

Expanding the Abu Dhabi Bone Marrow Transplant Program (AD-BMT®) Scope with the Collection and Cryopreservation of Cord Blood Stem Cells

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Abstract: *Introduction:* The umbilical cord blood (UCB) is the blood from the placenta's blood vessels and the portion of the umbilical cord that remains attached to the newborn after the delivery when the cord is clamped and cut. UCB is rich in hematopoietic stem cells (HSC) and other stem cells (SC). Between 1974 and 1988, scientific knowledge and UCB application possibilities for human therapy opened a new significative era in cell therapy, using UCB HSC as an alternative source of SC for bone marrow transplant and the cure of patients with malignant hematological diseases. *Objective:* The possibility of having a UCB bank (UCB-B) in Abu Dhabi encouraged us to make this analysis. *Method:* A literature review from Google Scholar, PubMed, SciELO, Scopus, and other sources, about the increasing application of UCB-SC and storage in UCB-B was done to update about all the possibilities for translational medicine. *Results:* We prepared a UCB overview, including the pioneering use of UCB-SC for HSC transplantation, their biological composition, characteristics, and the UC-associated tissues like Wharton-Jelly and the human term placenta, UCB advantages, and disadvantages in HSC transplantation, the number of clinical trials applying UCB donation samples, and promising possibilities for regenerative medicine. The existence of different types of UCB-Bs, and the development of new specific cellular manipulation techniques. The UCB-B regulatory framework and some ethical issues were also included in the review. *Conclusions:* After 30 years of UCB-B, more than 100 public UCB-Bs worldwide, with millions of UCB units donated altruistically, more than 800,000 clinical-grade products are now available: a great source of transplantable SC and other cellular material for the development of new therapies. Even though the UCB as a source of HSC for transplantation has been recently statistical ranked in third place, after HSC apheresis collected and bone marrow aspirates, until now, more than 50,000 UCB HSC allogeneic transplants (HSC-Allo-T) have been performed worldwide in both children and adults to treat many different diseases, including hematologic, metabolic, immunologic, neoplastic, and neurologic disorders. A significant effort has been focused on enhancing engraftment to reduce the risk of infection and cost. *Recommendations:* To that end, we must understand in detail the molecular mechanisms controlling SC self-renewal that may lead to the development of ex-vivo systems for HSCs expansion, characterize the mechanisms regulating the homing of HSC and determine the relative place of UCB HSC-Allo-T, as compared to other sources.

Keywords: Transplant, Blood, Umbilical Cord, Histocompatibility, Stem Cells, Regenerative Medicine, HLA

1. Introduction

Every year thousands of patients are diagnosed with diseases that could be treated through stem cell (SC), particularly hematopoietic stem cell (HSC) transplantation worldwide. Initially, HSCs were obtained by bone marrow (BM) aspirates from the same patient (autologous) or histocompatible relatives and/or unrelated histocompatible voluntary donors. However, the number of patients who do not find compatible HLA donors (allogeneic settings) from the 27 million registered in the international registry of the World Marrow Donor Association (WMDA) [1] was estimated to be around 10-15K. In contrast, another considerable number of patients fails to wait for the time necessary to find a donor due to the rapid progression of their disease, so umbilical cord blood (UCB) stem cells (UCB-SC) became a highly appreciated option. [2] It was the reason for developing UCB banks (UCB-B) for allogeneic HSC transplant (HSC-Allo-T) as one of the most used modalities for years. UCB and associated tissues as SC sources are increasingly crucial for Regenerative Medicine (RM). The possibility of having UCB banking in Abu Dhabi encouraged this review.

2. Objectives

A descriptive literature review about the increasing application of UCB-SC and storage in USC-B was done to update about all the possibilities for translational medicine of the umbilical cord (UC), describing an UCB overview, with comments about the pioneering use of UCB-SC for HSC transplantation, their biological composition and characteristics, and UC associated tissues like *Wharton-Jelly* and the human term placenta, UCB advantages and disadvantages in HSC transplantation, the number of clinical trials applying UCB donation samples, and promising possibilities for RM, the existence of different types of UCB-Bs worldwide distributed, including public, private or familiar ones, each of them with its characteristics, [3] and the new emerging mix public-private joint-ventures, the development of new specific cellular manipulation techniques in UCB-Bs, going from the sample collection, fresh storage and transport, product pharmaceutical specific handling techniques, as bags content volume-reduction, cryopreservation, and cold long-term storage, and finally all techniques related to UCB units (UCB-Us) for sending, delivery, defrosting, and transplantation, as UCB-B responsibilities. In addition, some considerations about the AD-BMT[®] Program expansion scope challenges and possibilities, the UCB-B international and national regulatory framework, and some ethical issues related to UCB-B were also included in the review.

3. Development

3.1. UCB Overview

The UCB is the blood from the placenta's blood vessels and the portion of the UC that remains attached to the newborn after the delivery when the UC is clamped and cut. UCB contains all the usual elements of blood: red blood cells,

white blood cells, platelets, and plasma, but it is also rich in HSC, like BM. The presence of HSC in the UCB was demonstrated for the first time in 1974 [4], and ten years later, the presence of primitive HSC was also confirmed. [5]

Gluckman E et al. informed that the first transplant using UCB among HLA-identical siblings to treat one with Fanconi anemia was performed in 1988. [6] This patient was able to a lymphohematopoietic system's complete reconstitution, opening a new era for HSC transplantation using UCB. [7] Since then, knowledge of the biological characteristics of UCB HSC has increased, and the advantages of its use for transplantation are more evident; hence UCB HSC-Allo-T is a standard practical option for both children and adults with malignant and non-malignant diseases, such as sickle cell anemia (SCA) and others. [8, 9]

UCB is also very important in regenerative cell therapy because in vitro experimental data suggests the high potential, perhaps unique, of these cells to produce biologically active products as therapeutic tools in graft facilitation and immunotherapy. [8]

3.2. Umbilical Cord-Associated Tissues

Nevertheless, not only has UCB-SC been used for HSC-Allo-T, the presence of SC in umbilical cord-associated tissues, with several reports about incorporating the WJ and placental tissue in UCB-B as sources of SC for cell therapy, especially mesenchymal/stromal stem cells (MSCs) in RM, has been published. [10–13] Cell therapy is one of the most promising research areas for regenerating damaged tissues and organs with UCB and associated tissues. RM encompasses several innovative medical treatments enabling the body to repair, replace, restore, and regenerate damaged or diseased cells, tissues, and organs because UCB and associated tissues SC has remarkable regenerative properties. [4, 5, 14]

3.2.1. Wharton's Jelly Stem Cells

On the other hand, the human UC comprises an outer layer of amniotic epithelium enclosing a vein and two arteries embedded within a mucoid connective tissue. The mucoid connective tissue surrounding the three umbilical vessels, or the UC matrix is called "*Wharton's Jelly*" (WJ). [11] The WJ is rich in MSCs (WJ-MSCs) with exceptional properties: in that, although they are bona fide MSCs [15], possessing similar properties to their adult BM counterparts, yet they also retain characteristics of primitive stem cells, like the expression of embryonic stem cells (ESC) markers. They may represent some intermediate state between adult and ECS. [16]

WJ-MSCs have several advantages over adult MSCs: they are easily isolated from UC and readily available if appropriately collected after delivery. Moreover, some reports showed a relatively high expression of pluripotency markers like POU5F-1, SOX-2, and NANOG compared to ESCs, which explains why they do not develop teratomas in WJ-MSCs compared to other sources MSCs, implying a more primitive status. [16, 17] Indeed, their transcriptomic profile compared to other MSCs was reviewed in detail and explained in a comprehensive review article. [17] As pointed out, compared

with ESCs, their unique transcriptomic profile can explain why WJ-MSCs do not form teratomas upon transplantation. [15, 18]

