CELL & GENE THERAPY INSIGHTS

LATEST ADVANCES IN CORD BLOOD APPLICATIONS & COMMERCIALIZATION

SPOTLIGHT

EXPERT INSIGHT

The history of cord blood transplantation/biology & perspective for future efforts to enhance the field

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Cord blood hematopoietic stem and progenitor cells have been used successfully for hematopoietic cell transplantation to treat a variety of malignant and non-malignant disorders. Use of cord blood has advantages and disadvantages as a source of transplantable cells compared to that of bone marrow and mobilized peripheral blood. Most recently, haplo-identical transplants have been competing with cord blood as a source of transplanted cells. Efforts are ongoing to modulate cord blood and recipients of cord blood transplantation for more efficacious transplant outcomes, in part in order to overcome the slower time to neutrophil, platelet and immune cell recovery of these compared to the other sources of transplantable cells. This review briefly describes the history of cord blood biology and hematopoietic cell transplantation, efforts to collect more stem cells and to expand and better allow them to home to the bone marrow for more efficient and rapid engraftment. A personal perspective for future efforts in these areas is also provided.

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HISTORY

The origins of the field of cord blood (CB) hematopoietic cell transplantation (HCT) have been previously reviewed [1–3]. In short, it started with our work that determined that numbers of hematopoietic progenitor cells (HPCs) in single CB unit collections were within the range of those numbers of HPCs that were associated with successful bone marrow (BM) HCT, and that it was possible to successfully freeze/cryopreserve and then have high efficiency recovery of the frozen hematopoietic stem cells (HSCs)/HPCs [4]. We now know that these cells can be retrieved at high efficiency after more than 23 years [5]. This original work [4] led to the first proof-of-principle CB bank in the

author's laboratory that assessed the content of HPCs within CB units sent from a distant obstetrical unit, and then froze the cells for use for HLA-matched sibling CB transplants [6]. The scientific paper that led to the first CB transplant was a collaborative national effort [4], and the first CB transplant itself, performed in Paris, France, with cells collected in Durham, NC, and sent to our laboratory for assessment and freezing prior to hand-delivery to the Hopital St Louis in Paris, was an international collaborative effort [6]. The first recipient of the CB transplant in October 1988 in Paris is still alive and well. Cryopreserved CB units from the first CB bank in my laboratory were then used for the next four CB transplants in Paris (n = 2), Baltimore and Cincinnati, as well as two more of the next five transplants [7–9].

The field of CB HCT has come a long way since these initial laboratory research and clinical efforts in terms of the transplants themselves [1,2] and our much-improved understanding of the biology of HSCs and HPCs and their regulation [10–12]. CB HCTs went from HLA-matched sibling transplants to partially matched related, and then to HLA-matched or partially HLA-disparate unrelated CB transplants. There have been more than 40,000 CB HCTs performed since our initial efforts, which have now treated a large variety of malignant and non-malignant disorders [1,2,13,14]. While there are many advantages to use of CB, versus either BM- or mobilized peripheral blood for transplantation, including ready availability of the units and lower levels of acute graft-versus-host disease, there are concerning disadvantages to the use of CB that have limited its use. These include slower time to neutrophil, platelet and immune cell recovery. Because of the low numbers of HSCs and HPCs in single collections of CB, clinical efforts moved to use of double CB unit transplants, which helped move the field to greater use of CB HCT for adults [15–17]. Double CB HCT was also utilized for children although there is currently no evidence to date that the time to engraftment is any faster with double compared to single CB HCTs for either adults or children [15–19]. Haploidentical (haplo) transplants [20–23] have recently competed with CB as a source of transplantable cells for HCT. The engraftment of haplo-transplants is more rapid than CB, and the use of haplo HCT may have an up-front economic advantage, regarding less monetary cost. However, the relapse rates after haplo transplants may be higher than with CB HCT, so it remains to be determined how in actuality haplo-HCT compares to that of CB HCT in terms of overall patient benefit, including relapse and survival rates of the patients, and the long-term costs of the transplant for society. Some investigators have begun using haplo-transplants in combination with a CB unit in order to elicit a more rapid up-front engraftment using haplo cells, with the longer-term engraftment apparently being mediated from the CB unit [24,25]. This combination of both a haplo and a CB unit for HCT has interesting possibilities, but it may be that scientific advances in the near future will obviate the need for this combination cell therapy, perhaps resulting in a single unit CB HCT eventually becoming the cell type of choice for all HCTs for a number of reasons, including economical ones. Efforts to counter the disadvantages of single unit CB HCT are currently

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underway in a number of research laboratories, and these efforts are covered in this review, along with a perspective on future efforts.

