyperoxic conditions, which within minutes decrease HSC numbers through the differentiation of HSCs to HPCs and not because of HSC cell death<sup>44,45</sup>. Studies dating from the 1970's compared culturing of HSCs and HPCs in low (~5% oxygen), *in vivo* physiological oxygen versus high (~21% oxygen) ambient air oxygen. Culturing human and mouse BM, human CB, and mouse fetal liver at low oxygen *in vitro* increased numbers of detectable functional HSCs/HPCs<sup>50-56</sup>. When cultured in low oxygen (48 mmHg, 6.8% oxygen), clonal growth of granulocyte macrophage progenitors (CFU-GM) from mouse BM was enhanced with increased colony numbers and size compared to a more conventional oxygen environment (135 mmHg, 19% oxygen)<sup>50</sup>. Culturing erythroid progenitors (BFU-E) and more mature erythropoietic precursors (CFU-E) from mouse BM or fetal liver at 5% oxygen increased erythropoietin sensitivity of cells and CFU-E colony numbers<sup>55</sup>. Human low-density CB cells cultured at 5% oxygen had increased CFU-GM,

BFU-E, and multipotential progenitors (CFU-GEMM) and were readily expanded *ex vivo*<sup>56</sup>. Human BM cultured at 5% oxygen had increased CFU-GM numbers<sup>51</sup>. Human BM Lin<sup>-</sup> CD34<sup>+</sup> CD38<sup>-</sup> cells (enriched for HSCs) cultured at 1.5% oxygen for 4 days had more functional SCID repopulating cells (an assay for functional human HSCs) than comparable human BM cells cultured at 20% oxygen for 4 days (~5.8-fold increase) or freshly isolated Lin<sup>-</sup> CD34<sup>+</sup> CD38<sup>-</sup> cells (~4.2-fold increase)<sup>53</sup>, events associated with stabilization of hypoxia-inducible factor (HIF)-1 $\alpha$ , increased surface angiogenic receptors, and VEGF secretion within cultures.

However, in all of these reports, hematopoietic cells were first collected under ambient (~21%) oxygen levels before being placed in culture under lower oxygen and thus the collected cells were already exposed to extra physiological oxygen stress/shock (EPOSS) or hyperoxia, which induces the production of mitochondrial reactive oxygen species (ROS), increased HSC differentiation, increased functional HPC numbers and cell cycling, and increased mitochondrial mass/activity. EPOSS effects are mediated by a p53-cyclophilin D-mitochondria permeability transition pore axis and involve HIF-1 $\alpha$  and the hypoxamir miR-210<sup>45</sup>. Collecting and processing of mouse BM and human CB under low oxygen (3% oxygen, where cells are never exposed to ambient air) resulted in ~two- to five-fold increases in functional HSC numbers (assessed by engraftment in NSG immune-deficient mice) compared to cells collected or processed under ambient air<sup>44,45</sup>. Methods to mimic the effects of low oxygen are being examined. Cyclophilin D inhibitor, cyclosporin A (CSA, used to alleviate GVHD in human HCT), resulted in increased mouse BM and human CB HSC numbers and engraftment capability<sup>45</sup>. However, CSA is difficult to work with. It is hard to get into solution and manifests batch-to-batch variations so that each batch needs to be titrated. Combinations of antioxidants and epigenetic enzyme inhibitors within the flush/collection fluids increased numbers of mouse BM HSCs with increased engrafting capacity in a competitive *in vivo* assay<sup>37</sup>, but effects of antioxidants and epigenetic enzyme inhibitors have not yet been verified with human CB cells.

### Ex vivo expansion of functional hematopoietic stem cells

Small molecules, including, but not limited to, diethylaminobenzaldehyde (DEAB), LG1506, StemRegenin 1 (SR1), UM171, BIO (GSK3 $\beta$  inhibitor), NR-101, trichostatin A (TSA), garcinol (GAR), valproic acid (VPA), copper chelator, tetraethylenepentamine, and nicotinamide, are reported agonists for experimental *ex vivo* expansion of human HSCs and HPCs<sup>58-65</sup>. Clinical studies with a few of these small molecules have been reported<sup>35-40</sup>. Verification of these clinical studies will take time. SR1 and UM171 are efficient HSC expansion compounds<sup>58,61</sup>. SR1, a purine derivative, was identified in a chemical compound screen for candidates promoting *ex vivo* expansion of human HSCs/HPCs<sup>58</sup>. SR1 binds aryl hydrocarbon receptor and antagonizes AhR signaling in CB HSCs/HPCs, but the exact molecular mechanisms remain unclear. SR1 has been tested in a phase I/II clinical trial<sup>40</sup>. However, the investigators transplanted both SR1-expanded and -unexpanded CB into patients, so it is too early to determine if SR1-expanded cells

contain long-term repopulating HSCs. UM171 promotes *ex vivo* expansion of long-term repopulating HSCs in experimental models<sup>61</sup>, but the clinical trial using UM171 has not yet been published.

Mechanisms behind mouse and human HSC expansion may be different. Neither SR1 nor UM171 stimulates mouse HSC *ex vivo* expansion<sup>58,61</sup>. Thus, mouse studies to evaluate these molecules are not possible. In contrast, overexpression of HOXB4 or co-culturing of recombinant HOXB4 significantly promoted the expansion of both human CD34<sup>+</sup> and mouse HSCs<sup>66,67</sup>. Activation of OCT4 was found to enhance *ex vivo* expansion of CB HSCs/HPCs by regulating HOXB4 expression<sup>68</sup>. Angiopoietin-like proteins support mouse and human HSC expansion in culture<sup>69</sup>. Overexpression of *MSI2*, an oncogene, antagonizes aryl hydrocarbon receptor signaling and expands human HSCs to levels similar to those seen with SR1<sup>70</sup>, even though SR1 does not promote mouse HSC expansion<sup>71</sup>.

Readout of HSC expansion is related to the culture systems used, which is one reason why the reproducibility of published research may not be easily confirmed. In our experience, serum-free medium such as SFEM (StemSpan™ Serum-Free Expansion Medium, Catalog #09650, Stemcell Technologies) or Stemline (Stemline II HSC expansion medium, Catalog #S0192, Sigma-Aldrich) with 100 ng/mL SCF, TPO, and Flt3L can efficiently maintain CD34<sup>+</sup> HSC and HPC numbers for 7–10 days. Antagonizing retinoid acid receptor (RAR) or PPAR-gamma (PPAR-G) signaling maintains CD34<sup>+</sup> CD38<sup>-</sup> stem and progenitor cell populations when CD34<sup>+</sup> starting cells are cultured in serum and cytokine-containing RPMI-1640 medium, thus facilitating the expansion or maintenance of HSCs in culture<sup>72,73</sup>. As SFEM medium is effective in maintaining CD34<sup>+</sup> CD38<sup>-</sup> cell populations, RAR or PPAR-G antagonists do not further enhance the expansion of human HSC production when CD34<sup>+</sup> cells are cultured in SFEM medium. PPAR-G expression was repressed when CD34<sup>+</sup> cells were cultured in SFEM medium<sup>72,73</sup>. Most recently, a simple HSC *ex vivo* expansion method was reported by replacing recombinant human serum albumin (HSA) with polyvinyl alcohol (PVA)<sup>74</sup>. It was suggested that potential contaminants in recombinant proteins might induce inflammatory responses, thus dampening HSC stemness maintenance. By this minor manipulation, the authors reported a massive 900-fold enhancement in functional HSC numbers after 28-day *ex vivo* culture<sup>74</sup>. This incredibly efficient expansion system needs to be confirmed by other labs. However, such massive increases in functional HSC numbers may not be needed for enhancement of CB HCT. A few fold increase in these cells may suffice to enhance time to engraftment, although the excess expanded cells can be frozen and stored for additional CB transplants.

