Fresh Umbilical Cord Blood

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Umbilical cord *blood* (UCB) is a rich source of hematopoietic cells that can be used to replace bone marrow components. Many blood disorders and systemic illnesses are increasingly being treated with stem cells as regenerative medical therapy. Collected blood has been stored in either public or private banks for allogenic or autologous transplantation.

umbilical cord blood | mesenchymal stem cells | collection | banking

1. Introduction

Before delving into umbilical cord blood banking, it is imperative to recognize that stem cells are components extracted from human blood, bone marrow, body tissues, skeletal muscles, and embryos [1]. Stem cells replenish themselves by dividing and producing similar daughter cells. Stem cells have the ability to withstand the process of differentiation into specific offspring cells [2]. When stem cells divide asymmetrically, they produce one stem and one non-stem cell; the daughter non-stem cell can differentiate into a more specialized one, but the daughter stem cell regains “stemness” properties [3]. Stem cells differentiated into tissues derived from germinal layers such as ectoderm, endoderm, and mesoderm are “pluripotent”. The inner cell mass is the source of embryonic cells that are suitable examples of pluripotent stem cells [4].

Three types of stem cells are commonly found, namely *embryonic*, *adult*, and *UCB*. Embryonic Stem Cells (ESCs) are commonly used in clinical trials, and specialized cells produced from ESCs are deployed in replacing the damaged cells in several degenerative disease conditions; however, this is still under research. It is challenging to understand the past and potential benefits for patients of human embryonic stem cells, adult stem cells, and umbilical cord blood stem cells. In some studies, authors have suggested that specialized neurons could be derived from embryonic stem cells and transplanted into the brains of Parkinson’s disease patients [5][6]. Hopefully, there will be more successful human trials in the future, enabling the production of cells as well as organs from embryonic or induced pluripotent stem cells. This will encourage clinicians to consider treatments in the future for an increasing number of disease conditions with the cells generated from ESCs [7]. Most adult stem cells are found in the bone marrow of the human body. Over the years, bone stem cells have been used to treat various hematological and other systemic disorders. As per the current study’s reports, the employment of stem cells has effective and swift work in the bone regenerative process [8].

2. UCB as a Regenerative Medicine

2.1. Stem Cell Transplants

Currently, hematopoietic cell transplants using stem cells from the UCB are deployed across the globe to treat cancerous and non-cancerous diseases [9]. A significant outcome from transplant procedures using this stem cell source is seen in treating different disease conditions, including hematologic, immunologic, malignant, and inherited metabolic disorders [9]. Blood stem cell transplants are required therapeutically to restore the body's ability to produce blood and immune cells [10]. Hematopoiesis, or the development of hematopoietic stem cells, can form three types of blood cells: white, red, and platelets [11]. Several studies have found that UCB is an exceptional source of ingenuous cells for creating positive pluripotent cells. The composition of umbilical cord blood is known to be 40% monocytes and 40% lymphocytes, and the remaining 20% are neutrophils and progenitor cells [12]. Recent studies have shown that UCB is a rich source of CD34+ stem cells, although it has an inadequate cell dose and takes longer to engraft. In vitro, CD34+ cells of UCB proliferate at a higher rate than other bone marrow stem cells. When UCB is transplanted in vivo, its ability to regulate is enhanced as compared to bone marrow stem cells [12] [13]. An expansion of adaptive immunotherapy employing other components of UCB, including regulating T cells, virus-specific T cells, and likely destroyer cells, has revolutionized the field and has enhanced the usefulness of UCB units [9].

According to current world count statistics (24 November 2022), more than 140 million babies are born annually. Thus, UCB is an abundant reservoir of regenerative cells waiting to be tapped [14]. As compared to other donor cell resources, the UCB collection is a safe, painless procedure, and it has a longer period of cryopreservation without affecting the characteristics of its viability and structure. It also has a reduced possibility of spreading viral infections and somatic mutations that can increase morbidity following a course of transplantation [15]. Furthermore, with the use of UCB, allogenic transplants are easily possible. It is estimated that over 115,000 solid organ transplants have been completed using UCB. Depending on the immunogenicity, some UCB cell populations verified intrinsic 'immune privileged' properties in reaction to interferon-gamma, by expressing the antigens class I and II HLA. It causes a reduction in UCB immunogenicity due to immaturity. As a result, specific UCB-derived cell lineages are valuable tools in modern regenerative medicine [16].