LABORATORY & CLINICAL EFFORTS TO ENHANCE CB HCT

The goals are to collect more highly potent HCSs and HPCs in single CB units, to effectively expand the collected cells and/or to enhance the homing efficiency of these cells so that they more efficiently travel to BM microenvironment niches, where they must reach for nurturing of the engrafted cells for both rapid and sustained long-term engraftment. Once in the BM, stromal-cell– and cytokine/chemokine–HSC/HPC interactions influence the self-renewal, survival, proliferation and differentiation capacities of the HSCs and HPCs [10–12]. Ultimately what is needed is the most efficient and cost-effective means to enhance single unit CB HCT. At best, this will entail the simplest procedures that can be carried out at any, and not just at selected, CB collection and transplant centers.

ENHANCING CB HSC COLLECTIONS

Most transplant centers request the largest CB collection available in CB banks for the closest donor HLA match to the recipient. It is left up to the staff where the CB collections are made to maximize the volume of CB collected. Recently, the American College of Obstetricians and Gynecologists released a position statement on delayed CB clamping that recommended an interval of 30–60 seconds after delivery of healthy term babies (see Cord Blood Association website), which means that a lesser volume of CB will be collected, which in turn means that fewer HSCs and HPCs will be present in the collected CB units. However, there are still ways to enhance the collection of HSCs even if clamping is delayed. One way that was tried in the laboratory previously is to perfuse the CB once the cord is separated from the body. This does result in collections of increased volumes of CB with increased numbers of HSCs and HPCs [26]. However, this is a cumbersome procedure that is not likely to find widespread use in collection centers, and has not been used for units stored in either unrelated or family (private) CB banks. Another more recent innovation from the author's laboratory that has resulted in obtaining 2–5-fold more HSCs/unit of CB collected is the collection and processing of cells in hypoxic (e.g., 3%) O_2 tensions [27,28], which is more closely related to the oxygen tension of the cells within the body (with O_2 tensions in the bone marrow being in the range of 1 and 5%, and CB being less than 10%, compared to collections of cells in ambient air of ~21%). This hypoxic collection/processing of the cells prevents the ambient air induced loss of HSCs through a phenomenon we termed extra physiological oxygen shock/stress (EPHOSS), which causes the very rapid differentiation, rather than cell death, of a large proportion of HSCs in the CB upon short-term exposure to ambient air [27]. Thus, CB collected and processed in ambient air has fewer HSCs and more HPCs, and the HPCs are in rapid cell cycle. By contrast, CB collected/

processed in 3% O_2 have more HSCs, but fewer HPCs, and these HPCs are in a slow or non-cycling state. EPHOSS is mediated through an intracellular networking axis that involves at the least tumor suppressor p53, the mitochondrial permeability transition pore (MPTP) and cyclophilin D, with hypoxia inducing factor (HIF)-1α, and the hypoxamir, miR210 playing a role. Upon sensing ambient air O_2 levels, the MPTP in cells open up with resultant release of reactive oxygen species (ROS), which induce HSCs to differentiate into HPCs. While countering EPHOSS by the hypoxic collection/processing could obviate problems with limiting HSC numbers in single CB collections, it is not a procedure that lends itself to routine use at CB collection centers. In alternative efforts to block EPHOSS induced differentiation, we found that if CB is collected/processed in air but in the continued presence of cyclosporine A (CsA), which maintains the MPTP in a closed position and reduces release of ROS from the mitochondria, one can collect more HSCs [27]. CsA would certainly be easier to use at CB collection centers since this obviates the need for collection of cells in an hypoxic chamber, but such procedures are not without problems. CsA is not easy to use, the best concentrations of CsA to use for each procedure needs to be worked out, and may vary with the lot of CsA obtained. Also, CsA is toxic to cells upon prolonged exposure, so it is clear that other means are needed to prevent EPHOSS [27,28]. We are currently working on such other procedures, including the evaluation of small molecule inhibitors of epigenetics and autophagy/mitophagy, amongst a number of other means alone or in combination.