N<sup>6</sup>-methyladenosine (m<sup>6</sup>A) modulates the expression of a group of messenger (m) RNAs critical for stem cell fate decisions by modulating their stability<sup>75</sup>. Suppressing m<sup>6</sup>A reader, Ythdf2, which promotes targeted decay of mRNA, promotes *ex vivo* expansion of mouse BM and human CB HSCs<sup>76</sup>. Conditional knock-out of mouse Ythdf2 increases functional HSC numbers without changing lineage differentiation and without apparent

manifestation of hematological malignancies. Knockdown of human YTHDF2 resulted in a 10-fold increase in cytokine-mediated *ex vivo* expansion of human CB HSCs, a 5-fold increase in HPCs, and a greater than 8-fold increase in serial transplantation<sup>76</sup>. This was associated with enrichment in mRNAs encoding transcription factors in HSCs previously shown to be critical for stem cell renewal. This procedure thus targets multiple effectors rather than one<sup>76,77</sup>.

Epigenetic reprogramming using VPA has been utilized to experimentally expand human CB HSCs *ex vivo*<sup>59</sup>. This required the coordination of cellular reprogramming with remodeling of mitochondria and activation of p53 that apparently limits ROS levels<sup>78</sup>, which induce HSC differentiation<sup>44,45</sup>. DEK, a nuclear heterochromatin remodeling agent, which can be secreted from the cell and act as a cytokine that manifests its effects through the chemokine receptor CXCR2 (the only known non-chemokine to bind CXCR2), enhances cytokine-mediated *ex vivo* expansion of human CB and mouse BM HSCs and HPCs<sup>79</sup>.

One challenge for *ex vivo* expansion is the lack of markers labeling functional HSCs during and after *ex vivo* culture. Some signaling pathways might stimulate the expansion of CD34<sup>+</sup> cells, most of which are progenitors. Markers including CD90 or CD49f have often been used to isolate HSCs from fresh human CB and BM samples. However, CD34<sup>+</sup> CD90<sup>+</sup> CD49f<sup>+</sup> phenotypic HSCs do not necessarily reflect functional HSCs, especially under stress conditions such as *ex vivo* expansion<sup>41</sup>. The only currently available way to confirm the expansion of human HSC numbers is through transplantation using sublethally irradiated immune-deficient mice. A logistical problem is that *ex vivo* clinical studies will likely have to be performed in very select centers with expertise for these procedures. Also, the economics associated with *ex vivo* expansion must be taken into account, as it will likely add significant additional costs to the clinical HCT procedure. While it does not appear that *ex vivo* expansion procedures have damaged HSCs or caused pre-leukemia/leukemia, anytime HSCs are manipulated *ex vivo*, there is potential for long-term detrimental effects, which may involve gene expression pattern changes and epigenetic modifications that might result in long-term counter-productive outcomes.

During *ex vivo* expansion, we must also keep in mind the different physical characteristics of the *in vivo* HSC BM niche that help maintain HSC homeostasis (e.g. interactions that HSCs have with the other cells within their BM niche and lower oxygen concentrations within the BM). Taking these factors into account, CB HSCs/HPCs have been expanded in the presence of mesenchymal stem/stromal cells and have been proven to be safe in a clinical study<sup>36</sup>. In addition, hypoxia culturing (5% oxygen) after cells were collected in ambient air potentiated *ex vivo* expansion of CB HSCs/HPCs<sup>80</sup>.

Although *ex vivo* expansion is a promising means to overcome limited numbers of CB HSCs collected for transplantation, there is still much work to be done in this area. More mechanistic insight is required regarding the regulation of HSC stemness.

## Improving hematopoietic stem cell homing to enhance cord blood hematopoietic cell transplantation

After infusion into peripheral blood, HSCs home to the BM microenvironment by sensing chemical gradients of chemoattractants<sup>81</sup>. The BM microenvironment provides a unique matrix bedding and conducive signaling environment supporting long-term engraftment and balances HSC proliferation and differentiation<sup>82,83</sup>. HSC homing is crucial for successful clinic outcomes<sup>84</sup>.

Directing HSC migration and homing from the peripheral circulation to the BM involves interactions between chemokine ligand CXCL12/stromal cell-derived factor (SDF)-1 and its receptor CXCR4<sup>85,86</sup>. CXCL12 is highly expressed by BM stromal cells padding the stem cell niche. Gradients of CXCL12 provide directional cues and orchestrate HSC migration towards the BM. CXCR4 is a seven-transmembrane G-protein-coupled chemokine receptor expressed on the surface of HSCs. Knockouts of CXCL12 or CXCR4 result in severe hematopoietic defects<sup>87-89</sup>. Sphingosine-1-phosphate (S1P) and ceramide-1-phosphate (C1P) also provide homing gradients guiding HSCs to BM niches<sup>90-92</sup>. Strategies to enhance HSC homing are classified into three categories: regulation from the cell membrane, regulation in the cytoplasm, and regulation in the nucleus.

### Regulation from the cell membrane

The cell membrane is a semi-permeable membrane separating the cell from the external environment. The cell membrane consists of phospholipid bilayers and many membrane-associated proteins, while lipids are fundamental structural elements, and proteins are responsible for performing specific membrane functions<sup>93,94</sup>. Lipid rafts are special membrane domains rich in glycosphingolipids and cholesterol and have been implicated in regulating membrane signaling<sup>95,96</sup>. Incorporation of CXCR4 into lipid rafts facilitates the sensing of CXCL12 gradients, enhancing homing and engraftment of HSCs<sup>97,98</sup>. Short-term (4-hour) mild heating (39°C) led to elevated membrane lipid raft formation, resulting in increased CXCR4 aggregation and co-localization with lipid rafts, and promoted human CB HSC homing and engraftment in an NSG mouse transplantation model<sup>99</sup>. One report showed a beneficial effect of dimethyl sulfoxide (DMSO) treatment on HSC homing, possibly because of lower internalization of the surface CXCR4 receptor<sup>100</sup>.

Another HSC homing regulator found on the cell membrane is dipeptidyl peptidase 4 (DPP4). DPP4, also referred to as cell surface CD26, a 110 kDa serine protease. It cleaves penultimate alanine or proline amino acids at the N-terminus of target substrates including cytokines and chemokines<sup>101,102</sup>. DPP4 is widely expressed in tissues, e.g. liver, spleen, lung, and BM, as a membrane-bound form and is also found in serum in soluble form. DPP4 is expressed on the surface of HSCs and HPCs, as well as on T lymphocytes; it is an important regulator of HSC and T cell function<sup>101-103</sup> and modulates HSC homing at least in part by modifying CXCL12<sup>104,105</sup>. DPP4 generates a truncated form of CXCL12, which is no longer chemotactic but is able to block chemotaxis of full-length CXCL12<sup>104</sup>. Blocking enzymatic



activity of DPP4 increases levels of non-truncated CXCL12, enhancing HSC homing and engraftment of human CB CD34<sup>+</sup> cells or mouse BM cells<sup>105,106</sup>. Sitagliptin, an FDA-approved orally active inhibitor of DPP4, has been used to enhance the engraftment of single CB transplantation in patients with leukemia and lymphoma<sup>107–109</sup>. Since it was subsequently realized that DPP4 truncated a number of other hematopoietic-regulating cytokines<sup>110</sup>, the time to engraftment may have been further decreased had sitagliptin been given over more days.

