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Cord blood hematopoietic stem cell transplantation

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ABSTRACT: Umbilical cord blood (CB) is a clinically useful source of hematopoietic stem (HSC) and progenitor (HPC) cells for treatment of a wide variety of malignant and non-malignant disorders. Amongst the benefits of CB, compared to bone marrow (BM) and mobilized peripheral blood (MPB), as a source of engrafting HSC and HPC are its ready availability through CB banks, and a relatively low level of graft vs. host disease (GVHD) elicited after transplantation. Disadvantages of CB, compared to BM and MPB, include the low, and sometimes limiting, number of cells collected in single donor units which can be less than optimal for engraftment of many adults and higher weight children, and the relatively slower speed to engraftment of neutrophils and platelets. While limiting numbers of nucleated cells found in single units of CB can be compensated for by transplantation of more than 1 unit of CB, this use of multiple cord blood units may be associated with increased GVHD, and has not meaningfully reduced the time to neutrophil and platelet engraftment. Thus, means to enhance numbers and/or potency of collected cells and their engrafting capability through ex-vivo and/or in-vivo maneuvers would likely enhance the efficacy and applicability of CB transplantation. Such efforts require a deeper understanding of the cell biology of HSC and HPC, the microenvironment that nurtures these cells, and greater mechanistic insight into cell surface receptors and intracellular signaling pathways regulating HSC/HPC function. This information could provide the means to modulate these cells for greater clinical advantage. There is also the potential, as yet far from proven in a clinical sense for use of mature cells generated from HSC/HPC, and for non-HSC/HPC uses of CB. Non-HSC/HPC include mesenchymal stem/stromal cells (MSC), endothelial progenitor cells (EPC), and induced pluripotent stem cells (iPSC). Caution is clearly required for non HSC/HPC stem/progenitor cell uses of CB, based on insufficient biological and preclinical information for MSC, EPC, and iPSC. This review addresses current knowledge and potential future means to enhance the quantity, quality and/or engrafting activity of CB HSC/HPC, and where the field stands in context of MSC, EPC, and iPSC from CB.

Introduction

Cord blood banking and transplantation

There have now been over 20,000 cord blood (CB) transplants done to treat the same variety of malignant and non-malignant disorders treated by bone marrow (BM) transplantation (Broxmeyer and Smith, 2009; Broxmeyer, 2010b). Within the malignant disorders, this includes acute and chronic myeloid and lymphoid leukemias, myelodysplastic syndromes (Broxmeyer and Smith, 2009; Hough and Rocha, 2010), and a variety of solid tumors, amongst other malignancies. Non-malignant disorders treated with CB include, but have not been limited to bone marrow failures, hemoglobinopathies (MacMillan *et al.*, 2010), metabolic disorders (Prasad and Kurtzberg, 2010), leukodystrophies (Orchard and Tolar, 2010),

and primary immunodeficiencies (Smith *et al*., 2010). Essentially all malignant and non-malignant disorders treated with BM transplantation have now been treated with CB transplantation. The year 2008 was the 20th Anniversary of the first CB transplant (Broxmeyer and Smith, 2009; Broxmeyer, 2010a). The recipient of the first CB transplant was a young boy with Fanconi Anemia who received HLA-matched CB from his sister (Gluckman *et al*., 1989); he is currently healthy and cured of the hematological manifestations of Fanconi Anemia. This first transplant (Gluckman *et al*., 1989), and subsequent CB transplants (Broxmeyer and Smith, 2009) were made possible by the biological laboratory studies that suggested CB as a potential source of transplantable hematopoietic stem (HSC) and progenitor (HPC) cells (Broxmeyer *et al*., 1989). The background to these studies and their references can be found in Broxmeyer and Smith, 2009. CB has been used in HLA-matched and- partially HLA-matched sibling, as well as related and unrelated HLA-matched and- partially HLA-matched allogeneic settings. There are more than 450,000 HLA-defined CB collections stored frozen in cryopreserved form in more than 50 CB banks and more than 2,000 CB transplants are being performed world-wide per year (Rocha and Broxmeyer, 2010). The banking of CB for related and unrelated transplantation through Public or Family/Private Banks are possible because of the ability to cryopreserve CB HSC and HPC long-term.

Cryopreservation of CB hematopoietic stem and progenitor cells

Cord blood was originally frozen and transplanted after defrost as totally unseparated cells, which included all nucleated cells and lysates from non-nucleated erythrocytes, without washing to ensure that all HSC/HPC collected were infused into the recipient (Broxmeyer *et al*., 1989; Gluckman *et al*., 1989). Now CB is minimally separated as nucleated cells, or mononuclear cells and washed before infusion. It is extremely rare that more sophisticated separations are used.

Our laboratory has the longest experience with storing CB long-term with efficient recovery of functional HSC and HPC, as determined by assessment of these cells post-thaw in comparison to pre-freeze numbers from the same donor. Our last publication reported efficient recovery after 15 years storage (Broxmeyer *et al*., 2003), but more recent work has demonstrated such efficient recovery after 24 plus years (Broxmeyer, unpublished observations, April 2010). This recovery was assessed by colony assay in vitro for granulocyte macrophage (CFU-GM), erythroid (BFU-E), and multipotential (CFU-GEMM) progenitors and in vivo for SCID Repopulating cells (SRC). SRC are cells that engraft sublethally irradiated mice with Non-Obese Diabetic-Severe Combined Immunodeficiency (NOD-SCID). We have found that $CD34^+$ cells isolated from frozen CB stored frozen for over 20 years can repopulate BM and blood of IL-2 receptor gamma chain null NOD-SCID (NSG) mice for over 6 months and that the human cells removed from BM from these human CB cell engrafted mice can repopulate the BM and blood of secondary irradiated NGS mice. This demonstrates that the cryopreserved CB contained HSC with long-term repopulating (as assessed in primary mice) and self-renewal capacity (as assessed in secondary mice).