Another interesting report showed that WJ-MSCs exhibit a unique gene expression profile compared to BM-MSCs using the high throughput single-cell RNA-sequencing technique. In that report, 436 genes were significantly differentially expressed when comparing the two cell types. Those genes are related to several processes, such as chemotaxis, apoptosis, anti-tumor activity, and immuno-modulation. The authors reported that those differences might, at least in part, explain many of the advantages which WJ-MSCs have over BM-MSCs. [19] However, unlike ESCs, WJ-MSCs have no ethical concerns. [20] Moreover, WJ-MSCs have been particularly found to be mainly immune-privileged after reports of their expression of human leukocyte antigen-locus G (HLA-G) besides their lack of expression of human leukocyte antigen D-related (HLA-DR), like other types of MSCs. [21]

3.2.2. Human Term Placenta

The human term placenta comprises various tissues from which different cells can be obtained, including HSC and MSCs. [12] Therefore, there is a possibility to incorporate placental tissue cells in UCB-B, mainly due to the human placenta features, the immune cells at the fetal-maternal interface, and the different cell populations isolated from the placenta, particularly important the MSCs. Furthermore, the question of why placenta-derived MSCs should be banked with their HSC counterparts has also

been addressed. [11] Some clinical trials that study the safety and efficacy of placenta tissue- derived MSCs in selected diseases after preclinical studies are conducted to evaluate therapeutic properties are shown in Table 1.

Therefore, the concomitant banking of non-hematopoietic cells from the placenta, which could be applied therapeutically, alone or combined with their hematopoietic counterparts, could exploit current banking processes while laying the foundation for clinical trials exploring placenta-derived cell therapies in RM, in the same way as for many years, products from UCB-SC saves lives worldwide.

Early results were promising, and results from some of the clinical trials generated more interest in UCB-SC treatments for several diseases:

- 1) Brain injury: Autologous UCB-SC is expected to improve outcomes for anoxic brain injury, cerebral palsy, and traumatic brain injury at birth. [22–24]
- 2) Juvenile diabetes: Studies conducted among children with this disease find improved insulin production through treatment with autologous transplants. [35]
- 3) Heart disease: A review from 2010 suggested the potential for UCB stem cells to improve outcomes in human patients following a heart attack. [26]
- 4) Corneal regeneration: UCB-SC could provide a future therapeutic option for individuals with disorders of the ocular surface, according to recent studies. [27, 28]

Table 1. Placenta-derived Stem Cell clinical trials as per ClinicalTrials.gov.

Trial Sponsor (Location)	Disease	Target Cell Therapy	No. Patients	Phase	Reference ClinicalTrials.gov Identifier:	Status
Cellularity Incorporated Celgene Corporation (NJ, US)	Diabetic Peripheral Neuropathy	Human placenta-derived cells	26	II	NCT02552277	Completed
	Peripheral artery disease	Human placenta-derived cells	15	I	NCT01859117	Completed
	Acute stroke	Human placenta-derived cells	44	II	NCT01310114	Terminated
	Pulmonary sarcoidosis (Stages 2 and 3)	Human placenta-derived cells	4	I	NCT01440192	Terminated
	Diabetic Foot Ulcer with and Without Peripheral Arterial Disease	Human placenta-derived cells	159	I	NCT02264288	Terminated
New York Medical College (US)	Rheumatoid arthritis	Human placenta-derived cells	26	II	NCT01261403	Terminated
	Certain Malignant Hematologic Diseases and Non-Malignant Disorders	Human placenta-derived cells	43	I	NCT01586455	Completed
Karolinska Institute (Sweden)	Hemorrhagic cystitis	Decidual stromal cells (MSCs-like)	12	I/II	NCT02172963	Completed
	GvHD	Decidual stromal cells (MSCs-like)	30	I/II	NCT02172924	Unknown
Prince Charles Hospital/Mater Medical Research Institute (Australia)	Idiopathic pulmonary fibrosis	Placental MSCs	8	I	NCT01385644	Completed
Cedars Sinai Medical Center, Inflammatory Bowel Disease Center Los Angeles, California (US)	Crohn's Disease	Human placenta-derived cells	14	I	NCT01769755	Completed
Tehran University of Medical Sciences (Iran)	Fistula Perianal	Human placenta-derived cells	80	I/II	NCT05402748	Recruiting
Division of Colorectal Surgery, Department of Surgery, Tehran University of Medical Sciences, Tehran (Iran)	Resistant Perianal Fistula in Crohn's Patients	Human Placenta- MSCs derived exosomes	80	I/II	NCT05499156	Active, non-recruiting

Legend: MSCs: Mesenchymal/Stromal Stem Cells.

For example, MSCs derived from chorionic villi of human term placentae (pMSCs) protect human endothelial cells from injury induced by hydrogen peroxide (H_2O_2), [29] like in diabetes hyperglycemia induced- H_2O_2 production, which causes endothelial dysfunction that underlies the enhanced immune responses and adverse complications associated with the diabetes and leads to thrombosis and atherosclerosis. In that paper, *Abumaree et al.* describe the ability of pMSCs to protect endothelial cell functions from the negative impact of the high glucose level. These isolated cells were cultured with endothelial cells isolated from human UC veins in glucose-enriched media. Endothelial cell functions were then determined, and the effect of pMSCs on gene expression in glucose-treated endothelial cells was also determined. The pMSCs reversed the effect of glucose on essential endothelial cell functions, including proliferation, migration, angiogenesis, and permeability. In addition, pMSCs altered the expression of many genes that mediate essential endothelial cell functions, including survival, apoptosis, adhesion, permeability, and angiogenesis. As described by the first comprehensive study to prove that pMSCs protect endothelial cells from glucose-induced damage, the pMSCs have potential therapeutic value as an SC-based therapy to repair the glucose-induced vascular injury and prevent the adverse complications associated with diabetes and cardiovascular disease. However, further studies are necessary to reveal more detailed aspects of the mechanism of action of pMSCs on glucose-induced endothelial damage in vitro and in vivo. [11]

3.3. Umbilical Cord Blood as a Source of Hematopoietic Stem Cells

There are three issues to be considered in applying the UCB as an alternative in the absence of a family donor: 1) the urgency of the transplant, 2) the patient's size, and 3) the potential need for lymphocyte infusion. Most human HSCs are CD34+ (a 90-120 kD membrane integral protein), a molecule probably functioning as a regulator of cell adhesion to the BM microenvironment stromal cells. The frequency of CD34+ cells in BM has been estimated between 1-3% of mononuclear cells (MNCs), but in UCB ranges between 0.2-1%. Nevertheless, UCB CD34+ frequency decreases with the age of gestation and the time since the collection of the UCB. Thus, at the 17 weeks of pregnancy, they account for 11% of MNCs, while at 38 weeks, they fall to approximately 1%. [30–33] In addition, they also decrease if the time in processing after collection becomes too long. The UCB, as a source of HSC, has several unique characteristics, which give it more advantages than disadvantages than the other sources. [10]

Advantages

The advantages of UCB can be summarized as follows:

- 1) The relative ease of collection;
- 2) The absence of risk for the mother or newborn if strict quality rules are followed;
- 3) Less time is needed for usage availability after processing;
- 4) Less costly collection compared with other HSC sources;

- 5) Less risk of blood-borne infections transmission if adequate pre-donation screening is established;
- 6) Less need of HLA compatibility is needed;
- 7) Less graft rejection after HSC transplantation. [3]

