STEM CELLS TRANSLATIONAL MEDICINE®

COMMENTARY

Long-Overdue Guidelines for the Cord Blood Banking Community

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The article entitled "Model Criteria for Regulation of Cord Blood Banks and Cord Blood Banking" [1] is a concise set of recommendations for the field of hematopoietic cell transplantation (HCT). Specifically, it relates to the field of cord blood (CB) transplantation. It was put together by members of the Government and Global Affairs Committee of the Cord Blood Association (CBA), who represent 15 different countries, and was adopted by the Board of Directors of the CBA on January 29, 2019. This is a long-overdue set of guidelines for the international and national communities and offers criteria for quality management, consent and contract with the family for private banking, donor screening and testing, collection procedures for CB units, manufacturing effects, potency of units and release of the CB units for transplantation, shipping and transplantation, monitoring of outcomes, registry participation and the sharing of data, and laboratory testing. These are noteworthy guidelines that help clarify present needs. The guidelines will likely be modified in time, as this model is adopted and other criteria for use of this life-saving procedure are used throughout the world. It is not a surprise that these model guidelines have been provided by an international group of investigators. While the biology and science of CB hematopoietic stem (HSC) and progenitor (HPC) cells that led to the first and subsequent CB HCTs was a national effort [2], the actual clinical use of these CB units for CB HCT was an international affair [3] that has been followed by well over 40,000 CB transplants that have been used to treat a large variety of malignant and non-malignant disorders that were previously treated by bone marrow (BM) HCT and that are now are being treated also by CB, BM, and cytokine-induced mobilized peripheral blood (mPB) HCT.

CB HCT has advantages and disadvantages as a source of donor cells, compared with BM- and mPB-HCT, which have been highlighted in numerous review articles, including those on behalf of my institution [4–6]. At this point in time, it is crucial for the field of CB HCT to not only set international guidelines for the use of CB HSC and HPC for HCT, but to move forward with enhancing the efficacy of CB HSC and HPC for more favorable results. This encompasses consistently using single CB units for transplantation and substantially decreasing the time to neutrophil, platelet, and immune cell recovery, which is presently substantially slower than that for BM, and especially for mPB HCT even with very much improved clinical care of patients undergoing CB HCT [6]. Efforts in these directions include the collection of increased numbers of HSC for banked CB units, the expansion of CB HSC ex-vivo, and enhancing the homing efficiency of the CB HSC so that they efficiently reach the host BM microenvironment where they can be nurtured for survival, proliferation, self-renewal, and appropriate differentiation. All these efforts are ongoing by many groups nationally and internationally and have been noted in several of review articles [4–6]. However, a major concern for clinical improvements in the field of CB HCT, which needs serious addressing, is that most of these efforts have not yet been adapted for clinical trials to test their efficacy of action. It is imperative that a way be found, and soon, to bring many of these interesting procedures for testing in a clinical situation; some may be useful, while others may not translate efficiently for clinical advantage. These procedures need to be readily adaptable for CB HCT, which means that the simpler the procedure, the better. They must also be cost effective, without addition of very high additional costs, unless the additional costs can be justified in terms of short- and long-term clinical effectiveness [7].

Preclinical and clinical efforts by my group, with regard to experimental strategies to improve clinical CB HCT, are diagrammed in Figure 1. This includes the collection of increasing numbers of HSC in CB units through the collection and processing of the cells in a hypoxic atmosphere of 3% O_2, while the cells are never subjected to ambient air (~21% O_2) [8]. While this procedure routinely allows collection of two- to fivefold more phenotypically and functionally (engrafting) HSC than that seen with the routine collection of such cells in ambient air, it is clearly not feasible to adapt such collection/processing