EX VIVO EXPANSION OF CB HSCS & HPCS

Efforts to *ex vivo* expand numbers of HSCs and HPCs have been ongoing for more than 30 years, and most recently a number of small molecules have been used to *ex vivo* expand these cells in CB. SR1 has been effectively used in the laboratory [29], and has shown promise for clinical translation [30]. UM171, is a small molecule that in laboratory studies appears more potent than SR1 [31]. Clinical trials with UM171 are ongoing, with clinical efficacy yet to be reported. Both SR1 and UM171 are not by themselves effective, but require addition of selected cytokines for their potent *ex vivo* expansion effects [29–31]. Clinical studies have been reported using Notch Ligand [32] and nicotinamide induced *ex vivo* expansion of CB [33]. The known mechanisms for these procedures have been elucidated in the individual papers, but it is clear that complete mechanistic insight into how these agents work is yet to be fully elucidated. Greater insight into how facets of HSC/HPC self-renewal, proliferation, survival and differentiation are mediated will no doubt provide added efficacy for these procedures. Other pre-clinical studies have also evaluated *ex vivo* expansion methods [34–36]. It remains to be determined which procedures will eventually be used on a larger scale, and if in fact such procedures will be cost effective, as they clearly will add costs to CB HCT, which already include the cost of the CB units themselves and the transplantation procedure. Our lab has also worked on means to expand CB HSCs and HPCs using Oct4 activators [37] or cytokines plus inhibition of the enzyme Dipeptidylpeptidase

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(DPP) 4 [38], with additional efforts in progress, including modulating glucose metabolism. Whether or not *ex vivo* expansion will eventually be used as a routine effort is currently not clear. It most likely will be performed in selected laboratories and by companies. Regardless, we will clearly learn much about how HSCs and HPCs are regulated, with the possibility that this information can in the future be used efficaciously to modulate the production and differentiation of these cells *in vivo* for quicker and more sustained engraftment of neutrophils, platelets and immune cells. It may actually be that the future of enhancing the efficacy of CB HCT lies in the *in vivo*, rather than *ex vivo*, expansion and subsequent differentiation of the engrafted cells and this is an area of research that requires intense investigation.

ENHANCING THE HOMING CAPACITIES OF HSCS

It may be that either or both of the enhanced collection of HSCs by blocking EPHOSS, or *ex vivo* expansion of these HSCs and HPCs can be made more effective for CB HCT by modulating the capacity of these donor cells to better home to the BM once they are injected into the recipients. There have been a number of efforts to enhance the homing capabilities of HSCs. These include: short term *ex vivo* enforced fucosylation of the cells [39–41], prostaglandin (PG) E pretreatment [42–44], inhibition of the enzyme DPP4 with small molecule inhibitors [38,45] or hyperthermia [46]. Perhaps using combinations of these pretreatment procedures may even further enhance the homing efficiency of *ex vivo* treated cells prior to their intravenous infusion.

CXCR4 is a receptor that binds and responds to the chemokine, stromal cell derived factor (SDF)-1/CXCL12. The SDF-1/CXCL12-CXCR4 axis has been implicated in chemotaxis, migration, survival and homing of HSCs, HPCs and other cell types [47]. DPP4 is found within many cell types and is present on the cell surface as CD26 [48]. It is also found in serum and plasma, and can truncate SDF-1/CXCL12 by removing the first two N-terminal amino acids where the second amino acid is usually an alanine or a proline. DPP4 truncated SDF-1/CXCL12 is much less active as a chemotactic and survival factor than its own full length form, and the truncated form blocks the activity of the full length chemokine [38,45,48]. Inhibiting DPP4 with small molecules such as the tripeptide Diprotin A (ILE-PRO-ILE), or sitagliptin (which is a DPP4 inhibitor used to treat Type 2 diabetes), enhances the activity of SDF-1/CXCL12 as well as other proteins (such as granulocyte macrophage [GM] colony stimulating factor [CSF], G-CSF, interleukin [IL]-3, and erythropoietin [EPO], which are amongst a large number of biologically active proteins that have DPP4 truncation sites) [49,50]. Deletion of the *dpp4* gene or inhibiting *dpp4* activity accelerates recovery of hematopoiesis in mice from stresses such as sub-lethal doses of radiation or chemotherapeutic drugs [38]. Moreover, treating end-stage patients with leukemic or lymphoma with short term administration of orally active sitagliptin once a day for 4 days starting 1 day before administration of the CB graft has accelerated time

to neutrophil engraftment after single unit CB HCT to a median of 21 days [51,52], and more recent clinical studies adjusting the sitagliptin administration to twice a day for 4 days has significantly shortened the time to neutrophil engraftment to a median of about 19 days [Farag and Broxmeyer, submitted for publication]. Another means to enhance engraftment is to place the recipients in a hyperbaric chamber prior to CB infusion in order to decrease O_2, as EPO has a negative effect on the chemotaxis and homing of HSCs and HPCs [53]. We recently found that a screen of small-molecule compounds identified glucocorticoid (GC) hormone signaling as an activator of the expresson of the chemokine receptor CXCR4 in human CB HSCs and HPCs, short-term pretreatment of these cells with GSs (Dexamethasone, Flonase, cortisol, Medrol) promoted the SDF-1/CXCL12-axis mediated chemotaxis, homing, and long-term engraftment when CB $CD34^+$ cells were transplanted into primary- and secondary-sublethally irradiated NSG immune-deficient mice. Mechanistically, the activated glucocorticoid receptor binds directly to a glucocorticoid response element in the CXCR4 promoter and recruits the SRC-1-p300 complex to promote H4K5 and H4K16 histone acetylation, thereby facilitating transcription of CXCR4 [54].