Advantages and disadvantages of CB as a source of HSC and HPC

Since our original clinical paper (Gluckman *et al*., 1989), there have been a number of reports documenting the efficacy of CB transplantation for treatment of children and adults (Reviewed in: Broxmeyer and Smith, 2009; Broxmeyer, 2010b; Rocha and Broxmeyer, 2010). The advantages of CB for HSC transplantation include, but are not necessarily limited to ease and rapid accessibility, an important consideration when a donor source of HSC is needed quickly, and the now well-documented lesser elicitation of acute and chronic graft vs. host disease (GVHD) when CB is used, compared for example to BM. While these advantages are noteworthy and a reason for the more than 20,000 CB transplants performed to date, there are noted disadvantages with CB as a source of transplantable HSC. These include the limiting numbers of cells collected in units of CB from a single donor, and the longer time to engraftment of neutrophils and platelets compared to BM or mobilized peripheral blood (mPB) (Rocha *et al*., 2000; 2001; 2004; Laughlin *et al*., 2004; Eapen *et al*., 2007; and reviewed in Broxmeyer

and Smith, 2009; and Rocha and Broxmeyer, 2010). The former disadvantage means that one cannot always get enough cells from a single CB donor to be able to successfully engraft an adult or high weight child. While a CB unit with a nucleated cell count less than 23 million per kgbwt of the recipient has successfully engrafted adults, the success rate is less than what physicians are comfortable with, and greater than 23 million nucleated cells per kgbwt is usually used for transplantation. However, even with this dose of CB cells, the time to neutrophil and platelet engraftment is slow, meaning a potentially longer hospital stay.

Enhancing the effectiveness of CB for transplantation

There are a number of means currently being investigated in the clinic to compensate for the limiting numbers of HSC and HPC in single collections of CB. Some of these have been reviewed (Rocha and Broxmeyer, 2010; Kelly *et al*., 2010; and Brunstein and Laughlin, 2010). The most successful to date is the use of more than one CB, usually 2 CBs, for transplantation (Barker *et al*., 2005; Brunstein *et al*., 2007; Ballen *et al*., 2007). The use of more than one CB has resulted in many more CB transplants to treat adults, and this has been an important advance in the field of CB transplantation.

However, of two or more CBs transplanted into one recipient it is usual for only one of those multiple CBs infused in the patient to be present in the patient after a month or two (Barker *et al*., 2005; Brunstein *et al*., 2007; Ballen *et al*., 2007). The ultimately engrafting CB unit can still not be predetermined, and it is not clear why only one unit usually "wins out", although it has been suggested that CB units with a low viability of $CD34^+$ cells within the total population of relatively unseparated cells have low probability of engraftment after double CB unit transplantation (Scaradavou *et al*., 2010). The disadvantages of using multiple CB units for transplantation is that this seems to be associated with increased GVHD (MacMillan *et al*., 2009), and one of the advantages of CB using a single unit is the lowered GVHD. Also, the use of multiple CB units does not appear to have significantly accelerated the time to engraftment of CB cells. A pre-engraftment syndrome, not associated with GVHD, has been noted after double CB unit transplantation, but this condition responds promptly to short-term use of corticosteroids (Patel *et al*., 2010). It is also not clear that the use of double CB units is more efficacious than single CB unit transplantation. It may be that with two CB units, one has double the chance to be infusing a more potent unit. CB units are purchased from Public banks. Use of multiple units entail a substantially increased cost compared to the use of one CB unit. In the meantime, it is important to better understand the biology and functional capabilities of human HSCs and HPCs, to be able to modulate these cells, especially those in CB, for enhanced clinical efficacy.

HSCs and HPCs and means to enhance their efficiency of engraftment

Characterization of human HSCs and HPCs

Most of what we know about the phenotype and functional capacity of HSCs and HPCs comes from mouse studies. The most rigorous assay for mouse HSCs is their functional capability to engraft and repopulate the blood cell system of mice receiving what would have been a lethal dose of radiation. In the mouse system there is a very good correlation between specific phenotype and functional activity for HSC, as well as for the different phenotyped HPCs including: common myeloid progenitor (CMP; most akin to a CFU-GEMM), common lymphoid progenitor (CLP), granulocyte macrophage progenitor (GMP; probably equivalent or close to that of a CFU-GM), and a myeloid erythroid progenitor (MEP) (Weissman and Shizuru, 2008). It should be noted that phenotype does not always recapitulate function, especially when cells have been manipulated ex-vivo prior to phenotyping. Also, the phenotypes for human HSC are not as rigorously identified as those for mouse HSC. The mouse NOD-SCID assay is used for functional detection of human HSC via the SRC which involves a xenogeneic transplant setting (human cells into sublethally irradiated mice). Regardless, efforts to better define human HSC and HPC phenotypically are ongoing (Weissman and Shizuru, 2008; Majeti *et al*., 2007). Phenotype is very helpful,

but I myself still prefer a functional assessment of HSCs and HPCs, where possible. Phenotype alone may not present the full functional range of activities of the HSC or HPC. Currently, CB HSCs are phenotypically characterized as being $CD34^+CD38^-CD90^+CD45RA^-$ and mature cell $lineage^-$, while candidate human multipotential progenitors are categorized as being $CD34^+CD38^-CD90^-CD45RA^-$ and $lineage^-$ (Majeti *et al*., 2007). There are a number of intracellular molecules that have been linked to functional activities of HSCs and HPCs (Shaheen and Broxmeyer, 2009), including cell survival, self-renewal, proliferation, differentiation, and migration (homing, mobilization, and chemotaxis (directed cell movement)). These intracellular molecules include, but are not limited to $p21^{cip1/waf1}$, $p27^{kip1}$, Stat3, Stat5, Notch, Wnt, β-catenin, GSK-3, sonic hedgehog, bone morphogenic protein, members of the Hox family (such as Hoxb4), FoxO, Pu.1, GATA-1, Sirt1 (and other members of the sirtuin family of deacetylases), HIF-1α, Rheb2, and the rapamycin sensitive m-TOR pathway (reviewed in Shaheen and Broxmeyer, 2009). In addition, a better understanding of the role mitochondria may play in HSC/HPC function could be useful. We don't yet know how to best and most efficiently manipulate these intracellular signaling molecules and their networks for enhancement of expansion, homing and engraftment, but such knowledge would enhance the capacity for limiting numbers of CB HSCs and HPCs to be expanded ex-vivo and/or in vivo, and for more efficient homing. Mouse HSCs have recently been characterized at a single cell level for transcriptional factors (Yashiro *et al*., 2009), cell division (Wu *et al*., 2007), spatio-temporal dynamics of cell cycle progression (Sakaue-Sawano *et al*., 2008), and telomere length analysis (Hills *et al*., 2009). Advances in analysis of single defined human cells, with direct correlations to functional activity will enhance our ability to better utilize CB HSCs.

