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# Umbilical Cord Blood: An Undervalued and Underutilized Resource in Allogeneic Hematopoietic Stem Cell Transplant and Novel Cell Therapy Applications

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## Abstract

**Purpose of review:** The purpose of this review is to primarily discuss the unwarranted decline in the use of umbilical cord blood (UCB) as a source of donor hematopoietic stem cells (HSC) for hematopoietic cell transplantation (HCT) and the resulting important implications in addressing health care inequities, and secondly to highlight the incredible potential of UCB and related birthing tissues for the development of a broad range of therapies to treat human disease including but not limited to oncology, neurologic, cardiac, orthopedic and immunologic conditions.

**Recent findings:** When current best practices are followed, unrelated donor umbilical cord blood transplant (CBT) can provide superior quality of life-related survival compared to other allogeneic HSC donor sources (sibling, matched or mismatched unrelated, and haploidentical) through decreased risks of relapse and chronic graft versus host disease. Current best practices include improved UCB donor selection criteria with consideration of higher resolution HLA typing and CD34+ cell dose, availability of newer myeloablative but reduced toxicity conditioning regimens, and rigorous supportive care in the early post-transplant period with monitoring for known complications, especially related to viral and other infections that may require intervention. Emerging best practice may include the use of ex vivo expanded single-unit CBT rather than double-unit CBT (dCBT) or "haplo-cord" transplant, and the incorporation of post-transplant cyclophosphamide as with haploidentical transplant and/or incorporation of novel post-transplant therapies to reduce the risk of relapse, such as NK cell adoptive transfer. Novel, non-HCT uses of UCB and birthing tissue include the production of UCB-derived immune effector cell therapies such as unmodified NK cells, CAR-NK cells and immune T-cell populations, the isolation of mesenchymal stem cells for immune modulatory treatments and derivation of iPSC haplobanks for regenerative medicine development and population studies to facilitate exploration of drug development through functional genomics.

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Conflicts of interest: New York Blood Center has an FDA-licensed cord blood bank. Deverra Therapeutics is currently developing UCB-derived allogeneic cell therapies.

**Summary:** The potential of allogeneic UCB for HCT and novel cell-based therapies is undervalued and underutilized. The inventory of high-quality UCB units available from public cord blood banks (CBB) should be expanding rather than contracting in order to address ongoing health care inequities and to maintain a valuable source of cellular starting material for cell and gene therapies and regenerative medicine approaches. The expertise in GMP-grade manufacturing provided by CBB should be supported to effectively partner with groups developing UCB for novel cell-based therapies.

### Keywords

allogeneic; umbilical cord blood; transplant; haplobank; gene therapy; immune effector cells; cord blood expansion; haplo-cord; immunotherapy; HLA; induced pluripotent stem cells; functional genomics; haplobank

## Introduction

UCB is a well-established source of allogeneic donor HSCs for hematopoietic cell transplantation (HCT) (in this case, referred to as cord blood transplant (CBT)). However, despite known advantages of UCB as a donor source for HCT and the availability of optimal practice guidelines for unrelated donor CBT [1–5] as well as the equivalency and even potential superiority of some outcomes observed after CBT compared to convention donor HCT (peripheral blood (PB) or bone marrow (BM))[6–8],** the number of CBTs performed annually has been declining in favor of haploidentical transplant [9,10] when a suitably matched related or unrelated adult volunteer donor cannot be identified. In addition, UCB and related birthing tissue are invaluable as starting cellular material for the generation of innovative cell therapies and regenerative medicines across multiple indications. This paper describes ways in which UCB is an undervalued resource for both standard hematopoietic stem cell (HSC) allogeneic transplant and for novel cell therapy applications.