Prostaglandin E2 (PGE<sub>2</sub>) is an important mediator of physiological and pathological systems<sup>111,112</sup>. Pulse treatment of human and murine HSCs with PGE<sub>2</sub> results in enhanced HSC homing and engraftment, mediated through the upregulation of surface CXCR4 levels<sup>22</sup>. A clinical trial evaluating the effects of PGE<sub>2</sub> in CB HCT has elicited promising results, with apparently faster neutrophil recovery and long-term dominance of the PGE<sub>2</sub>-treated CB unit<sup>34</sup>, but this study was done using PGE<sub>2</sub>-treated and -untreated CB. The long-term engrafting capability of the PGE<sub>2</sub>-treated cells is unknown. PGE<sub>2</sub> has four specific G-protein-coupled receptors on the cell membrane, EP1–EP4<sup>113</sup>. EP2 and EP4 were involved in the upregulation of CXCR4 and CXCL12 expression and promoted HSC migration towards CXCL12<sup>114</sup>. It may be practical to develop better EP2 and EP4 agonists to further enhance HSC homing and engraftment. In an animal model, combining PGE<sub>2</sub> treatment of donor cells and *in vivo* DPP4 inhibitor demonstrated additive effects on enhancing mouse BM engraftment into lethally irradiated mice<sup>115</sup>, suggesting potential enhancement in efficacy by combining two different treatment modalities.

Calcium-sensing receptor (CaR) is a cell membrane G-protein-coupled receptor mediating cell responses to extracellular calcium<sup>116</sup>. CaR knockout HSCs are defective in adherence to the BM microenvironment and fail to engraft after transplantation<sup>117</sup>. Treatment of murine HSCs with a CaR agonist, cinacalcet, led to enhanced HSC homing and engraftment, effects mediated through intracellular CXCR4 signaling<sup>117</sup>. CXCR4 mRNA and surface expression remained unaltered, so cinacalcet may stimulate enhanced CXCR4 signaling in an unconventional manner.

During the homing process, the first early step is considered to be HSCs rolling on P-selectins and E-selectins of endothelial cells in BM<sup>30</sup>. P-selectins and E-selectins are C-type lectins whose ligands must be properly  $\alpha$ 1,3-fucosylated to form mature glycan determinants. Increasing the levels of cell surface fucosylation has been shown to enhance the engraftment of CB cells in immunodeficient mice<sup>30,118,119</sup>. Furthermore, CB units were treated with guanosine diphosphate fucose and fucosyltransferase-VI to enhance cell surface fucosylation in a clinical trial, and the results showed improved engraftment efficiency of fucosylated cells<sup>27</sup>.

### Regulation in the cytoplasm

Heme oxygenase 1 (HO-1), an endoplasmic reticulum (ER)-anchored enzyme, plays important roles in anti-oxidative and inflammatory processes<sup>120</sup>. HO-1 acts as a negative regulator of HSC homing. HO-1 knockout HSCs have enhanced migration

towards CXCL12 and S1P gradients<sup>121</sup>. Transient treatment with HO-1 inhibitor (SnPP) increased chemotaxis and homing of HSCs/HPCs<sup>121</sup>.

### Regulation in the nucleus

The glucocorticoid receptor (GR) is an evolutionarily conserved nuclear receptor to which glucocorticoids bind<sup>122,123</sup>. Upon ligand binding, GR is transported into the nucleus and functions as a transcriptional factor to activate downstream gene transcription, regulating numerous physiological processes. Glucocorticoid treatment of human CB HSCs significantly elevated surface CXCR4 expression and increased chemotaxis towards CXCL12, HSC homing, and engraftment in NSG mice<sup>123</sup>. Activated GR transfers into the nucleus and binds to glucocorticoid response elements in the CXCR4 promoter in human CB HSCs, followed by recruitment of SRC1/p300 histone acetyltransferase complex. This promotes histone H4K5 and H4K16 acetylation in the CXCR4 promoter region, leading to upregulation of CXCR4 transcription. Knockdown of SRC1 or p300 suppresses the effects of activated GR on CXCR4 surface expression, while inhibition of p300 by a small molecule inhibitor, C646, blocks the enhanced homing effects of activated GR<sup>72</sup>, suggesting that activated GR depends on histone acetylation to promote HSC homing.

Histone deacetylases (HDACs) are crucial modulators in regulating histone acetylation levels<sup>124,125</sup>. HDACs remove acetyl groups from lysines of target proteins and play important roles in physiological processes<sup>124</sup>. The treatment of human CB HSCs with HDAC inhibitors substantially increased surface CXCR4 expression, improved chemotaxis towards CXCL12, and enhanced HSC homing and engraftment<sup>126</sup>. There are 18 HDAC enzymes in mammals, grouped into five subfamilies based on sequence similarity (class I, IIa, IIb, III, and IV)<sup>127</sup>. HDAC5 is the one HDAC specifically involved in the regulation of CXCR4 expression and HSC homing<sup>128</sup>. HDAC5 inhibition increased acetylation levels of histones at the CXCR4 promoter region as well as p65 acetylation levels in the nucleus. NF- $\kappa$ B subunit p65 is a crucial transcription factor regulating CXCR4 expression. The acetylation of p65 enhances its DNA-binding activity and promotes target gene transcription<sup>127–130</sup>. Blocking NF- $\kappa$ B signaling suppressed the effects of HDAC5 inhibition on CXCR4 upregulation and enhanced HSC homing<sup>126,128</sup>, indicating essential roles for NF- $\kappa$ B signaling in regulating HSC homing and demonstrating a previously unknown negative regulation of HSC homing by HDAC5.

HIF-1 $\alpha$ , a DNA-binding transcriptional factor, mediates cellular responses to hypoxia<sup>43,129</sup>. HIF-1 $\alpha$  is important during animal development and for energy metabolism. The BM microenvironment, where HSCs reside, is hypoxic<sup>43</sup>. HIF-1 $\alpha$  is stabilized in HSCs and regulates HSC activity/quiescence<sup>131,132</sup>. Pharmacological increases in HIF-1 $\alpha$  promote HSC homing and engraftment also by upregulating surface CXCR4 expression<sup>133</sup>. CXCR4 expression upregulation results from HIF-1 $\alpha$  binding with hypoxia response elements, located at -1.3 kb from the transcription start site of the CXCR4 promoter region. Caffeic acid phenethyl ester (CAPE) treatment promotes HSC homing and engraftment by inducing the

expression of HIF-1 $\alpha$ . CAPE administration upregulates HIF-1 $\alpha$  protein levels and CXCL12 in BM endothelial cells and inhibition of HIF-1 $\alpha$  by PX-478 suppresses CAPE-mediated enhanced HSC homing, further supporting the notion that HIF-1 $\alpha$  is important during HSC homing and engraftment.