UCB exhibits great proliferative potential and immunological immaturity. These characteristics allowed the performance of HSC transplants from UCBs that overcome the barriers of HLA compatibility since most of the UCB-Allo-Ts have been carried out to date with one or two incompatibilities HLA-A, -B, and DRB1. Its immediate availability in UCB-Bs, a great diversity of HLA combinations, and absence of donor risks decrease. The ready-to-use UCB bags, pre-tested for their HSC content, typed for the HLA, with lower severity of graft versus host disease (GvHD) in the transplant recipient, and the practically null risk of viral disease transmission because all are investigated for biological infectious agents, have allowed achieving a figure of 600 UCB HSC-Allo-T per year. [9]

These cells have an implant half-life of 25-36 days, less than those of other donors. The initial data reported variable results about the biology of the UCB cells and their transplantology. [34] A 100% HLA-compatible donor of UCB is also considered acceptable to increase the graft versus leukemia effect in the first line. [35] Its use extends the possibilities of the UCB Allo-T to ethnic groups or minorities underrepresented in the international registries of BM donors. [35] Accordingly, many UCB-derived SCs preparations have been granted marked authorization for use in unrelated donor HSCs transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in several disorders. [36]

Disadvantages

The disadvantages can be summarized as follow:

- 1) Slow engraftment;
- 2) Limited cell dose;
- 3) A small volume of UCB-Us;
- 4) Additional SC doses for reinfusion are unavailable from the same donor;
- 5) An autologous donation may have limited benefit in case of hereditary diseases;
- 6) Storage issues regarding sample quality control, timing, and cost in private banks. [3]

The low cellularity of UCB-Us and the delay of grafting are mainly related to the myeloid and platelet lines that initially hindered the use of UCB in adults. The minimal possibilities of using UCB-Us for donor lymphocyte infusion (DLI) after the transplant, but also the limited amount of immune effector cells, are considered among the disadvantages. However, ex vivo cell expansion and several UCB-Us in the same receptor appear as viable alternatives, and the scientific community has responded with ex vivo expansion techniques to increase the number of SC. [37-39]

The DLI is not viable in most cases due to the unique condition of UCB-Us. Their newborn donors will not be

allegedly available in the future, except for related UCB donations. However, it can be achieved with a preconceived cryopreservation strategy using appropriate bags. Another possible solution to this problem is using expanded CD3 lymphocytes *ex vivo* from a portion of the cryopreserved unit. Some studies demonstrate the feasibility of expanding human UCB lymphocytes, suggesting that UCB T cells are competent enough to generate cytotoxic T lymphocytes with a practical DLI effect. [38]

Regarding the limited amount of effector cells available in the UCB-Us, since placental and neonatal T immunity at birth is immature concerning its adult counterpart, it was demonstrated that they need to be "educated," and new lines of research in cellular engineering were started to achieve the desired effects. [38]

Phase I/II studies have already been carried out using expanded *ex vivo* UCB, showing only a slight increase in the incidence of GvHD, explained by the presence of dendritic cells among the expanded cells. [38] *Ballen et al.* report further advances due to better HLA typing in preventing inflammatory bowel disease and infections associated with allogeneic HSC transplantation, improving survival worldwide. [40]

3.4. Other Applications of Umbilical Cord Blood Stem Cells, Including Clinical Trials

After a search published by Frances Verter, Ph.D., Alexey Bersenev, MD, Ph.D., and Pedro Silva Couto, on the website of the Parent's Guide to Cord Blood Foundation, a total of 110 clinical trials recruiting UCB donation samples in 281 locations, recorded in China, Japan, South Korea, the EU, The Netherlands, Australia, New Zealand, India, Iran, and Germany databases, and 155 trials are going on for Umbilical Cord Tissue applications, mainly employing MSCs from that type of tissue and recruiting at 216 locations worldwide. [41]

The UCB-SC and related tissues have also shown the potential to treat several other diseases/conditions, and research shows great promise in these areas. For instance, Alzheimer's, autism, lupus, multiple sclerosis, muscular dystrophy, Parkinson's disease, rheumatoid arthritis, spinal cord injury, stroke, and liver diseases. [42]

Clinical investigations using SC products in RM address a broad spectrum of conditions using a variety of SC types. A few reports of safety issues have arisen from autologous or HSC-Allo-T. However, many cells administered show transient presence for a few days with trophic influences on immune or inflammatory responses. [43] Limbal SC has been registered as a product for eye burns in Europe, (45) and MSCs have been in clinical trials for pediatric GvHD in different countries. [45]

MSCs in the UCB and the UC tissue could contribute to the low levels of GvHD found in the UCB HSC-Allo-T and have a vast alternative therapeutic potential. (47) At the same time, it is suspected that the natural cytotoxic cells in the UCB are responsible for the increase in the DLI effect, which could also constitute a probable source of virus-specific T cells for

antiviral cell therapy. [47–49] Even the possibility of using the UCB HSC-Allo-T to cure patients with HIV infection has been published. [50, 51]

Although the results of traditional methods of UCB expansion using cytokines alone were not satisfactory, it is already known that when growth is achieved with MSCs, there is a substantially measurable increase in graft content and yield. Other methods use HSC differentiation blockers, such as nicotinamide analogs, copper chelators, which induce Notch signals, or an aryl-hydro-carbon receptor antagonist (StemRegenin-1). [38]

Many of these methods result in an expansion of total nucleated cells (TNC) and CD34+ cells and significant increases in neutrophil recovery time or platelet levels in transplanted patients compared to unhandled UCB receptors. These clinical trials differ in the expansion methods and the cytokines used; the population studied the conditioning regimens and transplant practices; some studies with a single unit of UCB and others with two. [38]

3.5. Umbilical Cord Blood Collection

Donation bags specially designed for the UCB are used for this purpose, with an appropriate anticoagulant. Usually, citrate-phosphate-dextrose (CPD) preservative solution and a closed collection system reduce contamination risks. [52] The bag's unique design also includes a small part for sample quality control without manipulating the rest of the content.

The UCB can be obtained after ligation of the cord 35 seconds after the child's birth. While the placenta remains in the uterus, UCB is collected by gravity. Once the placenta has been expelled, the collection can also be done by canalizing the umbilical vein previous injecting a heparinized saline solution. [52] In other cases, a heparinized saline solution can be injected through the umbilical artery and aspirated with another syringe through the vein, which increases the yield, both in volume and in the number of nucleated cells achieved. The volume of a UCB unit ranges from 42 to 240 mL, and the total number of total nucleated cells (TNC) varies between 4.7×10^8 and 4.6×10^9 . All cords obtained from normal deliveries with negative serological controls during pregnancy may be used for donation. In addition, there should be no maternal or paternal history involving a risk of genetic or infectious disease transmission through the CB. [52] Required and recommended test and test results for UCB to be used for HSC transplantation are shown in Table 2, including the content of TNC that should be $>1.2 \times 10^9$, viable CD34++ $\geq 1.25 \times 10^6$, and viable CD45+ 85% of the TNC. [53]

There is consensus that engraftment requires UCB-Us with $\geq 2.5 \times 10^7$ TNC/kg and $\geq 1 \times 10^5$ CD34/kg, respectively. [54] A higher threshold dose is appropriate in small children and non-malignant diseases. This consensus led banks to increase the quality of the CB product by prioritizing the inventory of large 'high-quality' units containing >1.2 to 1.5×10^9 TNC. [55] The most current recommendations establish that a UCB-B should define the size of its operating inventories based on the

definition of the minimum number of frozen cells (for example, at least more than 1.26×10^9 total nucleated cells and 4×10^6 CD34+ cells). There are other standard quality criteria (for example, those defined by the Foundation for the Accreditation of Cellular Therapy (FACT) and the NetCord Foundation for the selection of UCB operational units (see

Table 3), [56] based on strict eligibility questionnaires of mother's donor, appropriate records of lots and validation, availability of reference samples for serology testing. It is critical to have the presence of tubing segments attached to the UCB bag for identity and power verification tests, like the cloning capacity of the SC collected. [57]

Table 2. Required and recommended tests and test results per the US FDA for cord blood and HSC-CB transplantation (final cord blood product). Adapted from Reference [1].