## Overview of HSC sources for Allogeneic Transplant

In allogeneic HCT for both malignant and non-malignant diseases, the optimal donor source depends on level of HLA-matching between the donor and recipient, cell dose, urgency of the transplant (i.e., underlying disease), and donor availability. An 8/8 HLA-matched sibling donor (MSD)-sourced from peripheral blood (PB), bone marrow (BM), generally remains the standard of care [11] because of its ability to rapidly meet all the above donor selection criteria without concern for cell dose and with reduced risk of graft versus host disease (GVHD). However, only approximately 30% of allogeneic transplant candidates have an HLA-matched sibling [12]. An 8/8 or 10/10 matched unrelated donor (MUD) is typically the next choice in line [13] due to meeting HLA and cell dose requirements, although center transplant experience may favor UCB [14] and HLA matches for ethnicities other than whites of European descent [12], donor availability, and time to transplant can be limiting factors.

Next in line for consideration are typically HLA-haploidentical relatives or banked unrelated UCB over an HLA-mismatched unrelated donor [6**,15]. Both are rapidly available sources of HSC typically, but have their relative advantages and disadvantages. In terms of HLA

matching, the sources are thought to be similar, as UCB has relaxed HLA-matching requirements of 4/6 (at least one allele matched at HLA-A, -B, and -DRB1) without increased risk of GVHD due to fewer CD3+ T-cells and their immunologic naivete[16,17]. Use of haploidentical relatives is possible due to removal of CD3+ T-cells from the graft through in vitro positive or negative selection or more commonly now in vivo post-transplant cyclophosphamide [18]. In terms of HSC dose, which affects the kinetics of hematopoietic recovery (engraftment) [19,20], haploidentical transplant is the superior choice, and is one reason for the declining use of UCB transplant in favor of haploidentical transplant [11]. Nevertheless, it is worth considering that UCB HSCs compared to adult HSCs have longer telomeres, less DNA damage and higher proliferative and hematopoietic reconstitutive potential [21,22], which may have safety implications in regard to the replicative stress of HSC transplant[23]*. Finally, in regard to urgency of transplant and donor availability, UCB is already banked and HLA-typed and is thus the most readily available donor source and enabling of a flexible transplantation date. Furthermore, ~12% of patients have no HLA-haploidentical relative [24] and suitable relatives may be unviable donors due to the presence of anti-HLA antibodies in the recipient [24,25], their ineligibility or refusal to donate[26], or medical or psychological conditions that preclude donation[27]. Such considerations likely contribute to the continued demand for UCB units, particularly for pediatric patients and with inherited metabolic conditions, congenital leukodystrophies, and immune deficiency syndromes, where age at the time of transplant and time to transplant affect long-term outcomes. Furthermore, relatives may be carriers of the genetic disorder[28–31].

## Special Immune Characteristics of UCB HSCs for Allogeneic Transplant

When HCT is being utilized as the curative approach for hematologic malignancies, HLA-mismatched UCB donor T-cells have characteristics that may lead to a reduced risk of relapse as compared to MSD [32], MUD [6],** or haploidentical transplant [33], related to enhanced anti-tumor ability and cytotoxic CD8+ and CD4+ T-helper (Th1) profiles[34]. A higher CD8+ UCB content is associated with faster and higher myeloid and platelet engraftment, lower non-relapse mortality (NRM), lower relapse, and increased overall survival (OS).[35] A recent publication by Hiwarkar, et al., reports an important and very interesting finding wherein the normally delayed CD8+ T-cell recovery with UCB transplant can be reversed with granulocyte transfusion and was associated with eradication of refractory leukemia[36];** the mechanism is thought to be neutrophil cross-priming of naïve CD8+ T-cells that is as efficient as that by macrophages[37]. UCB units also have increased immature NK cells which are hyper-responsive, with similar secretion levels of perforin and granzyme B as mature NK cells[38].

Relevant in either malignant or non-malignant disease, UCB has characteristics which contribute to a relatively low incidence of chronic graft versus host disease (cGVHD) compared to haploidentical [39], MUD [40,41] and even MSD [7*,32] HSC sources which should favorably impact long-term quality of life and survival. For example, UCB is enriched in plasmacytoid dendritic cells (pDC), which unlike PB pDC, express low levels of TNFα [42]. Also possibly contributing to the low incidence of cGVHD is more rapid and higher recovery of naïve B, IgM and switched memory B cells in comparison to BM and PB, as naïve B cell recovery is critical for deletion of self-reactive B cells [38].