The above-mentioned approaches for homing range from the cell membrane (lipid rafts, DPP4, EP2 and EP4, and CaR) to the cytoplasm (HO-1) and inside the nucleus (GR, HDAC5, and HIF-1 $\alpha$ ). Which procedure would be the best to be tested in a clinical setting needs to be determined. Perhaps combinations of approaches can further increase the homing and engraftment of HSCs. It may be that short-term treatment of donor CB units for about 16 hours may provide significant enhancement for engraftment in the setting of CB HCT, possibly negating the necessity for *ex vivo* expansion efforts. Alternatively, it may be that the CB cells do not have to be pretreated *ex vivo* prior to infusion into the patient but rather that the cells can be infused into the patient who is then given the reagents *in vivo* to enhance the homing/engrafting capability of the infused cells. It is also possible that *ex vivo* expanded HSCs may better engraft if it turns out that homing of expanded HSCs is suboptimal and can be enhanced.

## Concluding remarks

Enhancing CB HCT efficacy will not only reduce the time of donor cell recovery but also make it possible to use more banked CB units that contain fewer HSCs/HPCs. There are a number of new ways to potentially enhance the efficacy of CB HCT<sup>134</sup>. However, most are laboratory efforts. How to get these new methods into clinical trials is a problem that needs to be solved. We believe that simpler is always better. The simpler the procedure, the more likely that it will be clinically translated. There are just not enough clinical CB HCTs available to set up phase I/II clinical trials to test these new procedures. Most investigators doing such trials are “wed” to their personal favorite procedure. If, in the future, we can deal with this problem and find means for additional clinical efforts, it is possible that several new procedures can be used together<sup>134</sup>. This, however, adds additional logistical problems versus the use of one procedure. Clinical trials are costly, and it is not clear where the money to pursue such trials will come from, or even if they can be supported at all, since current trials are funded by companies to test their own products. A gathering of interested scientists and clinical investigators who can think-tank this problem is desperately needed and strongly encouraged.

## References



- Ballen KK, Gluckman E, Broxmeyer HE: **Umbilical cord blood transplantation: the first 25 years and beyond.** *Blood.* 2013; **122**(4): 491–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Broxmeyer HE, Farag SS, Rocha V: **Cord blood hematopoietic cell transplantation.** In: Forman SJ, Negrin RS, Antin JH, Appelbaum FR, editors. *Thomas' Hematopoietic Cell Transplantation.* 5th ed. Oxford, England: John Wiley & Sons, Ltd; 2016; 437–55.  
[Publisher Full Text](#)
- Mayani H, Wagner JE, Broxmeyer HE: **Cord blood research, banking, and transplantation: achievements, challenges, and perspectives.** *Bone Marrow Transplant.* 2019.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- de Kruijff EFM, Fibbe WE, van Pel M: **Cytokine-induced hematopoietic stem and progenitor cell mobilization: unraveling interactions between stem cells and their niche.** *Ann N Y Acad Sci.* 2019.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Pelus LM, Broxmeyer HE: **Peripheral blood stem cell mobilization; a look ahead.** *Curr Stem Cell Rep.* 2018; **4**(4): 273–81.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Broxmeyer HE, Orschell CM, Clapp DW, et al.: **Rapid mobilization of murine and human hematopoietic stem and progenitor cells with AMD3100, a CXCR4 antagonist.** *J Exp Med.* 2005; **201**(8): 1307–18.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Liles WC, Broxmeyer HE, Rodger E, et al.: **Mobilization of hematopoietic progenitor cells in healthy volunteers by AMD3100, a CXCR4 antagonist.** *Blood.* 2003; **102**(8): 2728–30.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Liles WC, Rodger E, Broxmeyer HE, 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**(3): 295–300.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Broxmeyer HE, Douglas GW, Hangoc G, et al.: **Human umbilical cord blood as a potential source of transplantable hematopoietic stem/progenitor cells.** *Proc Natl Acad Sci U S A.* 1989; **86**(10): 3828–32.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Broxmeyer HE, Gluckman E, Auerbach A, et al.: **Human umbilical cord blood: a clinically useful source of transplantable hematopoietic stem/progenitor cells.** *Int J Cell Cloning.* 1990; **8 Suppl 1**: 76–89; discussion 89–91.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Gluckman E, Broxmeyer HA, Auerbach AD, et al.: **Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling.** *N Engl J Med.* 1989; **321**(17): 1174–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Broxmeyer HE, Kurtzberg J, Gluckman E, et al.: **Umbilical cord blood hematopoietic stem and repopulating cells in human clinical transplantation.** *Blood Cells.* 1991; **17**(2): 313–29.  
[PubMed Abstract](#)
- Kohli-Kumar M, Shahidi NT, Broxmeyer HE, et al.: **Haemopoietic stem/progenitor cell transplant in Fanconi anaemia using HLA-matched sibling umbilical cord blood cells.** *Br J Haematol.* 1993; **85**(2): 419–22.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Wagner JE, Broxmeyer HE, Byrd RL, et al.: **Transplantation of umbilical cord blood after myeloablative therapy: analysis of engraftment.** *Blood.* 1992; **79**(7): 1874–81.  
[PubMed Abstract](#)
- Broxmeyer HE: **The history of cord blood transplantation/biology & perspective for future efforts to enhance the field.** *Cell Gene Therapy Insights.* 2017; **3**(7): 521–30.  
[Publisher Full Text](#)
- Wagner JE, Kernan NA, Steinbuch M, et al.: **Allogeneic sibling umbilical-cord-blood transplantation in children with malignant and non-malignant disease.** *Lancet.* 1995; **346**(8969): 214–9.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Bock TA, Orlie D, Dunbar CE, et al.: **Improved engraftment of human hematopoietic cells in severe combined immunodeficient (SCID) mice carrying human cytokine transgenes.** *J Exp Med.* 1995; **182**(6): 2037–43.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Broxmeyer HE, Cooper S: **High-efficiency recovery of immature haematopoietic progenitor cells with extensive proliferative capacity from human cord blood cryopreserved for 10 years.** *Clin Exp Immunol.* 1997; **107 Suppl 1**: 45–53.  
[PubMed Abstract](#)
- Broxmeyer HE, Hangoc G, Cooper S, et al.: **Growth characteristics and expansion of human umbilical cord blood and estimation of its potential for transplantation in adults.** *Proc Natl Acad Sci U S A.* 1992; **89**(9): 4109–13.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Carow CE, Hangoc G, Broxmeyer HE: **Human multipotential progenitor cells (CFU-GEMM) have extensive replating capacity for secondary CFU-GEMM: an effect enhanced by cord blood plasma.** *Blood.* 1993; **81**(4): 942–9.  
[PubMed Abstract](#)