Product characteristics	Testing	Sample (type and timing)	Results of product testing
Safety	Infectious diseases—testing required (21 CFR 1271.45 through 1271.90)	Maternal peripheral blood obtained within 7 days of cord blood collection—type and timing required. (21 CFR 1271.80 (a) and (b))	All tests are negative except the non-treponemal test for syphilis when the confirmatory test is negative. CMV results are recorded). CMV report
	Sterility—bacterial and fungal cultures—testing required. (21 CFR 211.165 (b) and 21 CFR 610.12)	HPC-C ^a (pre-cryopreservation)	No growth
	Hemoglobin	Cord blood ^b or appropriate donor sample obtained at the time of cord blood recovery	No homozygous hemoglobinopathy
Purity and potency	TNCs	HPC-C (pre-cryopreservation)	$\geq 5.0 \times 10^8$ TNC ^c per unit HPC-C
	Viable nucleated cells	HPC-C (pre- cryopreservation)	$\geq 85\%$ viable nucleated cells
	Viable CD34+ cells (flow cytometry)	HPC-C (pre-cryopreservation)	$\geq 1.25 \times 10^6$ viable CD34+ cells ^d per unit HPC-C
Identity	HLA typing	Cord blood	Report
	Confirmatory HLA typing	The attached segment of HPC-C Cord blood	Confirms initial typing Blood group and Rh type Report

Legend: CMV: Cytomegalovirus; FDA: Food and Drug Administration; HLA: Human Leukocyte Antigens; HPC-C: Hematopoietic Progenitor Cell collected; TNC: total nucleated cells. ^aSample may be obtained before or after the addition of the cryoprotectant. ^bCord blood = cord blood before undergoing volume reduction. ^cBased on a 20 kg recipient, a target dose of $\geq 2.5 \times 10^7$ nucleated cells per kg and 70% post-thaw recovery. $\geq 1.7 \times 10^7$ nucleated cells per kg. ^dBased on CD34+ cells $\geq 0.25\%$ of TNC before freezing.

Table 3. Specification requirements for cord blood units stored for clinical administration¹. [56].

Test	Unrelated Specification		Related Specification	
	Post-Processing before cryopreservation Sample	Thawed contiguous segment or representative sample before release to the Clinical Program	Post-Processing before cryopreservation Sample	Thawed contiguous segment or representative sample before release to the Clinical Program
Total nucleated cell count	$\geq 5.0 \times 10^8$	--	Enumerated	--
Total nucleated cell recovery	Should be $\geq 60\%$	--	Should be $\geq 60\%$	--
Viability of total nucleated cell count	$\geq 85\%$	--	$\geq 70\%$	--
Viable CD34 count	$\geq 1.25 \times 10^6$	--	--	--
Viability of CD34 cells	--	$\geq 70\%$	--	--
CFU (or other validated potency assay) ²	--	Growth (or positive result for potency)	--	Growth (or positive result for potency)
Microbial Screen	Negative for aerobes, anaerobes, fungus	--	Negative for aerobic and anaerobic bacteria and fungi – OR – identify and provide results of antibiotic sensitivities	--
Donor screening and testing	Acceptable as defined by Applicable Law and NetCord-FACT Standards	--	Acceptable as defined by Applicable Law and NetCord-FACT Standards	--
Identity	--	Verified	--	Verified

Legend: CFU: Colony Forming Units. FACT: Foundation for the Accreditation of Cellular Therapy. ¹Endpoints for hematopoietic reconstitution. ²There should be evidence of potency by CFU or other validated potency assay on a fresh post-processing sample.

3.6. UCB Banks

The UCB HSC-Allo-T has similar survival rates in children to the transplantation of HSC from other sources (e.g., BM),

and results for adults continue to improve. For that reason and specific commercial interests, the number of UCB-B offering families the opportunity to store their babies' UCB for possible future uses has grown in countries mainly in North America,

Europe, and some Asian countries. Hence, parents now decide whether to donate their UCB for public use, keep it for private use, or to discard it after birth. This type of facility's recommended management structure and requirements have

been internationally established and subject to regulatory policies, including the staff (as shown in Table 4) and specifications regarding the UCB-Us stored for clinical administration described previously. [56]

Table 4. *Staff Required for the UCB-B [56].*

Position	Education and Experience	Job Responsibilities	Continuing Education (A minimum of 10 hours annually in any combination of these disciplines)
Director	1) Doctoral degree in medicine or a related scientific field 2) Training and a minimum of two (2) years of experience in immunogenetics of transplantation ¹ , basic or clinical immunology, immunohematology, basic or clinical hematology, transfusion medicine, blood or tissue banking, or cryobiology	1) Final responsibility for CBB operations 2) Overall CBB compliance with these Standards, including all components of the CBB's policies and Standard Operating Procedures.	CB banking. Cellular therapy product collection, processing, and administration.
Medical Director	Licensed physician. Training in hematopoietic cell transplantation or blood or tissue banking	1) Donor recruitment 2) Donor eligibility 3) Medical aspects of UCB collection procedures, UCB processing procedures, and review of the release and outcome data of the CB unit, including compliance with these Standards.	Donor safety; UCB banking; cellular therapy product collection, processing, and administration
CB Collection Director	1) Health care professional 2) Bachelor's degree 3) • Training and experience in hematopoietic cell transplantation, blood and tissue banking, or CB collection	1) Collection activities 2) Communication with individual CB Collection Sites	Donor safety; CB banking; cellular therapy product collection, processing, and administration
CB Processing Facility Director	1) Relevant doctoral degree 2) Qualified by training or experience for the scope of activities carried out in the CB Processing Facility	All operational aspects of all procedures related to receipt, testing, processing, cryopreservation, storage, release, and distribution of CB units and administrative operations of the CB Processing Facility, including compliance with these Standards	CB banking; cellular therapy product collection, processing, and administration
Quality Unit Manager ²	Relevant training in quality management	1) Establish and maintain systems to review, modify as necessary, approve, and implement all policies and Standard Operating Procedures 2) Monitor the performance of the Quality Management Program, the quality of the CB units, and compliance with these Standards 3) Release of CB units, as required by Applicable Law. 3	Quality management; CB banking; cellular therapy product collection, processing, and administration

Legend: ¹If the CBB Director does not have specific training and expertise in HLA, the CBB shall confirm that HLA expertise is available and utilized by the CBB. ²The Quality Unit Manager shall be a different individual from the CBB Director, CBB Medical Director, CB Collection Director, and the CB Processing Facility Director. ³The Quality Unit can override the release of a CB unit.

Both types of public and private banks [3] and mixed or hybrid ones recently emerged [9] are available. Public UCB-Bs do not charge parents for donating UCBs and collect donations and store them indefinitely for clinical use. These stored units are available to any patient with good HLA compatibility. All functional units should be incorporated into the records so that it is possible to find them in searches of the international donor's registry. [58] Traditionally, they are more widely accepted by the medical community. [59–62] Private UCB-B retains samples for the exclusive use of donors or family members in a future autologous or family transplant. The so-called UCB mixed, or hybrid banks collect and preserve both types of donations in the same facility, and it seems that they are trying to be more socially and

economically efficient than their predecessors.