FUTURE PERSPECTIVES FOR CB HCT

It is clear that if the field of CB HCT is to be sustained, and more importantly to progress, additional laboratory and clinical efforts are needed. The laboratory and clinical investigators must work together to make enhancement of CB HCT a reality. This is a very important goal that can be realized, but this author is convinced that whatever is done in order to sustain the field should be simple and cost effective. I envision a time in the near future when higher numbers of more potent HSCs will be able to be routinely collected through blocking EPHOSS or other like efforts, for example collecting cells in ambient air with DPP4 inhibition also results in EPHOSS-like protective effects with enhanced numbers of HSCs [38], but through a different mechanism than we reported for EPHOSS protection [Unpublished observations]. The potency of the cells can be assessed by limiting dilution of cells in colony assays *in vitro* or engraftment *in vivo* into sub-lethally irradiated immune deficient mice [27], and perhaps by chemical potency assays [55]. The cells will perhaps be expanded, although *ex vivo* expansion may not be needed if the collections contain enough increased HSCs. These cells could then be either pretreated for a few hours *ex vivo* to enhance their engraftment (by fucosylation, PGE, DPP4 inhibition, hyperthermia glucocorticoid stimulation, or combinations of these short-term treatments) and then infused into recipients who may be additionally pretreated to enhance self-renewal and/or differentiation of the infused cells (e.g., by DPP4 inhibition and/or by preconditioning in a hyperbaric chamber). Animal models have already shown that a combination of PGE pretreatment of cells followed by injection of these cells into hosts treated with sitagliptin (a DPP4 inhibitor) results in improved engraftment above that of either procedure itself [56]. So there is already experimental

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precedence for at least one possibly easily used combination procedure. Table 1 provides the various strategies that can be considered for enhancement of CB HCT beyond that of the usual currently used method of collection/processing in air without further manipulations. Any one, or combinations, of the procedures shown should allow for enhanced CB HCT. It is likely that simple and uncomplicated procedures that can be performed most cost effectively in many, not just selected, collection and transplant centers will have the most sustained beneficial effects on enhancing the efficacy of CB HCT. It is only with efforts such as these, or newer efforts to be determined, that the field of CB HCT will continue to move forward. It is up to laboratory and clinical investigators working together to make this envisioned future a reality.

FINANCIAL & COMPETING INTERESTS DISCLOSURE

Hal E Broxmeyer is on the Medical Scientific Advisory Board of Cord:Use, a cord blood banking company. No writing assistance was utilized in the production of this manuscript.

TABLE 1

Strategies for enhancing HSC in cord blood via collection/processing/*ex vivo* manipulations/homing/engraftment.

***Ex vivo* expansion of donor cells** With cytokines plus SRI, UM171 or other small molecules	**Enhance homing of donor cells** Pre-treat donor cells ex vivo with: DPP4 inhibitor, PGE, fucosylation, hyperthermia and/or glucocorticoid stimulation	**Engraftment: Enhance homing in recipient** Pre-condition recipient with: DPP4 inhibitor or hyperbaric O_2
Usual/standard method in ambient air (normoxia)* induces EPHOSS, ROS production or other mechanism, differentiation (more HPCs, fewer HSCs)		
X*	X*	X*
✓	X	X
X	✓	X
X	X	✓
✓	✓	X
✓	X	✓
X	✓	✓
✓	✓	✓
New method in hypoxia (e.g., 3% O_2) or in air with CsA or other EPHOSS protective agents blocks EPHOSS, ROS production or other mechanism, differentiation (more HSCs, fewer HPCs)		
X	X	X
✓	X	X
X	✓	X
X	X	✓
✓	✓	X
✓	X	✓
X	✓	✓
✓	✓	✓

*This is current procedure used routinely by most collection and transplant centers where cells are collected under normoxia (~21%) O_2 and used without further manipulation of cells or treating the recipient. Shown going from left to right for each column are the efforts to be done, alone or in combination.

✓: To be done; X: Not done.

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