Microenvironment for HSCs and HPCs

Within the body, HSCs and HPCs are nurtured for survival, self-renewal, proliferation, and differentiation in specified niches within the BM that are still not well-defined or- understood, but that are becoming better recognized (Kiel and Morrison, 2008). The microenvironment is composed of an interacting network of stromal cells, mesenchymal stem/stromal cells (MSC), endothelial cells, and endothelial progenitor cells (EPC), fibroblasts, and certain blood cell types. More in-depth knowledge of HSCs, HPCs, the environmental niche that nurture these cells at single cell-cell interactions and the cross-feeding interaction that likely moves in both directions (niche to HSC/HPC, and HSC/HPC to niche) are key to better manipulating the HSC engrafting process (Broxmeyer 2006). The chemokine-chemokine receptor interaction of stromal cell derived factor-1 (SDF-1/CXCL12) and its receptor, CXCR4 are important for chemotaxis, homing, mobilization, and survival of HSC and HPCs (Dar *et al*., 2006; Spiegel *et al*., 2008; Shaheen and Broxmeyer, 2009). Recent studies have reported that HSCs depend on Gα-mediated signaling to engraft BM (Adams *et al*., 2009), Transforming Growth Factor-β (TGF-β) (Basu and Broxmeyer, 2005), as well as the intracellular protein phosphatase (PP) 2A which is involved in SDF-1/CXCL12 actions on human CB $CD34^+$ HPC and SRC (Basu *et al*., 2007). TGF-β (Qian *et al*., 2007; Yamazaki *et al*., 2009, and references cited within these papers) and Thrombopoietin and its receptor, MPL (Yoshihara *et al*., 2007) have been identified as candidate BM signaling molecules in the niche that induce HSCs to decrease cell cycle progression and remain in a quiescent state. Nf2/Merlin is reported to regulate HSC function by effects on the architecture of the microenvironment (Larsson *et al*., 2008).

Expansion of CB HSCs and HPCs

Investigators have been trying to ex-vivo expand human HSCs for years, but have not yet succeeded in a clinically meaningful way, even though this was accomplished decades ago for mouse HSCs, and mouse and human HPCs (Broxmeyer, 2010a). The better such approaches include combinations of the cytokines Stem Cell Factor (SCF), Thrombopoietin (TPO) and Flt3 ligand (FL), collectively abbreviated STF, with various cytokines or cells added to this combination. However, a recent publication on Notch-mediated expansion of CB HPCs capable of rapid myeloid reconstitution (Delaney *et al*., 2010), may if

reproduced by others be a means to ex-vivo expand cells in a clinically useful manner. We recently demonstrated that the addition of SDF-1/CXCL12 to the STF combination doubles the output of CB HPCs (Broxmeyer *et al*., 2009). Whether or not this SDF-1-STF combination acts to expand HSCs ex-vivo remains to be determined. Expansion of human HSCs ex-vivo and/or in-vivo remains a fertile, if not yet realistically accomplished, area of investigation.

Efforts at enhanced homing and engraftment of CB HSCs

CD26/Dipeptidylpeptidase IV (DPPIV) Inhibition

CD26/DPPIV, SDF-1/CXCL12, and one of the SDF-1/CXCL12 receptors, CXCR4, are involved in HSC/HPC chemotaxis and homing (reviewed in Shaheen and Broxmeyer, 2009). We recently demonstrated that the cell surface protein CD26, which is a DPPIV with functional peptidase activity truncates SDF-1/CXCL12 into a molecule which no longer has chemotactic activity, but which can block full length SDF-1/CXCL12 induction of human CB CD34 cell chemotaxis (Christopherson *et al*., 2002), effects prevented by inhibition of CD26/DPPIV activity with small peptides such as Diprotin A (ILE-PRO-ILE) or the dipeptide VAL-PYR, or by deletion of CD26 in CD26 -/- mice (Christopherson *et al*., 2004). Importantly, inhibition or deletion of CD26/DPPIV in mouse BM HSCs greatly enhanced the homing and engrafting capability of limiting numbers of long-term marrow, competitive repopulating and self-renewing mouse HSCs into lethally irradiated primary and secondary mice (Christopherson *et al*., 2004), effects confirmed and extended by others using mouse BM cells (Tian *et al*., 2006; Peranteau *et al*., 2006; Wyss *et al*., 2009). We (Campbell *et al*., 2007) and others (Christopherson *et al*., 2007) demonstrated that peptide inhibition of CD26/DPPIV also enhanced engraftment of limiting numbers of CB $CD34^+$ cells into NOD-SCID mice, while others (Kawai *et al*., 2007) demonstrated the same effect with granulocyte-colony stimulating factor (G-CSF) mPB. Treatment of donor cells (Campbell *et al*., 2007; Christopherson *et al*., 2007) or of recipient mice (Kawai *et al*., 2007; Broxmeyer *et al*., 2007) enhanced engraftment. A clinical trial at the Indiana University School of Medicine is currently evaluating CD26/DPPIV inhibition for enhancement of the engrafting capability of CB cells in a clinical setting under the direction of Sherif Farag, MD.

Fucosylation of CB cells

Another means to enhance engraftment of adult human $CD34^+$ cells into NOD-SCID mice takes advantage of the noted roles of P-selectin and E-selectin that are expressed on endothelial cells (Xia *et al*., 2004). It was determined that surface fucosylation of human CB $CD34^+$ cells increased the binding of these cells to P- and E- selectin, and in the process enhanced engraftment of these cells in BM of NOD-SCID mice. This entailed treatment of $CD34^+$ cells with guanosine diphosphate fucose and exogenous α1–3 fucosyltransferase VI. This method of enhancing CB engraftment is under preclinical and clinical assessment at the MD Anderson Tumor Hospital in Houston, TX under the direction of Dr. E.J. Shpall.

Prostaglandin E_2 enhancement of homing and engraftment of HSCs

Prostaglandin E_2 (PGE_2) is a multifunctional eicosanoid that was first shown to suppress proliferation in-vitro and in-vivo of HPCs, especially that of macrophage progenitors (Pelus *et al*., 1979; 1981; Gentile *et al*., 1983). It also enhanced proliferation of BFU-E (Lu *et al*., 1984; 1987), and had enhancing activity on a subset of HSC, that was more closely associated with HPC, the colony forming unit-spleen (CFU-S) (Feher and Gidali, 1974). Studies by Pelus *et al*., (1982) suggested indirectly that PGE might also be acting on a cell giving rise to an HPC, perhaps an HSC. Most recently, it has been shown that PGE_2 enhances the engrafting capabilities of HSCs (North *et al*., 2007) and that this reflects both increases in homing and self-renewal events of HSCs (Hoggatt *et al*., 2009).

Since the mechanisms of action of the above HSC engrafting methods are likely different, it is possible that they may work in additive to synergistic ways, to greatly enhance homing and engraftment of limiting numbers of HSCs, effects that would potentially be of relevance to enhancing the engrafting capability of CB for clinical transplantation. As other means become available to enhance homing and/or in-vivo repopulation of HSCs, we may eventually be able to use single CBs routinely for engraftment of adults who require HSC transplantation for treatment and cure of malignant and non-malignant disorders. There may even come a time when CB from one donor will be used to treat more than one recipient.