2.2. Ex Vivo Modulation Strategies to Enhance the Therapeutic Potential of UCB

Human Cord Blood (HCB) is intrinsically characterized by a low hematopoietic stem cell (HSC) count, which is related to deferred time engraftment, increased graft failure rates, and initial impermanence. **Table 1** shows the number of HCTs performed and reported in reported in CIBMTR (2016–2020). Initially, it was hypothesized that 16-dimethyl prostaglandin E2 (dmPGE2) regulates hematopoietic stem cell homeostasis and has a short-lived ex vivo variation that could advance clients' outcomes by progressing the efficiency of HSC dosage. According to the findings of North et al., elements that increase prostaglandin synthesis can increase HSC numbers. Cyclooxygenases promote PGE2 synthesis, which helps in the formation of HSC [17]. Molecular profiling approaches advanced HSC formation in clinical settings by determining ex vivo modulation settings such as temperature, time, concentration, and media. A phase I clinical trial is required to estimate the protection and

probability of modulating a single UCB unit with dmPGE2 (ProHema) before abridged concentration binary UCB transplantation [18].

Table 1. Number of hematopoietic cell transplantations (HCTs) performed and reported in CIBMTR (2016–2020).

Donor Type	Cell Source	2016, No.	2016, Col %	2017, No.	2017, Col %	2018, No.	2018, Col %	2019, No.	2019, Col %	2020, No.	2020, Col %
Allogenic	Bone Marrow	2011	23	2071	23	2179	23	2014	21	1507	17
Allogenic	Cord Blood	682	8	621	7	557	6	512	5	422	5
Allogenic	Peripheral Blood	6065	69	6343	70	6580	71	6865	73	7097	79
Autologous	Bone Marrow	22	<1	35	<1	27	<1	23	<1	22	<1
Autologous	Cord Blood	0	0	0	0	4	<1	2	<1	1	<1
Autologous	Peripheral Blood	12,847	100	13,337	100	13,477	100	13,710	100	12,951	100

vely treat various illnesses, the rates of UCB transplantation remain lower when compared to other types of transplants.

2.3. Evolutions in the Use of Umbilical Cord Mesenchymal Stem Cells (MSCs)

Regenerative medicine uses pluripotent stem cell isolation and identification in clinical settings. Fresh UCB contains non-hematopoietic stem cells, endothelial cells, MSCs, and an unlimited number of somatic cells [19]. Currently, UCB stem cells are widely used to treat various cardiovascular, hepatic, ophthalmic, orthopedic, neurological, and endocrine disorders [9][20]. In 2006, the International Society for Cellular Therapy defined MSCs, and this was accepted by most researchers. The criteria are as follows: (a) MSCs are required to be plastic-free during conserved traditional culture settings, (b) MSCs induce endoglin-1, ecto-5′-nucleotidase, and thymocyte antigen-1 without CD45, integrin- M, or CD79-alpha [21]. Mesenchymal stem cells have the ability to self-renew and to differentiate in multi-lineage directions [22][23]. The major known sources of mesenchymal stem cells include bone marrow, umbilical cord tissue, Wharton's jelly of the umbilical cord, UC tissue, amniotic fluid, and adipose tissue (MSCs) [24].

Figure 1 shows different applications of UCB. It is a readily available blood resource for regenerative stem cells such as hematopoietic progenitor cells (HPCs) and MSCs to treat various human diseases. Promising outcomes have been observed in the treatment of brain injuries in infants and young children through the utilization of stem cells derived from UCB [25][26]. According to Dr. Harris' report, the density within the vascular system of the heart increased in the animals treated with umbilical cord blood versus untreated animals [27]. Improvements in neurologic function after being injected with UCB stem cells was also noted in animal studies. When mice with

weakened immune systems were given human cord blood-derived CD34(+) cells through their entire bodies, two days after experiencing a stroke, it led to the creation of new blood vessels in the area that lacked oxygen and nutrients due to the stroke. This also resulted in a positive setting for the regrowth of nerve cells [28].