Immune reconstitution, however, can be delayed due to the immunologic naivete of UCB T-cells, which do not immediately confer protective T-cell memory function, and the high number of regulatory T-cells[17], resulting in increased risk of post-transplant infectious complications, especially viral. In this regard, it is best to avoid ATG conditioning as it damages immune reconstitution of both CD4+ and CD8+ T-cells, which in turn worsens NRM and relapse[43,44]. ATG omission also simplifies considerations with KIR ligand incompatibility [45]and is associated with rapid early thymus-independent CD4+ T-cell recovery in both children and adults without increase in aGVHD [46,47]. ATG omission is also associated with decreased cGVHD compared to ≥ 8/10 HLA-matched unrelated donors [48] and decreased risk of relapse[49].

## The intricacies of UCB as the donor HSC source in Allogeneic Transplant

Given the need to choose between unrelated UCB versus haploidentical related donor sources, it is worthwhile to compare the safety and efficacy of their HSC recipient outcomes. There is no prospective randomized comparison in non-malignant disease, but in hematologic malignancy (leukemia and lymphoma) a prospective multi-center Phase III trial, BMT CTN 1101, randomized patients between reduced-intensity dCBT and haploidentical BM transplant. It found CBT recipients to have higher NRM (18% vs 11%, p=0.04) leading to lower 2-year overall survival (OS) (46% vs 57%, p=0.04) [26]. This NRM rate is similar to that reported at a highly experienced UCB transplant center [8]. Higher NRM in CBT vs haploidentical transplant recipients was also observed in a small (n=45) but randomized trial of myeloablative transplant for leukemia/MDS[24], a retrospective CIBMTR data comparison of 708 hematologic malignancy patients who had myeloablative conditioning [33], a large retrospective study of non-myeloablative transplant for lymphoma [50], and a recent meta-analysis[39]. BMT CTN 1101 found no differences in acute graft versus host disease (aGVHD), 2-year chronic graft versus host disease (cGVHD), 2-year relapse/progression, or 2-year progression free survival [26], but the meta-analysis [39] found a significant reduction in cGVHD with CBT vs haploidentical transplant.

There are various issues that need to be considered when interpreting the higher NRM with UCB. First, as previously discussed, ATG affects NRM and was used in one trial[24]. Second, dCBT predominated in the other studies and it must be recognized that single-donor CBT with adequate cell dose (e.g. ≥$2.5 \times 10^7$ total nucleated cells (TNC)/kg and ≥$1.5–2.0 \times 10^5$ $CD34^+$ cells/kg [4]) remains the standard of care, with double-UCB transplantation only appropriate for patients who lack a single unit with adequate cell dose [5,29,51]. This is due to higher rates of Grade III-IV aGVHD and Grade III-IV cGVHD and delayed platelet recovery with double versus single CBT [52–54].** In this light, it is worth considering that for overweight and obese patients, a recent study of single-unit CBT found comparable hematopoietic recovery and overall survival when dosing CD34+ cells/kg by ideal body weight rather than actual body weight [55].

Third, although increasing CD34+ cell dose may overcome the problem [8], HLA mismatch contributes to NRM in CBT. Indeed, the greater the allele level matching at HLA-A, -B, -C, and -DRB1, the lower the NRM and graft failure for malignant and non-malignant disease, respectively, and the higher the OS [56*,57], with >2 of 8 HLA-allele mismatch associated