Other means to enhance engraftment

There are a number of other ways to enhance engraftment of CB cells. These include: increasing the collection of CB cells at birth, perhaps by perfusing the placental vessels (Broxmeyer *et al.*, 2009; Rocha and Broxmeyer, 2010). It is also possible that now that the placenta itself has been identified as a source of HSCs and HPCs (Alvarez-Silva *et al.*, 2003; Gekas *et al.*, 2005; Ottersbach and Dzierzak, 2005; Mikkola *et al.*, 2005; Rhodes *et al.*, 2008; Robin *et al.*, 2009; Kieusseian and Cumano, 2008; and Yoshimoto and Yoder, 2009) that one can, in addition to collection of extra cells from the cord by perfusion, also collect cells directly from the placenta. These collection possibilities entail logistical problems that are not insignificant, and one must be careful and certain not to collect maternal cells along with the cord and placental cells, as this could result in enhanced, and potentially life-threatening GVHD. It is likely that such maneuvers will have to be done in selected centers set up for such collections.

Additional means to enhance CB transplantation entail direct administration of the cells to the BM, perhaps by-passing the homing problem, or the addition of other cell types with CB cells, such as MSC as a co-infusion (Rocha and Broxmeyer, 2010). Such efforts are also not without potential complicating effects.

Which of the above mentioned means in section 2.3 will prove to be a clinical value, and which may be most efficacious when used in combination, remain to be determined. These areas are clearly worthy of further laboratory and in-vivo preclinical evaluation.

Other potential uses for CB

Generation of mature blood cells

There is always a need in transfusion medicine for large quantities of mature blood cell types, especially those such as erythrocytes or platelets that are not easily stored ex-vivo for prolonged periods of time. In fact, DARPA, a government agency interested in innovative methods to protect troops in a battlefield setting issued an announcement a few years ago for continued production of type O red blood cells in a small apparatus that can be used near an active military engagement. In this context, it is of interest that a number of groups have reported efforts to produce red blood cells from a number of different stem/progenitor cell types, including $CD34^+$ CB cells (Neildez-Nguyen *et al.*, 2002; Giarratana *et al.*, 2005; Fujimi *et al.*, 2008; Vlaski *et al.*, 2009). A reasonable question for these studies is whether or not one can generate enough such erythrocytes to make the effort worthwhile, and can this be done on a continuous basis with the same starting population of cells. For example, can HSCs and HPCs in a population of $CD34^+$ cells in a single collected unit generate more erythrocytes than already present in that CB unit, and are the functional capacities of these generated cells as good for in vivo use as the erythrocytes in the original collection. The state-of-the-art of this process has recently been reviewed (Migliaccio *et al.*, 2009). Another question in a similar vein applies to the generation of platelets from immature subsets of CB cells.

Stem/progenitor cells in cord blood that are not HSCs or HPCs

There are a number of cells present in CB such as MSCs and EPCs, or those that may be able to be generated from immature CB cells via production of iPSCs and then the induced differentiation of the iPSCs to a cell of choice. Whether or not such cells are, or in the future will be, ready for clinical usage remains to be determined. These are exciting areas of investigation, but as so often happens, patients and physicians are so anxious to find and evaluate new treatment modalities that hype supersedes reality, and this could be very dangerous for patient safety. I recently reviewed this area in brief as a Forum (Broxmeyer, 2010a) trying to evaluate the current state of biological and clinical knowledge, and clinical or potential clinical use of iPSCs, MSCs, and EPCs. Some of this is mentioned in brief below, but overall there must be caution in how and when this information is translated from in-vitro and preclinical laboratory investigation to clinical assessment. Moving too fast without rigorous controls and safety considerations could result in no effective treatment, or at the worst it could result in harm to the patient. Either scenario could greatly reduce enthusiasm for future efforts in these arenas, or even stop these efforts. We all want to see the development of useful clinical procedures, but this is not something that should be rushed into without adequate and rigorously controlled preclinical studies.

MSCs

MSCs exhibit extensive proliferative capacity, and in vitro can generate bone, fat, and cartilage, and there is some evidence that MSCs also have immunomodulating activity (Bianco *et al*., 2008; Phinney and Prockop, 2007; Chamberlain *et al*., 2007). However, MSCs are still not that well defined in terms of phenotype and function (Prockop, 2009). MSCs are identified after culture in vitro from CB mononuclear cells, but whether or not CB will be the best source of a potentially clinical active MSC population is not clear, because many investigators have noted decreased frequency of MSCs in CB compared to other cellular sources of these cells, such as BM, and this reduced frequency may be why some CB samples were found to lack MSCs (Reviewed in Broxmeyer and Smith, 2009).

EPCs

EPCs are detected in CB (Ingram *et al*., 2004; Broxmeyer *et al*., 2010) only after culture in vitro of CB mononuclear or $CD34^+$ cells, and their proliferative capacity is extensive. However, there is not a definitive phenotype for these cells and there are still controversies as to what defines an EPC and the role of these cells in neoangiogenesis and cardiovascular cell-based therapies (Yoder and Ingram, 2009; Mund *et al*., 2009).

iPSCs

Since the original studies of Yamanaka's group (reviewed in Yamanaka, 2009), iPSCs have been generated from many different somatic cell types (reviewed in Maherali and Hochedlinger, 2008) including from differently isolated immature subsets of mPB (Loh *et al*., 2009), and CB cells (Haase *et al*., 2009; Giorgetti *et al*., 2009; Ye *et al*., 2009). The excitement with this relatively new technology is the capacity to start with mature or immature adult cell populations and generate an embryonic-like, or close to embryonic-like cell state, and from these cells generate cells, tissues, and perhaps organs of need. There has been proof for direct reprogramming of hematopoietic cells to pluripotency (Okabe *et al*., 2009), a mouse model of sickle cell anemia has been treated with iPSCs generated from autologous skin (Hanna *et al*., 2007), and iPSCs have been used to produce viable mice through tetraploid complementation (Zhao *et al*., 2009). However, this technology is not without serious potential problems (reviewed in Kaufman, 2009; Broxmeyer, 2010a), including the possibility of disease causing cells present in cell preparations generated from iPSCs (Saha and Jaenisch, 2009). This entails the inability yet to be able to produce pure populations of lineage restricted cells of choice, inherent in which is the

possibility that some, even very limited numbers of the cell population may contain embryonic-like cells that could generate teratomas. Also of consideration is whether enough cells can be generated for a therapeutic dose.