The public UCB-B of New York City (NYC) in the United States of America (US) [2, 57] stands out as a pioneer in this procedure. The American National Program initiated in NYC currently has more than 50K UCB donations, allowing them to find, on average, an HLA 4/6 compatibility or higher among the UCB for 85% of the patients searching in their registry. However, this compatibility varies depending on ethnic groups. Regarding these groups, thanks to the introduction of the UCBT, HSC-Allo-T's applicability has benefited the northern hemisphere countries, [35] where they are generally the least economically favored ethnic groups.

For example, in the US, there are 17 public banks. There are different sources for UCB-B's financial support, such as

government, institutional, philanthropic, and donations. Still, most of them renew their finances from the sale of the UCB-Us stored when they are to be used, which covers

storage costs and can make new collections, so it costs around \$ 30,000.00 to obtain the UCB from a public bank. This cost is usually charged to the patient's medical insurance. [58]

Table 5. UCB Family and Public Banks around the World. Adapted from Reference [3].

Groups of Countries	Country	Family Private Cord Banks	Public Health System Cord Banks
The G7 Group	United States of America	18	25
	Italy	9	19
	Germany	2	9
	Japan	2	6
	France	0	5
	Canada	7	3
	United Kingdom	4	3
Other big economic countries	PR China	10	8
	Russia	5	2
	Saudi Arabia	3	1
	United Arab Emirates	5	1-mixed
GCC Group	Bahrain	5	0
	Kuwait	5	0
	Oman	3	0
	Qatar	3	0
	Turkey	6	3
	Australia	2	3
	Vietnam	3	3
Middle East, Asia, and Pacific	India	11	1
	Lebanon	6	1
	Iran	1	1
	Egypt	5	0
	Philippines	3	0
	Pakistan	2	0
	Jordan	2	0
	Bangladesh	1	0
	Morocco	1	0
	Brazil	11	12
	Spain	9	9
	Mexico	6	5
Iberic-American	Argentina	10	1
	Colombia	5	1
	Portugal	5	1
	Chile	3	1
	Venezuela	5	0

The United Arab Emirates UCB-B					
Name	Laboratory	Accreditation	Therapies offered	Initial cost	Long Term Fee
Future Health - UAE	Future Health UK, Nottingham Science and Technology Park, UK	AABB, HTA, ISO	9	varies by country	25 years included
LifeCell Arabia	LifeCell, Chennai, India	AABB, AATB, FDA, cGMP, ISO, DCGI, CAP	76	AED 13,990	--
Smart Cells - UAE	Smart Cells, West Drayton, UK	HTA, ISO	200 FamiCord	--	--
CellSave Arabia	CellSave Arabia, Dubai Healthcare City, UAE. CSG-BIO Company, US.	AABB, FDA	21 (2 Arabia)	18,500 AED	30 years included
Cells4Life Middle East	Cells4Life, Burgess Hill, UK	AABB, HTA, ISO	17	--	--
DCRC	DCRC, Latifa Hospital, Dubai, UAE	--	--	--	--

Legend: DCRC: Dubai Cord Research Center; FDA: Federal Drug Administration; cGMP: Current Good Manufacturing Practice ISO: International Organization for Standardization; DCGI: Drugs Controller General of India; CAP: Certified Analytics Professional Certification; HTA: Health Technology Assessment; AABB: Association for the Advancement of Blood & Biotherapies; AATB: American Association of Tissue Banks; AED: United Arab Emirates Dirham

About 36 private banks are also located in the US. [58] The private banks charge for collecting, processing, and preserving the newborn UCB between \$1,300.00- 2,200.00 and an average annual storage fee of \$125.00. Prices vary by company and country. For instance, private UCB-B based in Dubai asks an average of 20,000.00 AED for registration. Other increasing feed quantities depend on how many years

the parents decided to keep their newborn UCB collected in cryopreservation.

However, unlike public banks, some private banks do not follow strict quality criteria, so not all stored samples can be later applied for their intended use. Many promises or advertise clinical measures, such as using UCB-SC as a panacea to cure heart disease or autism, do not support the

application. [57] Many parents are induced to believe that they are buying the biological safety of their children and feel at peace with their minds by getting private storage at any cost. Unfortunately, they are often misinformed and confused by inaccurate information, vague promises, and aggressive marketing techniques that explode their feelings of guilt if they lose *"the only chance to save their children's lives in the future."* For this reason, the scientific community questions the creation of private UCB-B, [61–63] and some initially oppose it. [64] Several public and private banks also offer targeted donation programs and collect samples from siblings considering first-degree blood relatives who have already been diagnosed with a treatable disease with UCB. [9]

The US is leading the number of private and public banks in the world's most developed economies (The G7). Inside the Gulf Cooperation Council (GCC), Saudi Arabia leads with a public bank, followed by the United Arab Emirates (UAE), with a mixed one. Other private ones are run by foreign companies in Dubai, as shown in Table 5. [65]

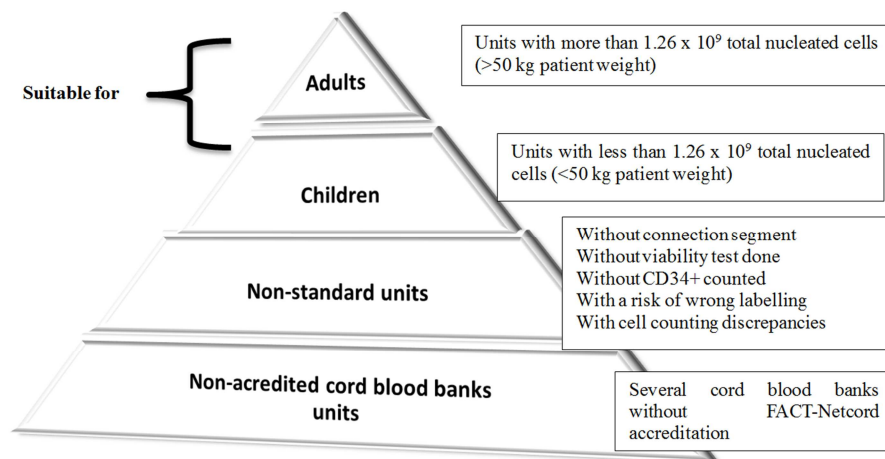


Figure 1. Figure representation of the quality of UCB-banking inventories all over the world suitable for transplantation in adults and children according to the International Registry data known as the "Iceberg Effect". Adapted from Reference [66].

UCB banks can be adapted to provide other cell products for immunotherapy and RM because of the reduced tendency for UCB-T compared to the total number of unrelated HSC-T as the percentage done globally changed from 13% in 2018 to 10% in 2021, as per the WMDA 2021 Financial and Activities report [67] rendering current CB collection programs inefficient. However, they are a source of UCB well suited for other applications. UCB-B can make available HLA-typed genetically diverse cells as starting material for off-the-shelf personalized therapies. Throughout these developments, the essential value of the altruistic gift that the donor initially expressed must be maintained. Consideration of the need to develop new products for advanced therapy medicinal products (ATMPs) from voluntary UCB donations will be facilitated by discussions among and collaborations between banks. Making the latest products available as starting material will facilitate their evaluation and clinical use, as recommended [68].

3.6.1. Cellular Manipulation Techniques

Techniques increasing the process's efficiency have been

In the Netherlands is a complete international database of BM and UCB donors, thanks to WMDA, a non-profit foundation that took over the Bone Marrow Donors Worldwide (BMDW) activities and the NetCord Foundation in 2017. They are keeping the Bone Marrow Donor Registry (BMDR), with 39,836,751 total donors, 804,475 total UCB units, and a total of 40,641,226 BM unrelated donors (of which 36,768,735 registered via the WMDA- accredited or qualified organizations), according to data submitted by 137 sources organizations of 55 countries. [1]

Unlike these figures, in the private non-accredited UCB-B, the number of stored UCB-Us is unknown. However, two of the largest in the US report on their websites amount to 500,000 units each. An analysis conducted in 2009 found that the most significant number of UCB-Us stored worldwide does not meet the quality criteria required for use in the UCB HSC transplantation, called the "Iceberg effect" (Figure 1). [66]

adapted and developed since the beginning of the activity in the UCB-B by defining the critical points of the process and automation.