with significantly prolonged neutrophil recovery independent of cell dose [56].* Only 2 HLA mismatches or single-allele mismatches at HLA-A, -B, and -DRB1 can increase the risk of Grade III-IV aGVHD [58,59]. Furthermore, mismatch at HLA locus C is associated with higher NRM [60]. Thus, it is worth considering that, although the aforementioned trials provided adequate cell doses (e.g. in BMT CTN 1101, each UCB unit had to contain at least $1.5 \times 10^7$ TNC/recipient kg), the HLA matching requirement was the minimum 4/6, and not all trials required high resolution typing at all loci [4], although BMT CTN 1101 required at least one allele match at HLA-A, HLA-B, and HLA-DRB1. It is therefore not surprising that these trials found higher NRM. For example, in the BMT CTN 1101 trial mortality from pulmonary or intracranial hemorrhage and viral or bacterial infection was higher in the UCB group, as would be expected from a platelet recovery of a median 42 versus 28 days and incidence of neutrophil recovery at day 56 of 95% versus 99% (p=0.05).

Fourth, thymic-dependent de novo production of T-cells is critical for long-term reconstitution of a broad and diverse T-cell repertoire as measured by recent thymic emigrants and T-cell receptor excision circles. [17,61] HLA mismatch can lead to donor-T cell induced thymic dysfunction [62,63], as suggested by better T-cell diversity after MSD than MUD transplant [64].

The data presented suggests that using more closely HLA-matched UCB units is likely to assuage the increased risk of NRM with CBT. However, this must be balanced with the positive effect of mismatched UCB donors and reduced risk of relapse [65]. Considering this, a 7/8 HLA match may be best over an 8/8 HLA-matched UCB donor, especially in patients with high risk leukemia placing them at higher risk of post-transplant relapse Importantly however, there is no clear evidence in UCB transplant that 6–8/8 HLA matching increases relapse risk compared to ≤ 5/8 HLA matching [8,33]. Furthermore, although the frequency of NIMA matching is estimated at < 10% [66], when the recipient's mismatched HLA antigen matches the non-inherited maternal HLA antigens (NIMA) of the UCB donor, such NIMA-matched recipients have greater neutrophil recovery, reduced NRM and improved overall survival compared to non-NIMA matched UBC recipients [67].

Thus, rather than transplant centers replacing CBT with haploidentical donor transplant, which will undoubtedly reduce critical physician training and transplant center experience with CBT, not to mention endangering the survival of public CBBs and the availability of high-quality UCB units, UCB collection should be expanded and diversified in order to provide the closer recipient HLA matching needed to improve their hematopoietic recovery and immune reconstitution. Importantly, ongoing UCB collection and banking is absolutely essential to establish and maintain availability of HSC donors that reflect the increasing genetic diversity and racial admixture of the population. Without this, future patients requiring HCT as a curative approach may not have any suitable unrelated donors available. It is also worth considering that the greater a center's experience with CBT, the lower the NRM [58,68,69], with at least 10 CBT per year qualifying as sufficient expertise. Indeed, in the hands of experienced CBT centers, GVHD-free and relapse free survival, which is a better measure of quality of life than OS [70], is better as compared to MUD or even MSD transplant[7*,14,32].

## Solutions to the higher NRM with CBT

The issue of the low cell dose in UCB units needs to be addressed herein [71]. Low cell dose, especially CD34+ cell dose, which can result in delayed kinetics of hematopoietic recovery [19,20] and thus NRM and OS[8], has resulted in the common use of dCBT to ensure adequate cell dose and engraftment [66]. This is especially critical given that ACOG has also made clear that delayed CB clamping should be routine standard of care [72] which will impact the numer of collected UCB units that will meet cell dose thresholds for processing and storage in the CBBs. Yet, importantly, there has been significant improvement in time to hematopoietic recovery observed following CBT simply due to higher quality CBUs available in the CBBs, the consideration of high-resolution HLA-typing and CD34+ cell dose[3,56*,73]