21. **F** Csaszar E, Kirouac DC, Yu M, *et al.*: **Rapid expansion of human hematopoietic stem cells by automated control of inhibitory feedback signaling.** *Cell Stem Cell.* 2012; **10**(2): 218–29.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
22. Hoggatt J, Singh P, Sampath J, *et al.*: **Prostaglandin E2 enhances hematopoietic stem cell homing, survival, and proliferation.** *Blood.* 2009; **113**(22): 5444–55.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
23. Lu L, Xiao M, Shen RN, *et al.*: **Enrichment, characterization, and responsiveness of single primitive CD34 human umbilical cord blood hematopoietic progenitors with high proliferative and replating potential.** *Blood.* 1993; **81**(1): 41–8.  
[PubMed Abstract](#)
24. Mayani H, Lansdorp PM: **Biology of human umbilical cord blood-derived hematopoietic stem/progenitor cells.** *Stem Cells.* 1998; **16**(3): 153–65.  
[PubMed Abstract](#) | [Publisher Full Text](#)
25. Peled T, Mandel J, Goussard RN, *et al.*: **Pre-clinical development of cord blood-derived progenitor cell graft expanded ex vivo with cytokines and the polyamine copper chelator tetraethylenepentamine.** *Cytotherapy.* 2004; **6**(4): 344–55.  
[PubMed Abstract](#) | [Publisher Full Text](#)
26. Piacibello W, Sanavio F, Garetto L, *et al.*: **Extensive amplification and self-renewal of human primitive hematopoietic stem cells from cord blood.** *Blood.* 1997; **89**(8): 2644–53.  
[PubMed Abstract](#)
27. **F** Popat U, Mehta RS, Rezvani K, *et al.*: **Enforced fucosylation of cord blood hematopoietic cells accelerates neutrophil and platelet engraftment after transplantation.** *Blood.* 2015; **125**(19): 2885–92.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
28. Vormoor J, Lapidot T, Pflumio F, *et al.*: **Immature human cord blood progenitors engraft and proliferate to high levels in severe combined immunodeficient mice.** *Blood.* 1994; **83**(9): 2489–97.  
[PubMed Abstract](#)
29. Vormoor J, Lapidot T, Pflumio F, *et al.*: **SCID mice as an in vivo model of human cord blood hematopoiesis.** *Blood Cells.* 1994; **20**(2–3): 316–20:discussion 320–2.  
[PubMed Abstract](#)
30. Xia L, McDaniel JM, Yago T, *et al.*: **Surface fucosylation of human cord blood cells augments binding to P-selectin and E-selectin and enhances engraftment in bone marrow.** *Blood.* 2004; **104**(10): 3091–6.  
[PubMed Abstract](#) | [Publisher Full Text](#)
31. **F** Broxmeyer HE, Lee MR, Hangoc G, *et al.*: **Hematopoietic stem/progenitor cells, generation of induced pluripotent stem cells, and isolation of endothelial progenitors from 21- to 23.5-year cryopreserved cord blood.** *Blood.* 2011; **117**(18): 4773–7.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
32. Broxmeyer HE, Srour EF, Hangoc G, *et al.*: **High-efficiency recovery of functional hematopoietic progenitor and stem cells from human cord blood cryopreserved for 15 years.** *Proc Natl Acad Sci U S A.* 2003; **100**(2): 645–50.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
33. Broxmeyer HE, Farag S: **Background and future considerations for human cord blood hematopoietic cell transplantation, including economic concerns.** *Stem Cells Dev.* 2013; **22** Suppl 1: 103–10.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
34. **F** Cutler C, Multani P, Robbins D, *et al.*: **Prostaglandin-modulated umbilical cord blood hematopoietic stem cell transplantation.** *Blood.* 2013; **122**(17): 3074–81.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
35. de Lima M, McMannis J, Gee A, *et al.*: **Transplantation of ex vivo expanded cord blood cells using the copper chelator tetraethylenepentamine: a phase I/II clinical trial.** *Bone Marrow Transplant.* 2008; **41**(9): 771–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
36. **F** de Lima M, McNiece I, Robinson SN, *et al.*: **Cord-blood engraftment with ex vivo mesenchymal-cell coculture.** *N Engl J Med.* 2012; **367**(24): 2305–15.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
37. **F** Delaney C, Heimfeld S, Brashem-Stein C, *et al.*: **Notch-mediated expansion of human cord blood progenitor cells capable of rapid myeloid reconstitution.** *Nat Med.* 2010; **16**(2): 232–6.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
38. Horwitz ME, Chao NJ, Rizzieri DA, *et al.*: **Umbilical cord blood expansion with nicotinamide provides long-term multilineage engraftment.** *J Clin Invest.* 2014; **124**(7): 3121–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
39. Horwitz ME, Wease S, Blackwell B, *et al.*: **Phase I/II Study of Stem-Cell Transplantation Using a Single Cord Blood Unit Expanded Ex Vivo With Nicotinamide.** *J Clin Oncol.* 2019; **37**(5): 367–74.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
40. **F** Wagner JE Jr, Brunstein CG, Boitano AE, *et al.*: **Phase I/II Trial of StemRegenin-1 Expanded Umbilical Cord Blood Hematopoietic Stem Cells Supports Testing as a Stand-Alone Graft.** *Cell Stem Cell.* 2016; **18**(1): 144–55.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
41. Chen Y, Yao C, Teng Y, *et al.*: **Phorbol ester induced ex vivo expansion of rigorously-defined phenotypic but not functional human cord blood hematopoietic stem cells: a cautionary tale demonstrating that phenotype does not always recapitulate stem cell function.** *Leukemia.* 2019.  
[PubMed Abstract](#) | [Publisher Full Text](#)
42. Dorrell C, Gan OI, Pereira DS, *et al.*: **Expansion of human cord blood CD34(+)/CD38(-) cells in ex vivo culture during retroviral transduction without a corresponding increase in SCID repopulating cell (SRC) frequency: dissociation of SRC phenotype and function.** *Blood.* 2000; **95**(1): 102–10.  
[PubMed Abstract](#)
43. Huang X, Trinh T, Aljoufi A, *et al.*: **Hypoxia Signaling Pathway in Stem Cell Regulation: Good and Evil.** *Curr Stem Cell Rep.* 2018; **4**(2): 149–57.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
44. Broxmeyer HE, O'Leary HA, Huang X, *et al.*: **The importance of hypoxia and extra physiologic oxygen shock/stress for collection and processing of stem and progenitor cells to understand true physiology/pathology of these cells ex vivo.** *Curr Opin Hematol.* 2015; **22**(4): 273–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
45. Mantel CR, O'Leary HA, Chitteti BR, *et al.*: **Enhancing Hematopoietic Stem Cell Transplantation Efficacy by Mitigating Oxygen Shock.** *Cell.* 2015; **161**(7): 1553–65.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
46. **F** Morrison SJ, Scadden DT: **The bone marrow niche for hematopoietic stem cells.** *Nature.* 2014; **505**(7483): 327–34.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
47. Nombela-Arrieta C, Pivarnik G, Winkel B, *et al.*: **Quantitative imaging of hematopoietic stem and progenitor cell localization and hypoxic status in the bone marrow microenvironment.** *Nat Cell Biol.* 2013; **15**(5): 533–43.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
48. Sjöstedt S, Rooth G, Caligara F: **The Oxygen Tension of the Blood in the Umbilical Cord and the Intervillous Space.** *Arch Dis Child.* 1960; **35**(184): 529–33.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
49. **F** Spencer JA, Ferraro F, Roussakis E, *et al.*: **Direct measurement of local oxygen concentration in the bone marrow of live animals.** *Nature.* 2014; **508**(7495): 269–73.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
50. Bradley TR, Hodgson GS, Rosendaal M: **The effect of oxygen tension on haemopoietic and fibroblast cell proliferation in vitro.** *J Cell Physiol.* 1978; **97**(3 Pt 2 Suppl 1): 517–22.  
[PubMed Abstract](#) | [Publisher Full Text](#)
51. Broxmeyer HE, Cooper S, Gabig T: **The effects of oxidizing species derived from molecular oxygen on the proliferation in vitro of human granulocyte-macrophage progenitor cells.** *Ann N Y Acad Sci.* 1989; **554**: 177–84.  
[PubMed Abstract](#) | [Publisher Full Text](#)
52. Broxmeyer HE, Cooper S, Rubin BY, *et al.*: **The synergistic influence of human interferon-gamma and interferon-alpha on suppression of hematopoietic progenitor cells is additive with the enhanced sensitivity of these cells to inhibition by interferons at low oxygen tension in vitro.** *J Immunol.* 1985; **135**(4): 2502–6.  
[PubMed Abstract](#)
53. Danet GH, Pan Y, Luongo JL, *et al.*: **Expansion of human SCID-repopulating cells under hypoxic conditions.** *J Clin Invest.* 2003; **112**(1): 126–35.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
54. Lu L, Broxmeyer HE: **Comparative influences of phytohemagglutinin-stimulated leukocyte conditioned medium, hemin, prostaglandin E, and low oxygen tension on colony formation by erythroid progenitor cells in normal human bone marrow.** *Exp Hematol.* 1985; **13**(10): 989–93.  
[PubMed Abstract](#)
55. Rich IN, Kubanek B: **The effect of reduced oxygen tension on colony formation of erythropoietic cells in vitro.** *Br J Haematol.* 1982; **52**(4): 579–88.  
[PubMed Abstract](#) | [Publisher Full Text](#)
56. Smith S, Broxmeyer HE: **The influence of oxygen tension on the long-term growth in vitro of hematopoietic progenitor cells from human cord blood.** *Br J Haematol.* 1986; **63**(1): 29–34.  
[PubMed Abstract](#) | [Publisher Full Text](#)
57. Cai Q, Capitano M, Huang X, *et al.*: **Combinations of antioxidants and/or epigenetic enzyme inhibitors allow for enhanced collection of mouse bone marrow hematopoietic stem cells in ambient air.** *Blood Cells Mol Dis.* 2018; **71**: 23–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
58. **F** Boitano AE, Wang J, Romeo R, *et al.*: **Aryl hydrocarbon receptor antagonists promote the expansion of human hematopoietic stem cells.** *Science.* 2010; **329**(5997): 1345–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
59. **F** Chaurasia P, Gajzer DC, Schaniel C, *et al.*: **Epigenetic reprogramming induces the expansion of cord blood stem cells.** *J Clin Invest.* 2014; **124**(6): 2378–95.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
60. Chute JP, Muramoto GG, Whitesides J, *et al.*: **Inhibition of aldehyde dehydrogenase and retinoid signaling induces the expansion of human hematopoietic stem cells.** *Proc Natl Acad Sci U S A.* 2006; **103**(31): 11707–12.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
61. **F** Fares I, Chagraoui J, Gareau Y, *et al.*: **Cord blood expansion. Pyrimidoindole derivatives are agonists of human hematopoietic stem cell self-renewal.** *Science.* 2014; **345**(6203): 1509–12.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
62. Ko KH, Holmes T, Palladinetti P, *et al.*: **GSK-3 $\beta$  inhibition promotes engraftment**