Perspective/Concluding thoughts

CB has proven to be a legitimate source of clinically useful HSCs and HPCs, with a number of already noted advantages that have resulted in over 20,000 CB transplants. Last year was the first in which the number of CB transplants exceeded the number of BM transplants. However, there is much experimental work to be done to make CB transplantation more efficacious.

CB contains non-HSC/HPC stem/progenitor cell types, including MSCs and EPCs, and iPSCs can be generated from immature subsets of CB. Whether or not these other stem/progenitor cell types will be of clinical utility needs to be further evaluated. Also, to be determined is whether or not the methods used to freeze and cryopreserve CB HSCs and HPCs are optimal for the cryopreservation of MSCs, EPCs and iPSCs. In fact, freezing techniques for HSCs and HPCs may not be optimal for these cells.

In addition to being able to eventually use a single CB unit for transplantation for all adults, an event I would very much like to see in the future in order to keep GVHD and purchase cost of CB lower, greater insight into why CB HSC/HPC engraft more slowly than similar cells from BM and MPB, and how to accelerate engraftment with CB is an important clinically relevant area of investigation. CB has been used in both myeloablative, and in reduced-intensity conditioning situations, and a recent paper has suggested the impact of HLA disparity in the graft vs. host direction (Matsuno *et al*., 2009). Whether all effects are entirely immune-related or can be accounted for by other cell-cytokine effects would be important information to know and use for clinical advantage (Matsuno *et al*., 2009). A recent example of improving transplant outcome from a clinical perspective, has suggested that re-exposure of CB to non-inherited maternal HLA antigens results in improved outcome for transplants of hematological malignancies (van Rood *et al*., 2009). Advancements in CB translation will be best served by close interactions in utilizing both laboratory and clinical findings.

The future of CB transplantation will be bright if we are smart, but cautious, enough to use the new knowledge in a responsible fashion.

References

1. Adams G.B, Alley I.R, Chung U.I, Chabner K.T, Jeanson N.T, Lo C.C, Marsters E.S, Chen M, Weinstein L.S, Lin C.P, *et al*. Haematopoietic stem cells depend on Galpha(s)-mediated signalling to engraft bone marrow. Nature. 2009; 459:103–107.
2. Alvarez-Silva M, Belo-Diabangouaya P, Salaun J.d, Dieterlen-Lievre F. Mouse placenta is a major hematopoietic organ. Development. 2003; 130:5437–5444.
3. Ballen K.K, Spitzer T.R, Yeap B.Y, McAfee S, Dey B.R, Attar E, Haspel R, Kao G, Liney D, Alyea E, *et al*. Double unrelated reduced-intensity umbilical cord blood transplantation in adults. Biol Blood Marrow Transplant. 2007; 13:82–89.
4. Barker J.N, Weisdorf D.J, DeFor T.E, Blazar B.R, McGlave P.B, Miller J.S, Verfaillie C.M, Wagner J.E. Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy. Blood. 2005; 105:1343–1347.
5. Basu S, Broxmeyer H.E. Transforming growth factor-{beta}1 modulates responses of CD34+ cord blood cells to stromal cell-derived factor-1/CXCL12. Blood. 2005; 106:485–493.
6. Basu S, Ray N.T, Atkinson S.J, Broxmeyer H.E. Protein phosphatase 2A plays an important role in stromal cell-derived factor-1/CXC chemokine ligand 12-mediated migration and adhesion of CD34+ cells. J Immunol. 2007; 179:3075–3085.
7. Bianco P, Robey P.G, Simmons P.J. Mesenchymal stem cells: revisiting history, concepts, and assays. Cell Stem Cell. 2008; 2:313–319.

8. Broxmeyer H.E, Douglas G.W, Hangoc G, Cooper S, Bard J, English D, Arny M, Thomas L, Boyse E.A. Human umbilical cord blood as a potential source of transplantable hematopoietic stem/progenitor cells. Proc Natl Acad Sci USA. 1989; 86:3828–3832.
9. Broxmeyer H.E, Srour E.F, Hangoc G, Cooper S, Anderson S.A, Bodine D.M. High-efficiency recovery of functional hematopoietic progenitor and stem cells from human cord blood cryopreserved for 15 years. Proc Natl Acad Sci USA. 2003; 100:645–650.
10. Broxmeyer H.E. Going Home: Inhibiting Stem Cell CD26. Inside Blood Capsule. Blood. 2006; 108:3966.
11. Broxmeyer H.E, Hangoc G, Cooper S, Campbell T, Ito S, Mantel C. AMD3100 and CD26 modulate mobilization, engraftment, and survival of hematopoietic stem and progenitor cells mediated by the SDF-1/CXCL12-CXCR4 axis. Ann N Y Acad Sci. 2007; 1106:1–19.
12. Broxmeyer H.E, Smith F.O. Cord Blood Hematopoietic Cell Transplantation. In: Appelbaum F.R, Forman S.J, Negrin R.S, Blume K.G, editors. In Thomas' Hematopoietic Cell Transplantation. 4th Edition. West Sussex, United Kingdom: Wiley-Blackwell; 2009. pp. 559–576.
13. Broxmeyer H.E, Cooper S, Hass D.M, Hathaway J.K, Stehman F.B, Hangoc G. Experimental basis of cord blood transplantation. Bone Marrow Transplant. 2009; 44:627–633.
14. Broxmeyer H.E. Will iPS Cells Enhance Therapeutic Applicability of Cord Blood Cells and Banking? Cell Stem Cell. 2010a; 6:21–24.
15. Broxmeyer H.E. Wagner J.E, editor. Umbilical Cord Blood Transplantation: Epilogue. Seminars in Hematology. 2010b. pp. 97–103.
16. Broxmeyer H.E, Srour E.F, Orschell C, Ingram D.A, Cooper S, Plett P.A, Mead L.E, Yoder M.C. 2010. Cord Blood Hematopoietic Stem and Progenitor Cells In: Essential Stem Cell Methods Klimanskaya I, Lanza R, editors. San Diego: Academic Press, Elsevier Science.
17. Brunstein C.G, Barker J.N, Weisdorf D.J, DeFor T.E, Miller J.S, Blazar B.R, McGlave P.B, Wagner J.E. Umbilical cord blood transplantation after nonmyeloablative conditioning: impact on transplantation outcomes in 110 adults with hematologic disease. Blood. 2007; 110:3064–3070.
18. Brunstein C.G, Laughlin M.J. Extending cord blood transplant to adults: dealing with problems and results overall. Semin Hematol. 2010; 47:86–96.
19. Campbell T.B, Hangoc G, Liu Y, Pollok K, Broxmeyer H.E. Inhibition of CD26 in human cord blood CD34+ cells enhances their engraftment of nonobese diabetic/severe combined immunodeficiency mice. Stem Cells Dev. 2007; 16:347–354.
20. Chamberlain G, Fox J, Ashton B, Middleton J. Concise review: mesenchymal stem cells: their phenotype, differentiation capacity, immunological features, and potential for homing. Stem Cells. 2007; 25:2739–2749
21. Christopherson K.W, Hangoc G, Broxmeyer H.E. Cell surface peptidase CD26/dipeptidylpeptidase IV regulates CXCL12/stromal cell-derived factor-1 alpha-mediated chemotaxis of human cord blood CD34 +progenitor cells. J Immunol. 2002; 169:7000–7008.
22. Christopherson K.W, Hangoc G, Mantel C.R, Broxmeyer H.E. Modulation of hematopoietic stem cell homing and engraftment by CD26. Science. 2004; 305:1000–1003.
23. Christopherson K.W, Paganessi L.A, Napier S, Porecha N.K. CD26 inhibition on CD34+ or lineage- human umbilical cord blood donor hematopoietic stem cells/hematopoietic progenitor cells improves long-term engraftment into NOD/SCID/Beta2null immunodeficient mice. Stem Cells Dev. 2007; 16:355–360.
24. Dar A, Kollet O, Lapidot T. Mutual, reciprocal SDF-1/CXCR4 interactions between hematopoietic and bone marrow stromal cells regulate human stem cell migration and development in NOD/SCID chimeric mice. Exp Hematol. 2006; 34:967–975.
25. Delaney C, Heimfeld S, Brashem-Stein C, Voorhies H, Manger R.L, Bernstein I.D. Notch-mediated expansion of human cord blood progenitor cells capable of rapid myeloid reconstitution. Nat Med. 2010; 16:232–236.
26. Eapen M, Rubinstein P, Zhang M.J, Stevens C, Kurtzberg J, Scaradavou A, Loberiza F.R, Champlin R.E, Klein J.P, Horowitz M.M, *et al*. Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: a comparison study. Lancet. 2007; 369:1947–1954.
27. Feher I, Gidali J. Prostaglandin E2 as stimulator of haemopoietic stem cell proliferation. Nature. 1974; 247:550–551.
28. Fujimi A, Matsunaga T, Kobune M, Kawano Y, Nagaya T, Tanaka I, Iyama S, Hayashi T, Sato T, Miyanishi K, *et al*. Ex vivo large-scale generation of human red blood cells from cord blood CD34+ cells by co-culturing with macrophages. Int J Hematol. 2008; 87:339–350.
29. Gekas C, Dieterlen-Lievre F, Orkin S.H, Mikkola H.K. The placenta is a niche for hematopoietic stem cells. Dev Cell. 2005; 8:365–375.