Another solution may be the “haplo-cord” approach, in which mobilized CD34+ cells isolated from a haploidentical donor, who may be related or unrelated[74], are infused with a single UCB unit in order to provide faster neutrophil and platelet recovery than is typically obtained from a single UCB unit transplant alone. ATG conditioning, however, is required for in-vivo T-cell depletion of the UCB to prevent rejection of the CD34+ selected (and therefore T-cell depleted) haploidentical HSCs. [75,76] A retrospective study comparing this approach to MUD transplants showed no significant differences in transplant outcomes [77]. A retrospective study comparing it to haploidentical BM, however, showed haplo-cord to have faster neutrophil and platelet recovery and lower cGVHD at 1 year (4% versus 16%, $p < .0001$); there were no differences in OS, progression-free survival (PFS), relapse, or NRM including Grade III-IV aGVHD [78]. These findings support the previous meta-analysis showing reduction in cGVHD with UCB [39]. An important study will be prospective comparison of haploidentical PB to haplo-cord transplant, since haploidentical mobilized PB versus haploidentical BM may lower relapse risk but possibly at the cost of higher Grade III-IV aGVHD and cGVHD[33,79–81].

A potential impediment to the “haplo-cord” approach is the cost associated with haploidentical CD34+ selection. A different “haplo-cord” approach is to infuse unmanipulated mobilized PB from a haploidentical donor along with a low-dose UCB unit (median UCB MNC= $1.8 \times 10^7$/kg)[82]. Median time to engraftment and 30 day engraftment rate showed no differences compared to a concurrent MUD cohort. This approach resulted in engraftment of the haploidentical donor HSCs rather than the UCB unit, with a lower relapse risk than in the MUD cohort. Yet another important and cost-saving study to reduce NRM with UCB transplant is the effect of using, as with haploidentical donor transplant, post-transplant cyclophosphamide (PT-CY) (NCT03802773) for aGVHD prophylaxis [83], given the immune reconstitution issues with ATG. [43,44] Use of PT-CY may also help retain anti-viral immunity, which is mediated by persisting virus-specific recipient T-cells [84].

Although also likely expensive and with increased logistical difficulty and potential delays in time to transplant, infusion of ex-vivo expanded UCB CD34+ cells from one UCB unit along with an unmanipulated UCB unit or as a stand alone graft also appears to be an effective method to address delayed engraftment with UCB and can be done by

several methods, such as co-culture with Notch ligand [85], mesenchymal stromal cells [86], aryl hydrocarbon receptor antagonist [87], or nicotinamide. [87] Recently, both nicotinamide-expanded and UM171-expanded grafts were successfully used as stand-alone single UCB unit transplants. [88–90] This is possible as the negative fraction obtained when isolating the CD34+, which contains the donor T-cells, is re-cryopreserved, and infused at the time of transplant with the expanded cell graft. A randomized Phase III trial of nicotinamide-expanded versus standard unmanipulated 1–2 unit UCB transplant using myeloablative conditioning for heme malignancy found the nicotinamide transplant to result in faster neutrophil and platelet recovery and reduced grade 2–3 bacterial or invasive fungal infection[89].* A helpful follow-up trial would be to compare this product to haploidentical transplant or the haplo-cord approach which does not require manipulation/ex vivo expansion and therefore does not delay time to transplant. Finally, co-infusion of additional UCB cell types has been explored, such as UCB-derived and expanded regulatory T-cells to reduce the risk of aGVHD and cGVHD[91], and in a pre-clinical model, UCB mesenchymal stem cells (MSC) to promote engraftment of non-expanded UCB HSCs.[92]

## UCB as a source material for generation of iPSC haplobanks

Pluripotent stem cells (PSCs), including embryonic stem cells (ESCs), have the ability to self-renew and give rise to all types of cells in the body. The discovery of factors that can reprogram adult cells into induced pluripotent stem cells (iPSCs) sidesteps the ethical controversy surrounding ESCs and has therefore made an invaluable contribution to the field of regenerative medicine. In theory, sourcing and scaling of iPSCs for mass production of cellular teraputics for clinical trials makes the potential clinical utility virtually unlimited. Furthermore, since sampling of primary tissues from living donors at the scale necessary to study large cohorts of patients is not tenable, *in vitro* differentiation of iPSCs into mature cell types have the potential to generate *in vitro* representations for disease modeling and drug validation.[93] Ultimately, the use of iPSCs for tissue engineering and cellular replacement therapies could revolutionize regenerative medicine. The first published clinical trial utilizing iPSCs explored the safety and efficacy of iPSC-derived mesenchymal stromal cells in reducing inflammation associated with graft-versus-host disease.[94]* Currently, 19 clinical trials are testing the therapeutic value of iPSC-derived cells worldwide, including a trial for iPSC-derived platelets for treatment of thrombocytopenia in alloimmune patients with aplastic anemia.[95]