The critical procedures in the process are: [66]

- 1) UCB collection technique.
- 2) Fresh storage and transport techniques.
- 3) Product handling techniques include volume reduction, cryopreservation, and cold storage.
- 4) Technique of sending, delivery, defrosting, and unit transplantation.

All techniques must have a prior validation, which ensures the achievement of provided initial product for the donor and obtained respecting their rights; a well-defined and safe final product for the patient; and a revalidation program to ensure the maintenance of the performance of the techniques. [66]

Analytical tests and quality controls

During the process, analytical tests are performed to quantify and qualify the defined properties of the product. In addition, these properties are verified by quality controls, and criteria issued by qualified professionals are included in the

screening of infectious diseases. [66]

Donation Phase

It is necessary to act in the following ethical aspects: [66, 69]

- 1) Respect for individual human rights: The donor is the pregnant woman who acts on behalf of the newborn. She must be informed before delivery about the program, the benefits of the donation, and the possible risk of damage. With the information received, she must sign a consent that authorizes the manipulation of her product for the proposed therapeutic use, which is usually a document signed in triplicate copies (for the mother, maternity hospital, and the UCB-B). The donation must be altruistic, accepting that there is no financial compensation and assigning ownership of the product to the UCB-B; The donor must be of legal age (over 18 years of age) and be in adequate mental conditions to make these decisions. [69]
- 2) Safety for the donor: The only potential risk described in the scientific literature derives from realizing an early grip conditioned by the donation. However, it has been found that early impingement can prepare an average reduction of 1 g/dL of hemoglobin over the average of newborns but can cause problems only for newborns under 34 weeks, explicitly excluded from the program. On the other hand, there is no risk to the mother's or newborn's health. [66, 70]
- 3) Safety for the recipient: HSC transplantation can transmit genetic or infectious diseases from the donor to the recipient. Therefore, screening measures are included during the donation process to minimize that risk and based on the review of the clinical history and the previous serological studies before delivery. [66, 70] Nevertheless, other ethical related issues will be covered at the end of this review.

Handling phase

It includes the entire process from the collection of the UCB to the delivery to the transplant center. The measures used to control quality are:

- 1) Product characterization, defining the cellular content, the content of hematopoietic progenitors, and their transfusion characteristics such as blood group and HLA.
- 2) Sterility studies after performing manipulations and before and after the cryopreservation of the sample.
- 3) Monitoring of target cells during the process.
- 4) Storage log.
- 5) Registration of transport from maternity to the bank and the transplant center. [66]

Shipping and transplant phase

It depends on the transplant center, and it is the medical team's responsibility that treats the receiving patient. However, the UCB-B must ensure that the destination center is an authorized center for performing this type of therapeutic procedure and should follow the result of the infusion and transplant to detect possible anomalies. [66]

- 1) Thawing result: cell characterization and viability.
- 2) Clinical follow-up: on learning, GvHD, and survival.
- 3) Recommended checklist to avoid incidents in the reception of the UCB-B product in the transplant center is shown in Table 6. [66]

3.6.2. Use of the Stored UCB in UCB-Banks

Only some samples of UCB collected are viable for transplants because they need to contain more cells, are contaminated, or could have low viability. [59] In some public centers, these not useful samples for clinical use can reach up to 70% of the total collections. [57] However, they serve for experimental research and development.

Table 6. Recommended checklist for each cryopreserved cord blood unit on arrival at the Transplant Center. Adapted from Reference [4].

Quality Area	Features	Checking
Safety/Identity	Traceability	Alphanumeric labelling Labels
	Leakage	Transportation cage sealing Bag integrity
	Confirmatory testing realized in the connected tubing attached	Cord Blood HLA Blood mother HLA ABO grouping Gender
	Standard Operational Procedures	Instruction on arrival Program fulfilment
	Transportation associated risks	Internal transference inside the center Weight of the thermic transportation cage Position of the thermic transportation cage
Potency	Significant dangerous events (>-150 °C)	Cold data-logger registry The temperature reading on arrival Nucleated cells viability (>50%)
	Results of the testing carried out in the connected tubing attached	Viable CD34+ cells recovery (>50%) Growing of Colony Forming Units (CFU) Clone >10%
	Standard Operational Procedures	Thawing procedure validated

Legend: HLA: human histocompatibility antigens.

3.7. Establishment of an Abu Dhabi-Based UCB Collection and Cryopreservation Program

Saving lives with UCB is unquestionable; in the practical scenario of Abu Dhabi, several patients could benefit from the new scope of the AD-BMT® Program UCB by incorporating a mixed or hybrid UCB-B, especially those without an HLA compatible relative or with rapid progress or their disease. The location of the UCB-B in Abu Dhabi needs to have a maternity hospital or several ones as a source of UCB donors, which would facilitate the start of UCB collection work and its refrigerated initial conservation and transport. The "*Abu Dhabi UCB Collection and Cryopreservation Program*" designed to provide thousands of donations requires the participation of many parent couples and maternal hospitals trained staff and will improve the perinatal care process. Public health education campaigns promoting the altruistic donation of the UC are necessary to have a public or mixed UCB-B that responds to national demand and, eventually, to international requests, so it is essential to consider the practical implications and limitations to optimize the bank's usefulness [41, 71] and to avoid the so-called "Iceberg effect." [66]

First, it is necessary to determine the number of patients who could benefit from this initiative; second, select the optimal size of the bank according to the predefined quantifiable targets. Other factors should be considered, such as the costs and quality of the program. [9, 13, 34, 72] ADSCC's laboratories can carry out HLA studies by automated molecular biology methods with state-of-the-art technology, cell quantification by flow cytometry, and initial serological test for syphilis, HIV-1, HIV-2, HTLV-I, HTLV-II, Hepatitis B, and C, EBV, CMV, and other bloodborne pathogens, with their respective nuclear acid PCR confirmatory test. Although, even with a small space, we can be equipped to have the specialized UCB and associated tissue processing and cryopreservation infrastructure, such as a specific "clean room" laboratory area for the UCB bags' cellular manipulation, a cryogenic laboratory with a programmable freezer for the initial processing to finally keep samples in high-efficiency liquid nitrogen (L2N) tanks, such as a robotized system for the prolonged cryopreservation at -196°C, and the previous use of another quarantine smaller L2N tanks, all needed for this objective. This cryogenic area, at the service of the AD-BMT® program, would also store HSC from other programs and even apheresis-collected products. Both institutions need to have highly qualified scientific staff in this matter and well-organized quality management. The size of the UCB-B should have at least 5,000 UCB-Us with these characteristics.

3.8. Umbilical Cord Blood Banks' Responsibilities

The primary function of the UCB-Bs is to assure patients, family members, and their health providers that they are committed to providing high-quality, potent, and pure products and will not transfer any infectious, hematological,

or immunological disease to their recipients. [57] The UCB-Bs have a wide diversity in the methodology used, and it has become necessary to make a standardization effort that contributes to improving the quality of the units stored. In 1988, NetCord was founded, a group formed by long-experienced UCB HSC banks from the US, Europe, Japan, and Australia. This Group has developed standards based on national and international regulations accepted by the different accreditation-related bodies, such as the FACT of the University of Nebraska, in the US, in operation since 1994, JACIE, and ISHAGE, among others. [56, 73]

3.9. Regulatory Framework for Umbilical Cord Blood Banks

UCB-B regulations, standards, and accreditation promote such assurances and continue to work to improve and achieve progress in the quality of products for transplant treatments and cell therapy and to develop RM applications. It is a paradigm that all those involved in the collection and supply of UCB for clinical use work with the same goals and the same standards, including the analysis of the results of transplants as part of their quality programs [56, 73] that is why a new UCB-B must work from the beginning in the accreditation process.