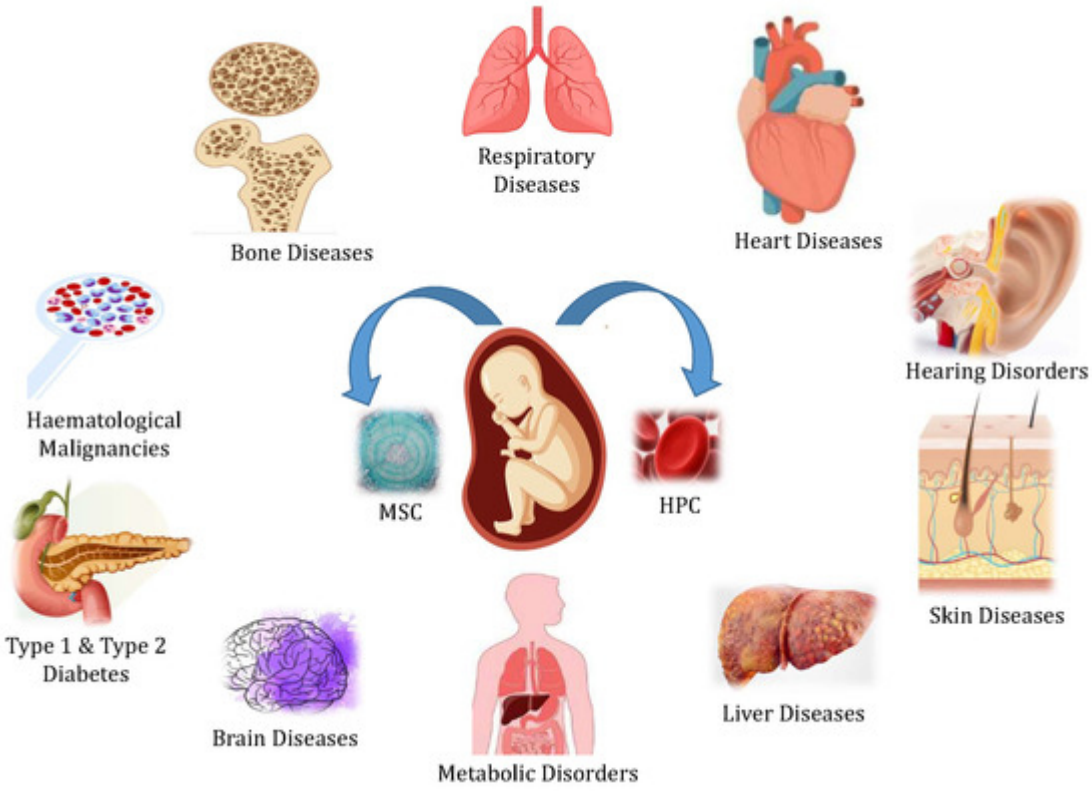

Figure 1. Use of UCB stem cells in various disease conditions—UCB stem cells are currently used in a variety of clinical applications.

Recent studies have stated that MSC-derived exosomes are easily manipulated and applied to be used in therapeutic regimens for the treatment of different disease conditions [29]. Current research shows that mesenchymal stem cells obtained from umbilical cord blood play a crucial role in wound healing, and that they produce exosomes to promote various signaling pathways that are advantageous for repairing damaged tissues, and the development of new cells [30].

UCB stem cells are one of the potential future therapeutic options for treating optical related diseases [31]. A study enrolled 68 patients with haematological malignancies who were administered myeloablative acclimatizing therapy. They were disease-free after forty months of umbilical cord blood transplantation [32]. The administration of mesenchymal stem cells has been shown to cause a reduction in inflammation in the respiratory system by suppressing transforming growth factor-β, interferon-γ, and pro-inflammatory cytokines [33]. Patients with bone disorders, such as orthogenetic disorders, benefited from treatment with umbilical cord mesenchymal stem cells [34]. Mesenchymal stem cell administration has shown improved an auditory brainstem response and distortion product otoacoustic emissions in children with hearing disorders. Additionally, promising results have shown a reduction in wound size by more than 80% [35][36].