- of *ex vivo*-expanded hematopoietic stem cells and modulates gene expression. *Stem Cells*. 2011; **29**(1): 108–18.  
[PubMed Abstract](#) | [Publisher Full Text](#)
63. Nishino T, Miyaji K, Ishiwata N, *et al.*: *Ex vivo* expansion of human hematopoietic stem cells by a small-molecule agonist of c-MPL. *Exp Hematol*. 2009; **37**(11): 1364–1377.  
[PubMed Abstract](#) | [Publisher Full Text](#)
64. Nishino T, Wang C, Mochizuki-Kashio M, *et al.*: *Ex vivo* expansion of human hematopoietic stem cells by garcinol, a potent inhibitor of histone acetyltransferase. *PLoS One*. 2011; **6**(9): e24298.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
65. Safi R, Muramoto GG, Salter AB, *et al.*: Pharmacological manipulation of the RAR/RXR signaling pathway maintains the repopulating capacity of hematopoietic stem cells in culture. *Mol Endocrinol*. 2009; **23**(2): 188–201.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
66. Antonchuk J, Sauvageau G, Humphries RK: HOXB4-induced expansion of adult hematopoietic stem cells *ex vivo*. *Cell*. 2002; **109**(1): 39–45.  
[PubMed Abstract](#) | [Publisher Full Text](#)
67. Krosil J, Austin P, Beslu N, *et al.*: *In vitro* expansion of hematopoietic stem cells by recombinant TAT-HOXB4 protein. *Nat Med*. 2003; **9**(11): 1428–32.  
[PubMed Abstract](#) | [Publisher Full Text](#)
68. Huang X, Lee MR, Cooper S, *et al.*: Activation of OCT4 enhances *ex vivo* expansion of human cord blood hematopoietic stem and progenitor cells by regulating HOXB4 expression. *Leukemia*. 2016; **30**(1): 144–53.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
69. Zhang CC, Kaba M, Ge G, *et al.*: Angiopoietin-like proteins stimulate *ex vivo* expansion of hematopoietic stem cells. *Nat Med*. 2006; **12**(2): 240–5.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
70. **F** Rentas S, Holzapfel N, Belew MS, *et al.*: Musashi-2 attenuates AHR signalling to expand human haematopoietic stem cells. *Nature*. 2016; **532**(7600): 508–11.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
71. **F** Kharas MG, Lengner CJ, Al-Shahrour F, *et al.*: Musashi-2 regulates normal hematopoiesis and promotes aggressive myeloid leukemia. *Nat Med*. 2010; **16**(10): 903–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
72. Guo B, Huang X, Broxmeyer HE: Enhancing human cord blood hematopoietic stem cell engraftment by targeting nuclear hormone receptors. *Curr Opin Hematol*. 2018; **25**(4): 245–52.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
73. Guo B, Huang X, Lee MR, *et al.*: Antagonism of PPAR- $\gamma$  signaling expands human hematopoietic stem and progenitor cells by enhancing glycolysis. *Nat Med*. 2018; **24**(3): 360–7.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
74. **F** Wilkinson AC, Ishida R, Kikuchi M, *et al.*: Long-term *ex vivo* haematopoietic-stem-cell expansion allows nonconditioned transplantation. *Nature*. 2019; **571**(7763): 117–21.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
75. Guo M, Liu X, Zheng X, *et al.*: m<sup>6</sup>A RNA Modification Determines Cell Fate by Regulating mRNA Degradation. *Cell Reprogram*. 2017; **19**(4): 225–31.  
[PubMed Abstract](#) | [Publisher Full Text](#)
76. **F** Li Z, Qian P, Shao W, *et al.*: Suppression of m<sup>6</sup>A reader Ythdf2 promotes hematopoietic stem cell expansion. *Cell Res*. 2018; **28**(9): 904–17.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
77. Huang X, Broxmeyer HE: m<sup>6</sup>A reader suppression bolsters HSC expansion. *Cell Res*. 2018; **28**(9): 875–6.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
78. **F** Papa L, Zimran E, Djedaini M, *et al.*: *Ex vivo* human HSC expansion requires coordination of cellular reprogramming with mitochondrial remodeling and p<sup>32</sup>activation. *Blood Adv*. 2018; **2**(20): 2766–79.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
79. Capitano ML, Mor-Vaknin N, Saha AK, *et al.*: Secreted nuclear protein DEK regulates hematopoiesis through CXCR2 signaling. *J Clin Invest*. 2019; **129**(6): 2555–70.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
80. Roy S, Tripathy M, Mathur N, *et al.*: Hypoxia improves expansion potential of human cord blood-derived hematopoietic stem cells and marrow repopulation efficiency. *Eur J Haematol*. 2012; **88**(5): 396–405.  
[PubMed Abstract](#) | [Publisher Full Text](#)
81. Lapidot T, Dar A, Kollet O: How do stem cells find their way home? *Blood*. 2005; **106**(6): 1901–10.  
[PubMed Abstract](#) | [Publisher Full Text](#)
82. **F** Crane GM, Jeffery E, Morrison SJ: Adult haematopoietic stem cell niches. *Nat Rev Immunol*. 2017; **17**(9): 573–90.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
83. Yu VWC, Scadden DT: Heterogeneity of the bone marrow niche. *Curr Opin Hematol*. 2016; **23**(4): 331–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
84. Huang X, Broxmeyer HE: Progress towards improving homing and engraftment of hematopoietic stem cells for clinical transplantation. *Curr Opin Hematol*. 2019; **26**(4): 266–72.  
[PubMed Abstract](#) | [Publisher Full Text](#)
85. Kim CH, Broxmeyer HE: *In vitro* behavior of hematopoietic progenitor cells under the influence of chemoattractants: Stromal cell-derived factor-1, steel factor, and the bone marrow environment. *Blood*. 1998; **91**(1): 100–10.  