30. Gentile P, Byer D, Pelus L.M. In vivo modulation of murine myelopoiesis following intravenous administration of prostaglandin E2. Blood. 1983; 62:1100–1107.
31. Giarratana M.C, Kobari L, Lapillonne H, Chalmers D, Kiger L, Cynober T, Marden M.C, Wajcman H, Douay L. Ex vivo generation of fully mature human red blood cells from hematopoietic stem cells. Nat Biotechnol. 2005; 23:69–74.
32. Giorgetti A, Montserrat N, Aasen T, Gonzalez F, Rodriguez-Piza I, Vassena R, Raya A, Boue S, Barrero M.J, Corbella B.A, *et al*. Generation of induced pluripotent stem cells from human cord blood using OCT4 and SOX2. Cell Stem Cell. 2009; 5:353–357.
33. Gluckman E, Broxmeyer H.A, Auerbach A.D, Friedman H.S, Douglas G.W, Devergie A, Esperou H, Thierry D, Socie G, Lehn P, *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; 321:1174–1178.
34. Haase A, Olmer R, Schwanke K, Wunderlich S, Merkert S, Hess C, Zweigerdt R, Gruh I, Meyer J, Wagner S, *et al*. Generation of induced pluripotent stem cells from human cord blood. Cell Stem Cell. 2009; 5:434–441.
35. Hanna J, Wernig M, Markoulaki S, Sun C.W, Meissner A, Cassady J.P, Beard C, Brambrink T, Wu L.C, Townes T.M, *et al*. Treatment of sickle cell anemia mouse model with iPS cells generated from autologous skin. Science. 2007; 318:1920–1923.
36. Hills M, Lucke K, Chavez E.A, Eaves C.J, Lansdorp P.M. Probing the mitotic history and developmental stage of hematopoietic cells using single telomere length analysis (STELA) Blood. 2009; 113:5765–5775.
37. Hough R, Rocha V. Transplant outcomes in acute leukemia. II. Semin Hematol. 2010; 47:51–58.
38. Hoggatt J, Singh P, Sampath J, Pelus L.M. Prostaglandin E2 enhances hematopoietic stem cell homing, survival, and proliferation. Blood. 2009; 113:5444–5455.
39. Ingram D.A, Mead L.E, Tanaka H, Meade V, Fenoglio A, Mortell K, Pollok K, Ferkowicz M.J, Gilley D, Yoder M.C. Identification of a novel hierarchy of endothelial progenitor cells using human peripheral and umbilical cord blood. Blood. 2004; 104:2752–2760.
40. Kaufman D.S. Toward clinical therapies using hematopoietic cells derived from human pluripotent stem cells. Blood. 2009; 114:3513–3523.
41. Kawai T, Choi U, Liu P.C, Whiting-Theobald N.L, Linton G.F, Malech H.L. Diprotin A infusion into nonobese diabetic/severe combined immunodeficiency mice markedly enhances engraftment of human mobilized CD34+ peripheral blood cells. Stem Cells Dev. 2007; 16:361–370.
42. Kelly S.S, Parmar S, De L.M, Robinson S, Shpall E. Overcoming the barriers to umbilical cord blood transplantation. Cytotherapy. 2010; 12:121–130.
43. Kiel M.J, Morrison S.J. Uncertainty in the niches that maintain haematopoietic stem cells. Nat Rev Immunol. 2008; 8:290–301.
44. Kieusseian A, Cumano A. Are hematopoietic stem cells generated in the placenta? Cell Stem Cell. 2008;2:197–198.
45. Larsson J, Ohishi M, Garrison B, Aspling M, Janzen V, Adams G.B, Curto M, McClatchey A.I, Schipani E, Scadden D.T. Nf2/merlin regulates hematopoietic stem cell behavior by altering microenvironmental architecture. Cell Stem Cell. 2008; 3:221–227.
46. Laughlin M.J, Eapen M, Rubinstein P, Wagner J.E, Zhang M.J, Champlin R.E, Stevens C, Barker J.N, Gale R.P, Lazarus H.M, *et al*. Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia. N Engl J Med. 2004; 351:2265–2275.
47. Loh Y.H, Agarwal S, Park I.H, Urbach A, Huo H, Heffner G.C, Kim K, Miller J.D, Ng K, Daley G.Q. Generation of induced pluripotent stem cells from human blood. Blood. 2009; 113:5476–5479.
48. Lu L, Pelus L.M, Broxmeyer H.E. Modulation of the expression of HLA-DR (Ia) antigens and the proliferation of human erythroid (BFU-E) and multipotential (CFU-GEMM) progenitor cells by prostaglandin E. Exp Hematol. 1984; 12:741–748.
49. Lu L, Pelus L.M, Piacibello W, Moore M.A, Hu W, Broxmeyer H.E. Prostaglandin E acts at two levels to enhance colony formation in vitro by erythroid (BFU-E) progenitor cells. Exp Hematol. 1987; 15:765–771.
50. MacMillan M.L, Weisdorf D.J, Brunstein C.G, Cao Q, DeFor T.E, Verneris M.R, Blazar B.R, Wagner J.E. Acute graft-versus-host disease after unrelated donor umbilical cord blood transplantation: analysis of risk factors. Blood. 2009; 113:2410–2415.
51. MacMillan M.L, Walters M.C, Gluckman E. Transplant outcomes in bone marrow failure syndromes and hemoglobinopathies. Semin Hematol. 2010; 47:37–45.
52. Maherali N, Hochedlinger K. Guidelines and techniques for the generation of induced pluripotent stem cells. Cell Stem Cell. 2008; 3:595–605.