3.9.1. National and International Umbilical Cord Blood Banks Standards.

In the US, the Food and Drug Administration (FDA) regulates the UCB under "Human Cells, Tissues, and Human Tissue and Cell-derived products" (HCT/P). [74, 75] After October 2011, all unrelated UCB donations used for transplants in the US must have an FDA license or be covered by a New Drug Research (NDR) acceptance license for the FDA. [53] UCB can be used in HSC transplantation procedures in patients with some disorders affecting the hematopoietic system. [53, 74]

All UCB banks, public and private, must comply with FDA requirements for establishing records and lists, current regulations on Good Tissue Practices, and donor research and testing of infectious agents (except when the UCB is going to be used in the donor itself). The FDA periodically inspects both types of banks. Public banks must also obtain a Biological License as the FDA considers that UCB products for HSC-Allo-T have a systemic effect and must be regulated as biological products and medicines. [76] Nevertheless, the UCB stored for personal use or used in first and second-degree relatives of consanguinity does not require the approval of this agency before use. The European Union (EU) regulates the UCB regarding safety and quality related to donation, search, testing, procedures, preservation, storage, and distribution of human tissues and cells. [77]

The similarity between these regulations is that they adhere to Good Manufacturing Practices (GMP) to obtain safe and effective products for their intended use. The Abu Dhabi's Department of Health (DOH) issued guidelines on cell therapy and bone marrow transplantation and warned about the risks

of unauthorized use. [78, 79]

All standards for UCB-B are designed to provide minimum guidelines for all operations to be carried out in a bank to ensure the supply of quality products while protecting research, development, and new products. Adherence to these standards is not an exclusive means of adhering to industry standards or local, national, or international laws. [56] The criteria for UCB-B must be internationally accepted or harmonized because the best UCB product, selected for its HLA compatibility and cell count, is usually found in another country. [58] Transportation across borders requires compliance with the regulations of the sending and receiving countries. The standards are developed by consensus, based on the best available scientific evidence, emphasizing the research results related to clinical application in UCB recipients. When no published data is available, they are based on accepted scientific theories. The standards are written by world leaders in invited cell therapy and UCB-B programs: recognized clinicians, scientists, technologists, and quality experts who have gone through the continuity of work in the UCB-B processes. The standards do not dictate how to meet a requirement, and even if international, its intention is not to include each of the needs issued by government regulations. [57]

As UCB-Bs is in a rapidly evolving area and standards need to develop dynamically, they are revised and adjusted based on periods, with the option to publish interim measures based on changes in applicable laws and regulations, field experience, or misinterpretations. In addition to standards, an accreditation manual was parallel developed to offer guides to each site applicant and inspector. This manual is intended to explain and rationalize specific criteria and provide explanations, examples, and alternative tools that could be useful in the accreditation process. They are not an exhaustive list of the possible ways of complying with the standards, and their only intention is to offer examples since there are many

effective mechanisms to achieve compliance with the standards and to inspect the UCB-B that aspires to its accreditation. [57]

The NetCord-FACT standards apply to UCB-Us for use in unrelated and related receivers. To comply with both standards, the UCB-B must maintain the quality management program documentation and the use of validated procedures and have certified suppliers, reagents, and equipment. Additionally, the NetCord-FACT standards require traceability of the results in the clinical use of the products received from the bank. [57]

3.9.2. Umbilical Cord Blood Banks Accreditation

The accreditation is based on a documented demonstration of compliance with the updated standards edition. It establishes a uniform level of practice and promotes high-quality practices/products, leading to better results in the UCB-B product's clinical application in patients and raising the range of the establishment as a quality organization to inform patients, insurance companies, and governments that the organization is dedicated to excellence in patient care and laboratory practices. [57]

It includes the provision of evidence for external validation through on-site inspections and facilitates the establishment of quality management and process control to minimize errors and non-conformities. [57] Voluntary accredited institutions search through rigorous processes, demonstrating their belief that patients' needs are their paradigm. All FACT- NetCord inspectors are expert, trained, and active volunteers in the field. Generally, three inspectors spend two full-time days at the facilities to observe and review. [58] Any UCB-B that wishes to list its UCB-Us in the BMDW Registry must be certified by the FACT- NetCord [56] or the Association for the Advancement of Blood & Biotherapies (AABB) as summarized in Table 7, [80] and NetCord members must possess FACT accreditation. [57]

Table 7. UCB-Bs accredited by the Association for the Advancement of Blood & Biotherapies (AABB); adapted from the AABB website [80].

No.	State/Territory	Description	City	Country
1	ANDORRA	Cellab *	Sant Julià De Lòria	Andorra
2	SP	Hospital Israelita Albert Einstein *	Sao Paulo	Brazil
3		CordVida *		
4	ON	Create Cord Blood Bank	Toronto	Canada
5		Inception Lifebank Cord Blood Program Inception Bioscience	Mississauga	
6		Progenics Cord Blood Cryobank *	Toronto	
7	BC	Canadian Blood Services' Cord Blood Bank	Ottawa	
8		HealthCord Cryogenics Corporation	Vancouver	
9	AB	Canadian Blood Services' Cord Blood Bank	Edmonton	
10	QC	OVO Biosurance	Montreal	
11	VITACURA	Vidacel	Santiago de Chile	Chile
12	JILIN	Sunbird Regenerative Medical Engineering Co, Ltd.	Changchun	
13	YUHANG	Zhejiang Cord Blood Bank/Zhejiang Lvkou Biotechnology Co Ltd *	Hangzhou	
14	GUANGDONG	Shenzhen Beike Biotechnology Co., Ltd. *	Shenzhen	
15		Guangdong Cord Bld Bk Guangzhou Tianhe Nuoya Bio-Eng. Co LTD *	Guangzhou	
16	BEIJING	Beijing Cord Blood Bank, Beijing Jiachenhong Bio-Tech Co. LTD *	Beijing	China, PR
17		Boyalife Inc.	Wuxi	
18	JIANGSU	Jiangsu Beike Bio-Technology Co., Ltd *	Taizhou	
19	LIAONING	Shenyang Engineering Technology R&D Center of Cell Therapy	Shenyang	
20	HONG KONG	HealthBaby Biotech (HK.) Co, Ltd *	Shatin, NT	