[PubMed Abstract](#) | [Publisher Full Text](#)
86. Nagasawa T: CXCL12/SDF-1 and CXCR4. *Front Immunol*. 2015; **6**: 301.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
87. Ma Q, Jones D, Borghesani PR, *et al.*: Impaired B-lymphopoiesis, myelopoiesis, and derailed cerebellar neuron migration in CXCR4- and SDF-1-deficient mice. *Proc Natl Acad Sci U S A*. 1998; **95**(16): 9448–53.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
88. Nagasawa T, Hirota S, Tachibana K, *et al.*: Defects of B-cell lymphopoiesis and bone-marrow myelopoiesis in mice lacking the CXC chemokine PBSF/SDF-1. *Nature*. 1996; **382**(6592): 635–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
89. Zou YR, Kottmann AH, Kuroda M, *et al.*: Function of the chemokine receptor CXCR4 in hematopoiesis and in cerebellar development. *Nature*. 1998; **393**(6685): 595–9.  
[PubMed Abstract](#) | [Publisher Full Text](#)
90. Golan K, Vagima Y, Ludin A, *et al.*: S1P promotes murine progenitor cell egress and mobilization via S1P1-mediated ROS signaling and SDF-1 release. *Blood*. 2012; **119**(11): 2478–88.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
91. Juarez JG, Harun N, Thien M, *et al.*: Sphingosine-1-phosphate facilitates trafficking of hematopoietic stem cells and their mobilization by CXCR4 antagonists in mice. *Blood*. 2012; **119**(3): 707–16.  
[PubMed Abstract](#) | [Publisher Full Text](#)
92. Ratajczak MZ, Lee H, Wysoczynski M, *et al.*: Novel insight into stem cell mobilization-plasma sphingosine-1-phosphate is a major chemoattractant that directs the egress of hematopoietic stem progenitor cells from the bone marrow and its level in peripheral blood increases during mobilization due to activation of complement cascade/membrane attack complex. *Leukemia*. 2010; **24**(5): 976–85.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
93. Goñi FM: The basic structure and dynamics of cell membranes: an update of the Singer-Nicolson model. *Biochim Biophys Acta*. 2014; **1838**(6): 1467–76.  
[PubMed Abstract](#) | [Publisher Full Text](#)
94. Nicolson GL: The Fluid-Mosaic Model of Membrane Structure: still relevant to understanding the structure, function and dynamics of biological membranes after more than 40 years. *Biochim Biophys Acta*. 2014; **1838**(6): 1451–66.  
[PubMed Abstract](#) | [Publisher Full Text](#)
95. Ando J, Kinoshita M, Cui J, *et al.*: Sphingomyelin distribution in lipid rafts of artificial monolayer membranes visualized by Raman microscopy. *Proc Natl Acad Sci U S A*. 2015; **112**(15): 4558–63.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
96. Simons K, Ehehalt R: Cholesterol, lipid rafts, and disease. *J Clin Invest*. 2002; **110**(5): 597–603.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
97. Ratajczak MZ, Adamiak M: Membrane lipid rafts, master regulators of hematopoietic stem cell retention in bone marrow and their trafficking. *Leukemia*. 2015; **29**(7): 1452–7.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
98. Wysoczynski M, Reza R, Ratajczak J, *et al.*: Incorporation of CXCR4 into membrane lipid rafts primes homing-related responses of hematopoietic stem/progenitor cells to an SDF-1 gradient. *Blood*. 2005; **105**(1): 40–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
99. Capitano ML, Hangoc G, Cooper S, *et al.*: Mild Heat Treatment Primes Human CD34<sup>+</sup> Cord Blood Cells for Migration Toward SDF-1 $\alpha$  and Enhances Engraftment in an NSG Mouse Model. *Stem Cells*. 2015; **33**(6): 1975–84.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
100. **F** Jarocha D, Zuba-Surma E, Majka M: Dimethyl Sulfoxide (DMSO) Increases Percentage of CXCR4<sup>+</sup> Hematopoietic Stem/Progenitor Cells, Their Responsiveness to an SDF-1 Gradient, Homing Capacities, and Survival. *Cell Transplant*. 2016; **25**(7): 1247–57.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
101. O'Leary H, Ou X, Broxmeyer HE: The role of dipeptidyl peptidase 4 in hematopoiesis and transplantation. *Curr Opin Hematol*. 2013; **20**(4): 314–9.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
102. Ou X, O'Leary HA, Broxmeyer HE: Implications of DPP4 modification of proteins that regulate stem/progenitor and more mature cell types. *Blood*. 2013; **122**(2): 161–9.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
103. Ohnuma K, Takahashi N, Yamochi T, *et al.*: Role of CD26/dipeptidyl peptidase IV in human T cell activation and function. *Front Biosci*. 2008; **13**: 2299–310.  
[PubMed Abstract](#) | [Publisher Full Text](#)
104. Christopherson KW, Hangoc G, Broxmeyer HE: Cell surface peptidase CD26/dipeptidylpeptidase IV regulates CXCL12/stromal cell-derived factor-1 alpha-mediated chemotaxis of human cord blood CD34<sup>+</sup> progenitor cells. *J Immunol*. 2002; **169**(12): 7000–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
105. Christopherson KW, Hangoc G, Mantel CR, *et al.*: Modulation of hematopoietic stem cell homing and engraftment by CD26. *Science*. 2004; **305**(5686): 1000–3.  
[PubMed Abstract](#) | [Publisher Full Text](#)
106. Campbell TB, Hangoc G, Liu Y, *et al.*: Inhibition of CD26 in human cord