The success of iPSC therapies relies on identifying high quality adult somatic cells as well as the maintaining the reprogamming and directed differentiation of iPSCs in a fully Good Manufacturing Practice (GMP)-compliant environment such that they can be used safely and effectively in the clinical setting. Despite the potential of iPSCs to generate cellular therapeutics, practical issues related to the time and expense needed to generate autologous (i.e., patient-derived) iPSCs have cast uncertainty as to their practicality in the clinical environment. Alternatively, allogeneic (i.e., unrelated) iPSC ‘haplobanks’ could overcome the challenges of quality control and availability[96]. However, the complexity of immune matching allogeneic iPSCs to a diverse population is a major challenge.

UCB units are an excellent source of somatic cells for creation of allogeneic iPSCs lines for a number of reasons. First, HLA typing of UCB allows for identification of units with optimal immunotolerance properties best suited for allogeneic therapeutics: mainly $O^-$ blood type and homozygous HLA haplotypes. In this way, HLA homozygote donors can match a significant numbers of recipients using a relatively small number of well selected donors that are representative of the population. Second, CBUs are manufactured under GMP-conditions and have been screened for infectious diseases, which ensures the source of the somatic cells are of the highest quality. Third, UCB cells have less somatic mutation and exposure to environmental damage, and can be reprogrammed into iPSCs with high efficiency[97].* In fact, precedent for the repurposing of CBU for iPSC line derivation exists and several iPSC haplobanks have been successfully created using UCB. [98,99] Thus, UCB cells represent a novel and attractive resource for the purposes of iPSC production towards platforms for drug discovery as well as regenerative and cellular therapy manufacturing.

## Importance of the racial-ethnic diversity of UCB to health care equity

The American College of Obstetricians and Gynecologists (ACOG) has emphasized the importance of public over private CBB and contribution from all ethnicities and races.[72] Even though racial and ethnic minority groups are underrepresented in UCB registries [100],* they are still better represented than in volunteer adult unrelated donor registries despite the expansion of such registries. [12,101–103] Public cord blood banks are therefore critical resources for health equity. UCB is a critical option for ethnic minorities and mixed race individuals even with a haplo-identical relative, as 65% of recipients of African ancestry have a suitable UCB graft versus 44% having a suitable haplo donor.[27] Even though UCB inventories should be expanded and diversified to provide closer HLA matching, the less stringent HLA matching requirement compared to other HSC sources allows for ethnicity difference between donor and recipient. Indeed, a person of mixed race appears to be cured of HIV using a single partially matched UCB unit from a donor with a CCR5 co-receptor variant, which is more common in people of European heritage; furthermore, the patient has had no GVHD in the 4 years since the transplant, despite HLA mismatch. [104,105]

In the setting of autologous gene therapy for sickle cell disease (SCD), collection of autologous UCB is a potential critical resource for health care equity because HSC mobilization and collection is currently not feasible in much of Africa, where SCD is most prevalent. Exploring this potential resource is critical because in allogeneic transplant for SCD, HSC donor sources other than the rare 8/8 HLA-matched sibling are plagued by high rates of graft failure and cGVHD. [106,107]