53. Majeti R, Park C.Y, Weissman I.L. Identification of a hierarchy of multipotent hematopoietic progenitors in human cord blood. Cell Stem Cell. 2007; 1:635–645.
54. Matsuno N, Wake A, Uchida N, Ishiwata K, Araoka H, Takagi S, Tsuji M, Yamamoto H, Kato D, Matsuhashi Y, *et al*. Impact of HLA disparity in the graft-versus-host direction on engraftment in adult patients receiving reduced-intensity cord blood transplantation. Blood. 2009; 114:1689–1695.
55. Migliaccio A.R, Whitsett C, Migliaccio G. Erythroid cells in vitro: from developmental biology to blood transfusion products. Curr Opin Hematol. 2009; 16:259–268.
56. Mikkola H.K, Gekas C, Orkin S.H, Dieterlen-Lievre F. Placenta as a site for hematopoietic stem cell development. Exp Hematol. 2005; 33:1048–1054.
57. Mund J.A, Ingram D.A, Yoder M.C, Case J. Endothelial progenitor cells and cardiovascular cell-based therapies. Cytotherapy. 2009; 11:103–113.
58. Neildez-Nguyen T.M, Wajcman H, Marden M.C, Bensidhoum M, Moncollin V, Giarratana M.C, Kobari L, Thierry D, Douay L. Human erythroid cells produced ex vivo at large scale differentiate into red blood cells in vivo. Nat Biotechnol. 2002; 20:467–472.
59. North T.E, Goessling W, Walkley C.R, Lengerke C, Kopani K.R, Lord A.M, Weber G.J, Bowman T.V, Jang I.H, Grosser T, *et al*. Prostaglandin E2 regulates vertebrate haematopoietic stem cell homeostasis. Nature. 2007; 447:1007–1011.
60. Okabe M, Otsu M, Ahn D.H, Kobayashi T, Morita Y, Wakiyama Y, Onodera M, Eto K, Ema H, Nakauchi H. Definitive proof for direct reprogramming of hematopoietic cells to pluripotency. Blood. 2009; 114:1764–1767.
61. Orchard P.J, Tolar J. Transplant outcomes in leukodystrophies. Semin Hematol. 2010; 47:70–78.
62. Ottersbach K, Dzierzak E. The murine placenta contains hematopoietic stem cells within the vascular labyrinth region. Dev Cell. 2005; 8:377–387.
63. Patel K.J, Rice R.D, Hawke R, Abboud M, Heller G, Scaradavou A, Young J.W, Barker J.N. Pre-engraftment syndrome after double-unit cord blood transplantation: a distinct syndrome not associated with acute graft-versus-host disease. Biol Blood Marrow Transplant. 2010; 16:435–440.
64. Pelus L.M, Broxmeyer H.E, Kurland J.I, Moore M.A. Regulation of macrophage and granulocyte proliferation. Specificities of prostaglandin E and lactoferrin. J Exp Med. 1979; 150:277–292.
65. Pelus L.M, Broxmeyer H.E, Moore M.A. Regulation of human myelopoiesis by prostaglandin E and lactoferrin. Cell Tissue Kinet. 1981; 14:515–526.
66. Pelus L.M. Association between colony forming units-granulocyte macrophage expression of Ia-like (HLA-DR) antigen and control of granulocyte and macrophage production. A new role for prostaglandin E. J Clin Invest. 1982; 70:568–578.
67. Peranteau W.H, Endo M, Adibe O.O, Merchant A, Zoltick P.W, Flake A.W. CD26 inhibition enhances allogeneic donor-cell homing and engraftment after in utero hematopoietic-cell transplantation. Blood. 2006; 108:4268–4274.
68. Phinney D.G, Prockop D.J. Concise review: mesenchymal stem/multipotent stromal cells: the state of transdifferentiation and modes of tissue repair–current views. Stem Cells. 2007; 25:2896–2902.
69. Prasad V.K, Kurtzberg J. Transplant outcomes in mucopolysaccharidoses. Semin Hematol. 2010; 47:59–69.
70. Prockop D.J. Repair of tissues by adult stem/progenitor cells (MSCs): controversies, myths, and changing paradigms. Mol Ther. 2009; 17:939–946.
71. Qian H, Buza-Vidas N, Hyland C.D, Jensen C.T, Antonchuk J, Mansson R, Thoren L.A, Ekblom M, Alexander W.S, Jacobsen S.E. Critical role of thrombopoietin in maintaining adult quiescent hematopoietic stem cells. Cell Stem Cell. 2007; 1:671–684.
72. Rhodes K.E, Gekas C, Wang Y, Lux C.T, Francis C.S, Chan D.N, Conway S, Orkin S.H, Yoder M.C, Mikkola H.K. The emergence of hematopoietic stem cells is initiated in the placental vasculature in the absence of circulation. Cell Stem Cell. 2008; 2:252–263.
73. Robin C, Bollerot K, Mendes S, Haak E, Crisan M, Cerisoli F, Lauw I, Kaimakis P, Jorna R, Vermeulen M, *et al*. Human placenta is a potent hematopoietic niche containing hematopoietic stem and progenitor cells throughout development. Cell Stem Cell. 2009; 5:385–395.
74. Rocha V, Wagner J.E Jr., Sobocinski K.A, Klein J.P, Zhang M.J, Horowitz M.M, Gluckman E. Graft-versus-host disease in children who have received a cord-blood or bone marrow transplant from an HLA-identical sibling. Eurocord and International Bone Marrow Transplant Registry Working Committee on Alternative Donor and Stem Cell Sources. N Engl J Med. 2000; 342:1846–1854.
75. Rocha V, Cornish J, Sievers E.L, Filipovich A, Locatelli F, Peters C, Remberger M, Michel G, Arcese W, Dallorso S, *et al*. Comparison of outcomes of unrelated bone marrow and umbilical cord blood transplants in children with acute leukemia. Blood. 2001; 97:2962–2971.
76. Rocha V, Labopin M, Sanz G, Arcese W, Schwerdtfeger R, Bosi A, Jacobsen N, Ruutu T, de Lima M, Finke J, Frassoni F, Gluckman E. Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. N Engl J Med. 2004; 351:2276–2285.
77. Rocha V, Broxmeyer H.E. New Approaches for Improving Engraftment after Cord Blood Transplantation. Biol Blood Marrow Transplant. 2010; 16:S126–S132.
78. Saha K, Jaenisch R. Technical challenges in using human induced pluripotent stem cells to model disease. Cell Stem Cell. 2009; 5:584–595.
79. Sakaue-Sawano A, Kurokawa H, Morimura T, Hanyu A, Hama H, Osawa H, Kashiwagi S, Fukami K, Miyata T, Miyoshi H, *et al*. Visualizing spatiotemporal dynamics of multicellular cell-cycle progression. Cell. 2008; 132:487–498.