- blood CD34<sup>+</sup> cells enhances their engraftment of nonobese diabetic/severe combined immunodeficiency mice. *Stem Cells Dev.* 2007; 16(3): 347–54.  
[PubMed Abstract](#) | [Publisher Full Text](#)
107. Farag SS, Nelson R, Cairo MS, *et al.*: High-dose sitagliptin for systemic inhibition of dipeptidylpeptidase-4 to enhance engraftment of single cord umbilical cord blood transplantation. *Oncotarget.* 2017; 8(66): 110350–111057.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
108. Farag SS, Srivastava S, Messina-Graham S, *et al.*: In vivo DPP-4 inhibition to enhance engraftment of single-unit cord blood transplants in adults with hematological malignancies. *Stem Cells Dev.* 2013; 22(7): 1007–15.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
109. Vélez de Mendizábal N, Strother RM, Farag SS, *et al.*: Modelling the sitagliptin effect on dipeptidyl peptidase-4 activity in adults with haematological malignancies after umbilical cord blood haematopoietic cell transplantation. *Clin Pharmacokinet.* 2014; 53(3): 247–259.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
110. Broxmeyer HE, Hoggatt J, O'Leary HA, *et al.*: Dipeptidylpeptidase 4 negatively regulates colony-stimulating factor activity and stress hematopoiesis. *Nat Med.* 2012; 18(12): 1786–96.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
111. Jia Z, Zhang Y, Ding G, *et al.*: Role of COX-2/mPGES-1/prostaglandin E2 cascade in kidney injury. *Mediators Inflamm.* 2015; 2015: 147894.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
112. Nørregaard R, Kwon TH, Frøkiær J: Physiology and pathophysiology of cyclooxygenase-2 and prostaglandin E2 in the kidney. *Kidney Res Clin Pract.* 2015; 34: 194–200.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
113. Dey I, Lejeune M, Chadee K: Prostaglandin E2 receptor distribution and function in the gastrointestinal tract. *Br J Pharmacol.* 2006; 149: 611–23.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
114. Wang Y, Lai S, Tang J, *et al.*: Prostaglandin E2 promotes human CD34<sup>+</sup> cells homing through EP2 and EP4 *in vitro*. *Mol Med Rep.* 2017; 16(1): 639–646.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
115. Broxmeyer HE, Pelus LM: Inhibition of DPP4/CD26 and dmPGE<sub>2</sub> treatment enhances engraftment of mouse bone marrow hematopoietic stem cells. *Blood Cells Mol Dis.* 2014; 53(1–2): 34–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
116. Adams GB, Chabner KT, Alley IR, *et al.*: Stem cell engraftment at the endosteal niche is specified by the calcium-sensing receptor. *Nature.* 2006; 439(7076): 599–603.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
117. Lam BS, Cunningham C, Adams GB: Pharmacologic modulation of the calcium-sensing receptor enhances hematopoietic stem cell lodgment in the adult bone marrow. *Blood.* 2011; 117(4): 1167–75.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
118. Hidalgo A, Frenette PS: Enforced fucosylation of neonatal CD34<sup>+</sup> cells generates selectin ligands that enhance the initial interactions with microvessels but not homing to bone marrow. *Blood.* 2005; 105(2): 567–75.  
[PubMed Abstract](#) | [Publisher Full Text](#)
119. Robinson SN, Simmons PJ, Thomas MW, *et al.*: Ex vivo fucosylation improves human cord blood engraftment in NOD-SCID IL-2R $\gamma$ (null) mice. *Exp Hematol.* 2012; 40: 445–56.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
120. Wysoczynski M, Ratajczak J, Pedziwiatr D, *et al.*: Identification of heme oxygenase 1 (HO-1) as a novel negative regulator of mobilization of hematopoietic stem/progenitor cells. *Stem Cell Rev Rep.* 2015; 11(1): 110–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
121. Adamiak M, Moore JB 4th, Zhao J, *et al.*: Downregulation of Heme Oxygenase 1 (HO-1) Activity in Hematopoietic Cells Enhances Their Engraftment After Transplantation. *Cell Transplant.* 2016; 25(7): 1265–76.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
122. Tan CK, Wahli W: A trilogy of glucocorticoid receptor actions. *Proc Natl Acad Sci U S A.* 2016; 113(5): 1115–7.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
123. Guo B, Huang X, Cooper S, *et al.*: Glucocorticoid hormone-induced chromatin remodeling enhances human hematopoietic stem cell homing and engraftment. *Nat Med.* 2017; 23(4): 424–428.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
124. Peserico A, Simone C: Physical and functional HAT/HDAC interplay regulates protein acetylation balance. *J Biomed Biotechnol.* 2011; 2011: 371832.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
125. Yang XJ, Seto E: HATs and HDACs: from structure, function and regulation to novel strategies for therapy and prevention. *Oncogene.* 2007; 26(37): 5310–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
126. Huang X, Guo B, Liu S, *et al.*: Neutralizing negative epigenetic regulation by HDAC5 enhances human hematopoietic stem cell homing and engraftment. *Nat Commun.* 2018; 9(1): 2741.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
127. Zhi Y, Lu H, Duan Y, *et al.*: Involvement of the nuclear factor- $\kappa$ B signaling pathway in the regulation of CXC chemokine receptor-4 expression in neuroblastoma cells induced by tumor necrosis factor- $\alpha$ . *Int J Mol Med.* 2015; 35(2): 349–57.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
128. Huang B, Yang XD, Lamb A, *et al.*: Posttranslational modifications of NF- $\kappa$ B: Another layer of regulation for NF- $\kappa$ B signaling pathway. *Cell Signal.* 2010; 22(9): 1282–90.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
129. Forristal CE, Winkler IG, Nowlan B, *et al.*: Pharmacologic stabilization of HIF-1 $\alpha$  increases hematopoietic stem cell quiescence *in vivo* and accelerates blood recovery after severe irradiation. *Blood.* 2013; 121(5): 759–69.  
[PubMed Abstract](#) | [Publisher Full Text](#)
130. Galbraith MD, Allen MA, Bensard CL, *et al.*: HIF1A employs CDK8-mediator to stimulate RNAPII elongation in response to hypoxia. *Cell.* 2013; 153(6): 1327–39.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
131. Speth JM, Hoggatt J, Singh P, *et al.*: Pharmacologic increase in HIF1 $\alpha$  enhances hematopoietic stem and progenitor homing and engraftment. *Blood.* 2014; 123(2): 203–7.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
132. Takubo K, Goda N, Yamada W, *et al.*: Regulation of the HIF-1 $\alpha$  level is essential for hematopoietic stem cells. *Cell Stem Cell.* 2010; 7(3): 391–402.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
133. Chen X, Han Y, Zhang B, *et al.*: Caffeic acid phenethyl ester promotes haematopoietic stem/progenitor cell homing and engraftment. *Stem Cell Res Ther.* 2017; 8(1): 255.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
134. Broxmeyer HE: Long-Overdue Guidelines for the Cord Blood Banking Community. *Stem Cells Transl Med.* 2019; 8(4): 320–322.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

## Open Peer Review

Current Peer Review Status:   

---

### Editorial Note on the Review Process

F1000 Faculty Reviews are written by members of the prestigious F1000 Faculty. They are commissioned and are peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

---

### The reviewers who approved this article are:

#### Version 1

- Elizabeth J Shpall**  
Stem Cell Transplantation and Cellular Therapy, University of Texas MD Anderson Cancer Center, Houston, TX, USA  
**Competing Interests:** No competing interests were disclosed.
- Mariusz Ratajczak**  
Stem Cell Program, Department of Medicine, Division of Hematology and Oncology, University of Louisville, Louisville, Kentucky, USA  
**Competing Interests:** No competing interests were disclosed.
- Jonathan Hoggatt**  
Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, 02138, USA  
**Competing Interests:** No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact [research@f1000.com](mailto:research@f1000.com)

F1000Research