No.	State/Territory	Description	City	Country
21		Cryolife Company Limited (CRYOLIFE) *	Shatin	
22		Cordlife (Hong Kong) Ltd. *	Shatin, New Territories	
23		Mononuclear Therapeutics Limited *	Hong Kong	
24		StemCyte Taiwan Co., Ltd.	Linkou	
25	NEW TAIPEI CITY	Healthbanks Biomedical Co, Ltd	New Taipei City	China,
26		Taiwan Advance Bio-Pharm, Inc. *		Taiwan
27	NEIHU DISTRICT	Bionet Corporation *	Taipei City	
28		Bionet Corporation	Tainan City	
29	NICOSIA	CBB Lifeline Biotech LTD *	Strovolos	Cyprus
30		BioKryo GmbH	Saarbrücken	Germany
31	CUMBAYÁ, LA PRIMAVERA	Biocells Discoveries Internacional SA *	Quito, Pichincha	Ecuador
32		Cell Safe Cord Blood Bank *	Cairo	Egypt
33	ENGLAND	Future Health Technologies, Ltd	Nottingham	Great Britain
34		Medstem Services	Marousi, Athens	
35		Biohellenika S. A. *	Thessaloniki	Greece
36		PT Cordlife Persada *	Jakarta Pusat	
37	WEST BENGAL	Cordlife Sciences India Pvt. Ltd. *	24 Paraganas (south)	India
38	TAMIL DU	LifeCell International Pvt. Ltd., Chennai *	Chennai	
39	ISRAEL	Chaim Sheba Medical Center	Tel-Hashomer	Israel
40		Babycord-Jordan *	Qastal	Jordan
41		EIL, Inc.	Tokyo	
42		StemCell Institute	Minato-ku, Tokyo	Japan
43		Cordon Vital S. A. DE C. V.	Mexico DF	Mexico
44	CYBERJAYA	CryoCord Sdn Bhd *	Cyberjaya, Selangor	Malaysia
45	Kuala Lumpur	Stemlife Berhad *	Kuala Lumpur	
46		Cordon de Vida S. A	Panamá City	Panama
47		Cordlife Medical Philippines, Inc. *	Quezon City	Philippines
48		Polski Bank Komórek Macierzystych S. A. *	Warszawa	Poland
49	COIMBRA	Stemlab SA (Crioestaminal) *	Cantanhede	Portugal
50		Cryoviva Singapore Pte Ltd *	Mapex Building	
51	SG.	Singapore Cord Blood Bank Limited		Singapore
52		Cordlife Group Limited *	Singapore	
53		Next Biosciences (Netcells) *	Midrand, Johannesburg	South Africa
54		Vidacord S. L. *	Alcala De Henares, Madrid	Spain
55		MEDEZE Group Public Co., Ltd.		
56	N/A	Cryoviva (Thailand) Ltd. *	Nakhon Pathom	Thailand
57	Dubai	Dubai Cord Blood *	Dubai	UAE
58		CellSave Arabia		
59		CBR Systems, Inc.	Tucson	
60	AZ	Celebration Stem Cell Centre	Gilbert	
61		Celularity, Inc	Florham Park	
62	NJ	Vitalant Cord Program - Allendale	Allendale	
63		StemCyte Inc.	Baldwin Park	
64	CA	San Diego Blood Bank	San Diego	
65		Cryo-Cell International Inc.	Oldsmar	
66	FL	Oneblood, Inc Ft. Lauderdale	Ft. Lauderdale	USA
67		Cord For Life	Altamonte Springs	
68		Stem Cell Cryobank	Boynton Beach	
69	MA	New England Cryogenic Center, Inc.	Marlborough	
70		Norton Healthcare, Inc.	Louisville	
71	KY	Viacord	Hebron	
72	MI	Versiti Blood Center of Michigan - Grand Rapids	Grand Rapids	
73	CO	St. Louis Cord Blood Bank and Cellular Therapy Laboratory	Aurora	
74	TX	South Texas Blood & Tissue - Donor Pavilion	San Antonio	
75	WA	Bloodworks Northwest	Seattle	
76	CO	Clinimmune Labs (CL)	Aurora	
77	OH	Cleveland Cord Blood Center	Cleveland	
78	IN	Cryopoint, LLC	Brownsburg	
79		Vinmec International Hospital Joint Stock Company *	Hanoi	
80		Mekostem Stem Cell Bank *	Ho Chi Minh City	Vietnam

Legend: The list of AABB Accredited Cord Blood Facilities specifies those cord blood banks in the US and worldwide which have attained AABB accreditation. These facilities are responsible for procuring, processing, and storing umbilical cord blood stem cells that can be used for transplantation. *Indicates that this facility has received a variance from a specific standard.

3.10. Ethical Issues in Umbilical Cord Blood Banks

There are other ethical issues we should also consider when we review UCB-B. Depending on the type of banking, public or private, bioethical principles like justice, autonomy, beneficence, and non-maleficence have been sometimes interpreted and applied differently. [3] As already mentioned, marketing campaigns of private banks are usually not accurate regarding the risk and benefits [64] Regarding justice, the private bank service is primarily unavailable due to the high prices, especially in low-income countries. The principle of autonomy is directly related to informed consent for collecting the sample. If the information is inaccurate, even if it is done as mandatory in all cases, the autonomy principle becomes vulnerable. Also, most of the time, it is taken only from the mother as a donor representing her child before birth, although the father, who is biologically and legally involved with the newborn birth, is not considered to sign. [81] Sometimes, collection during the delivery process is done to fulfill banking procedures' exigencies in obtaining as much CB as possible and not considering some risk associated with the moment of cord clamping and cutting. [81] Collection standard operation procedures and regulations must avoid such behavior because the cord nourishes and removes waste until it is clamped or spontaneously stops pulsing. [82] Any early clamp of the UC will be unethical and lead the infant to become anemic. All ethical violations must be avoided and denounced is committed because mother and child health is a priority for all healthcare services. [85]

4. Conclusion

After 30 years of UCB banking, more than 100 public UCB-Bs worldwide, and millions of UCB-Us donated altruistically, more than 800,000 clinical grade UCB-Us are now available in an international network of neonatal public UCB HSC and immune cell biobanks: a phenomenal resource of transplantable SC and other cellular material for the development of new therapies. [80] More than 4 million UCB-Us are in private banks worldwide.

An analysis of more than 50,000 UCB HSC-Allo-T performed worldwide in both children and adults to treat many different diseases, including hematologic, metabolic, immunologic, neoplastic, and neurologic disorders, concluded that the HSC dose and the degree of HLA match determined clinical success and defined the 'optimal donor-recipient pair'. [68]

During these 30 years, research in the UCB field has transformed the hematopoietic transplantation arena.

Today, scientific and clinical teams are still working on different ways to improve and expand the use of UCB cells. A significant effort has been focused on enhancing engraftment to reduce the risk of infection and cost. To that end, we must understand in detail the molecular mechanisms controlling SC self-renewal that may lead to the development of ex vivo systems for HSCs expansion, characterize the mechanisms regulating the homing of HSCs and HPCs, and

determine the relative place of UCB HSC-Allo-T, as compared to other sources. [84]

The very recent FDA approval of an UCB expanded *Gamida Cell Company* commercial product called "*Omisirge*" on April 17, 2023, means the UCB has been cultured in a laboratory to selectively increase the number of cells and thereby compensate for the limited number of blood-forming SC in a UCB-U. [85, 86]. *Omisirge* will help patients who can't find a suitable donor for a transplant, and it is hoped that *Omisirge* will take over a significant share of the market for stem cell transplants, not just the share that is currently held by UCB. In a 2021 report on the *Gamida Cell* phase 3 trial that *Omisirge* (then *Omidubicel*) is like a "gryphon", a mythical beast which has the forequarters of an eagle but the hind limbs of a lion. This is because *Omisirge* combines the best features for which transplant doctors are inclined to choose either bone marrow or UCB as the graft source for an HSC-Allo-T. [87] *Omisirge* engrafts significantly faster than BM, with a median time to neutrophil engraftment (ANC > 500) of 10 days, versus 15-17 days for BM. This is much faster than UCB transplants, which take about 20-24 days, either for single unit or double UCB transplants. [87]

5. Recommendations

This kind of results and challenges encourage us to work harder in innovative research on the basic biology of HSCs and Hematopoietic Progenitor Cells (HPCs), developing new clinical trials, and introducing the UCB-B as a research scenario in Abu Dhabi. Given the need for a UCB-B to provide cells for HSC-Allo-T based on international requirements, its construction and development will enhance the Emirate Healthcare System's capabilities. Furthermore, it will allow the Emirate to join forces with the international scientific community to fight to cure malignant and non-malignant diseases, improving the quality of life and medical services using the RM.

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