80. Scaradavou A, Smith K.M, Hawke R, Schaible A, Abboud M, Kernan N.A, Young J.W, Barker J.N. Cord blood units with low CD34+ cell viability have a low probability of engraftment after double unit transplantation. Biol Blood Marrow Transplant. 2010; 16:500–508.
81. Shaheen M, Broxmeyer H.E. The humoral regulation of hematopoiesis. In: Hoffman R, Benz E.J Jr, Shattil S.J, Furie B, Silberstein L.E, McGlave P, Heslop H, Anastasi J, editors. In Hematology: Basic Principles and Practice. 5th Edition. Elsevier Churchill Livingston; Philadelphia, PA: 2009. pp. 253–275. Part III, Chapter 24.
82. Smith A.R, Gross T.G, Baker K.S. Transplant outcomes for primary immunodeficiency disease. Semin Hematol. 2010; 47:79–85.
83. Spiegel A, Kalinkovich A, Shivtiel S, Kollet O, Lapidot T. Stem cell regulation via dynamic interactions of the nervous and immune systems with the microenvironment. Cell Stem Cell. 2008; 3:484–492.
84. Tian C, Bagley J, Forman D, Iacomini J. Inhibition of CD26 peptidase activity significantly improves engraftment of retrovirally transduced hematopoietic progenitors. Gene Ther. 2006; 13:652–658.
85. van Rood J.J, Stevens C.E, Smits J, Carrier C, Carpenter C, Scaradavou A. Reexposure of cord blood to noninherited maternal HLA antigens improves transplant outcome in hematological malignancies. Proc Natl Acad Sci USA. 2009; 106:19952–19957.
86. Vlaski M, Lafarge X, Chevaleyre J, Duchez P, Boiron J.M, Ivanovic Z. Low oxygen concentration as a general physiologic regulator of erythropoiesis beyond the EPO-related downstream tuning and a tool for the optimization of red blood cell production ex vivo. Exp Hematol. 2009; 37:573–584.
87. Weissman I.L, Shizuru J.A. The origins of the identification and isolation of hematopoietic stem cells, and their capability to induce donor-specific transplantation tolerance and treat autoimmune diseases. Blood. 2008; 112:3543–3553.
88. Wu M, Kwon H.Y, Rattis F, Blum J, Zhao C, Ashkenazi R, Jackson T.L, Gaiano N, Oliver T, Reya T. Imaging hematopoietic precursor division in real time. Cell Stem Cell. 2007; 1:541–554.
89. Wyss B.K, Donnelly A.F, Zhou D, Sinn A.L, Pollok K.E, Goebel W.S. Enhanced homing and engraftment of fresh but not ex vivo cultured murine marrow cells in submyeloablated hosts following CD26 inhibition by Diprotin A. Exp Hematol. 2009; 37:814–823.
90. Xia L, McDaniel J.M, Yago T, Doeden A, McEver R.P. Surface fucosylation of human cord blood cells augments binding to P-selectin and E-selectin and enhances engraftment in bone marrow. Blood. 2004; 104:3091–3096.
91. Yamanaka S. A fresh look at iPS cells. Cell. 2009; 137:13–17.
92. Yamazaki S, Iwama A, Takayanagi S, Eto K, Ema H, Nakauchi H. TGF-beta as a candidate bone marrow niche signal to induce hematopoietic stem cell hibernation. Blood. 2009; 113:1250–1256.
93. Yashiro Y, Bannai H, Minowa T, Yabiku T, Miyano S, Osawa M, Iwama A, Nakauchi H. Transcriptional profiling of hematopoietic stem cells by high-throughput sequencing. Int J Hematol. 2009; 89:24–33.
94. Ye Z, Zhan H, Mali P, Dowey S, Williams D.M, Jang Y.Y, Dang C.V, Spivak J.L, Moliterno A.R, Cheng L. Human-induced pluripotent stem cells from blood cells of healthy donors and patients with acquired blood disorders. Blood. 2009; 114:5473–5480.
95. Yoder M.C, Ingram D.A. Endothelial progenitor cell: ongoing controversy for defining these cells and their role in neoangiogenesis in the murine system. Curr Opin Hematol. 2009; 16:269–273.
96. Yoshihara H, Arai F, Hosokawa K, Hagiwara T, Takubo K, Nakamura Y, Gomei Y, Iwasaki H, Matsuoka S, Miyamoto K, *et al*. Thrombopoietin/MPL signaling regulates hematopoietic stem cell quiescence and interaction with the osteoblastic niche. Cell Stem Cell. 2007; 1:685–697.
97. Yoshimoto M, Yoder M.C. Developmental biology: Birth of the blood cell. Nature. 2009; 457:801–803.
98. Zhao X.Y, Li W, Lv Z, Liu L, Tong M, Hai T, Hao J, Guo C.L, Ma Q.W, Wang L, *et al*. iPS cells produce viable mice through tetraploid complementation. Nature. 2009; 461:86–90.

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