In the setting of genetic studies into the biology of complex traits and drug development, genetic variation between ethnicities contributes significantly to disease manifestations [108] and response to potential treatments. Thus, efforts to remediate the disproportionate focus in genetic research on individuals with Northern European white ancestry, including the creation of iPSC from ethnic minority CB units, are critical.[109–112]* This is a pressing need, as iPSCs are a platform for modeling disease and drug discovery, so including diverse and under-represented groups in iPSC research enables the application of genetic

findings equally across all races and ancestries. For example, only rarely do genome-wide association studies (GWAS) deliver a result indicating a sequence change within a gene as the association with the disease. Instead, GWAS has revealed the importance of sequence variation at the non-coding regulatory loci between genes or within introns. Understanding which how these non-coding variants influence gene expression is the focus of the field of functional genomics. Indeed, it has already been shown that the use of samples from individuals with diverse ancestries in functional genomics studies improves our ability to identify functional variants in the non-coding majority of the genome.[113–115*]

Finally, for the purpose of iPSC haplobank creation, unsurprisingly the coverage provided by homozygous HLA haplobanks across a particular population is proportional to the diversity of the CB bank demographic.[98] Thus, rigorous cross-referencing of HLA haplotypes present in the intended target population with chosen CBUs for reprogramming will improve the feasibility of homozygous HLA haplobanks for clinical application.

## Importance of UCB and Cord Blood Banks for Other Innovative Cell Therapies

UCB is not just a source of stem cells for HCT and iPSC haplobanks, but UCB and birthing tissue are also an important source of starting material for other cellular therapy applications. For example, UCB-derived HLA-mismatched CAR NK cells are an effective alternative to CAR NK cells due to their better side effect profile. [116]** UCB-derived polyclonal multivirus-specific cytotoxic T-cells are being developed for viral infections in immunosuppressed states.[117] In neonates, UCB and CB tissue is being explored in lung, brain, and cardiac injury and disease.[118] UCB-derived myeloid-derived suppressor cells, which have immune suppressive effects, are being explored for treatment of feto-maternal intolerance, GVHD, and autoimmunity.[119] These are just a few examples of why CBB must be supported as a key foundation for innovative cell therapies. CBB are regulated and have all the required infrastructure to manufacture high quality starting material, and to lose these invaluable resources would impact innovation and slow progress.

## Conclusion

UCB is an undervalued and underutilized source for both standard allogeneic HSC transplant and novel cell therapy indications. Compared to adult HSC sources, it is the most readily available HSC source with unique immune properties and the least replicative stress damage, which can lead to the lowest risks of relapse, cGVHD, and possibly post-transplant hematologic malignancy. The higher risk of non-relapse mortality observed in allogeneic HSC transplant can be overcome by considerations such as ATG alternatives, better HLA matching, use of expanded single UCB units, and center experience. UCB is also an ideal source for iPSC generation for functional genomic studies and haplobanks for regenerative medicine. Last but not least, it is a critical resource for health care equity in regard to standard allogeneic transplant, autologous gene therapy, regenerative medicine applications, and drug development through functional genomics.

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## Key points

1. UCB compared to adult HSC sources have the advantage of having undergone less replicative stress and are already banked and HLA-typed, and are thus the least age-affected and most readily available and transplant date-flexible HSC source.
2. HLA-mismatched UCB transplant can result in lower relapse and lower chronic GVHD compared to adult HSC sourced from matched sibling donors, matched unrelated donors, and haploidentical donors.
3. The observed increase in non-relapse mortality with UCB transplant must be considered in the light of the increased non-relapse mortality risks with ATG conditioning with its suboptimal risk-to benefit-ratio; two versus one (expanded or not) UCB unit; and previous minimum requirements of only a 4 out of 6 HLA match.
4. In regard to the contribution of UCB cell dose to non-relapse mortality, the future is bright with multiple existing and evolving solutions including haplo-cord options, post-transplantation cyclophosphamide, UCB unit expansion, and co-infusion of other CB-derived cell populations.
5. Its immunotolerant properties, high iPSC reprogramming efficiency, and easy availability make UCB an ideal source for haplobank creation.
6. Health care equity demands that public cord blood bank inventory be expanded and diversified in order to provide higher degrees of HLA matching for allogeneic transplant and iPSCs for functional genomics studies and haplobanks.