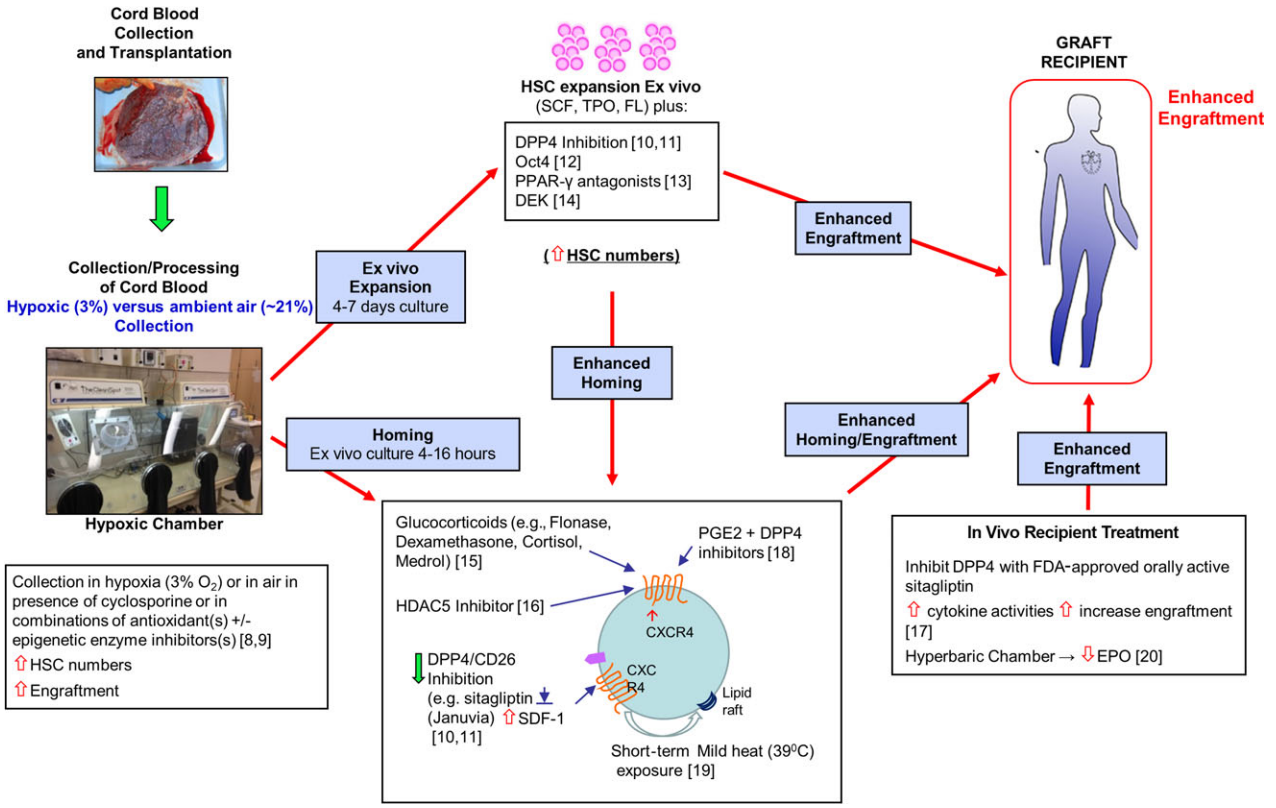

Figure 1. Recent strategies from the author's laboratory to improve cord blood (CB) hematopoietic cell transplantation. This includes isolating more HSCs through collection and processing of the cord blood in hypoxia (3% O_2), or in ambient air with cyclosporine A or with combinations of antioxidant(s) plus/minus epigenetic enzyme inhibitor(s), the ex vivo expansion of these cells by modulating DPP4, Oct4, PPAR-γ, or DEK in the context of stem cell factor, thrombopoietin, and Flt3-ligand, enhancing the homing efficiency of HSCs with short-term pretreatment of CB with glucocorticoids, inhibition of HDAC5, inhibition of DPP4, and PGE, along with inhibition of DPP4, exposure of CB cells to mild hyperthermia, or the in vivo treatment of recipients with sitagliptin, an orally active DPP4 inhibitor, or by subjection of the recipients to hyperbaric chamber exposure to reduce levels of erythropoietin. The references for each of the related publications are noted in brackets. The red arrows suggest possibilities for sequencing these procedures for possible enhanced CB engraftment. Abbreviations: DPP, dipeptidylpeptidase; EPO, erythropoietin; FDA, U.S. Food and Drug Administration; FL, Flt3-ligand; HDAC, histone deacetylase; HSC, hematopoietic stem cells; PG, prostaglandin; PPAR-γ, peroxisome proliferator-activated receptor-γ; SCT, stem cell factor; TPO, thrombopoietin.

methods for routine use. Hence efforts are being investigated to collect CB in ambient air but in the presence of cyclosporine A or combinations of antioxidant(s) plus/minus epigenetic enzyme inhibitor(s), which mimic to a degree the collection/processing of cells in hypoxia [8, 9]. There is also a means to increase numbers of already collected CB HSCs by expansion. In this context, we have looked at adding either inhibitors of dipeptidylpeptidase (DPP)4 [10, 11], enhancing expression of Oct4 [12], using antagonists of peroxisome proliferator-activated receptor (PPAR-γ) [13], or adding the heterochromatin remodeling nuclear protein DEK [14]. DEK acts in this effect through a cytokine-mediated CXCR2 chemokine receptor-signaling pathway, rather than through the remodeling of nuclear heterochromatin [14]. Ongoing efforts in this also include modulating CD166 expression [J. Zhang, C. Zhang, X. Huang et al., manuscript submitted for publication]. We have also investigated agents to enhance the homing capabilities of CB HSC. This includes the roles of glucocorticosteroids [15], inhibitors of histone deacetylase (HDAC) 5 [16], inhibitors of DPP4 in vitro [10, 11] and in vivo in patients using the FDA-approved orally active DPP4-inhibitor sitagliptin [17], combinations of a DPP4 inhibitor plus prostaglandin (PG)E [18], and short-term exposure of cells to mild heat (39°C) exposure [19]. Treatment of recipients undergoing CB HCT has also used hyperbaric chambers [20]. All of the above-described laboratory/clinical procedures, as well as those noted in my reviews [4–6], can be used alone to enhance preclinical/clinical CB HCT of human cells, but there is no reason that they cannot also be used in combination in sequence as noted in Figure 1, efforts currently ongoing in the laboratory, to see if such sequential combinations can more effectively enhance the efficacy of the CB cells for HCT than each single procedure. Regardless of the preclinical outcomes, it is crucial that a way be found to investigate these efforts for clinical translation. This is not an easy undertaking, because there are just so many transplant centers doing CB HCT, and most centers have their favorite efforts, which leaves little time or desire to pursue other areas. This will likely require international CB HCT collaborative efforts, such as that which helped start the field of CB HCT [3].

These additional efforts, if successful in a clinical setting, will no doubt require additional modifications to the suggested model criteria [1]. All in the field of lab-based scientific and clinical efforts for enhanced CB HCT look forward to these

clinical translations of ongoing lab and preclinical work and will gladly welcome further modifications to the present proposed guidelines, as necessary.

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Disclosures

The author indicated no potential conflicts of interest.

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