3. Collection and Cryopreservation of UCB

3.1. Umbilical Cord Blood Collection

Umbilical cord blood is replete with stem cell sources; thus, these cells are widely used to treat genetic disorders, blood cancers, and immunological disorders. UCB stem cells are also used to treat relatives and siblings who have immunological or other non-immunological diseases [37]. Before collecting blood from the umbilical cord, midwives/doctors must obtain informed consent from the donors. Mothers must be tested for biological infectious diseases such as HIV reactivity, and Hepatitis B and Hepatitis C. Furthermore, blood is tested for sterility using bioMérieux (Hazelwood, MO) [38]. In most cases, the blood from the cord is collected immediately after the newborn's birth and before the placenta is expelled [39]. The first clamp needs to be applied just near the placenta, and the second clamp is applied at least 5 cm away from the baby's umbilicus. The umbilical cord is smeared with spirit or betadine before blood collection to ensure sterility.

Umbilical cord blood can be collected either via syringe or bag systems. In the case of the syringe system, UCB is collected using syringes of various sizes, such as a 60 cc large syringe and a 200 mL small-sized bag. Experienced collectors usually collect blood with a syringe while maintaining high sterility. Blood collection for these collectors could take up to 5 min before the placenta is expelled. According to Burton's theory, an accurate timing of cord clamping and the withdrawal of UCB is critical since umbilical blood vessels are prone to collapse due to the interruption of blood flow caused by pressure. Furthermore, this procedure is simple, noninvasive, and painless. The blood is drained into a sterile container after a simple venipuncture procedure. Nonetheless, the chances of UCB contamination are high during this simple procedure. Therefore, sterile techniques must be used when collecting umbilical cord blood [40][41][42]. Usually, neither the mother nor the baby experience risk during the collection of the blood samples as it is collected after the clamping of the cord. The collection of cord blood or cord tissue is considered to be safe for both vaginal and cesarean deliveries.

Bag collection is used by most collectors because, in their opinion, bag collection is easier than syringe collection as this procedure will be completed in two minutes. However, in both types of blood collection, sterile kits are pre-anticoagulated. They must be available with all of the necessary transportation materials, such as a double-layered restraint and a crush-resistant container. These kits must also have an optimal temperature of pH, carbon dioxide, and oxygen levels. Optimal temperature maintenance is necessary for transportation and storage prior to sending for processing, since this may have a substantial effect on cell viability, and several research papers had mentioned different ranges of temperatures for storage and shipping of the Umbilical Cord Blood Units (CBUs) such as 4 °C [43][44], 4 °C–7 °C [45], 4 °C–10 °C [46], and 4 °C–24 °C [47]. Additionally, there are debates about transporting CBUs at temperatures ranging from 15 °C to 25 °C [41]. The clotting of the entombed UCB delays the withdrawal of uncoagulated blood, which is the immediate significance of vascular obstruction. Clotting is one of the most challenging obstacles to optimal sample withdrawal. Furthermore, these kits are adequately shielded and padded with soft material to facilitate safe and secure transport by preventing physical damage. This facility also aids in temperature maintenance during transportation [40][41][48].

Before UCB collection, blood samples must be obtained from the mother for infectious disease marker (IDM) testing, which is a regulatory requirement, using the provided vacutainers. The blood drawn from the umbilicus must be transported to the lab within 28 to 34 h. The shipping process to laboratories can be successful within meticulous and recorded conditions. Preferably, a large number of UCBs should be processed partially via automation. Red Blood Cells (RBCs) are primarily depleted from UCB before cryopreservation [40][41]. Since the majority of stem cells reside in the mononuclear cell (MNC) fraction, which is only required for banking, this procedure ensures a greater number of stem cell retrievals, as red blood cells account for more than 50% of the blood collection. Furthermore, volume reduction benefits the UCB banks by reducing storage space and allowing for a reduction in dimethyl sulfoxide (DMSO) quantities in cellular products; it also reduces cytotoxicity caused by RBC defrosting [49][50][51]. Multiple procedures are used to improve the viability of stem cells, including density gradient separation and gelatin sedimentation [52].

The UCB must be padded and insulated to regulate the temperature after being collected in the kit. Before entering the main laboratory, the external surfaces of the UCB bags must be disinfected with an alcohol-based solution. After RBC sedimentation with hydroxyethyl starch and centrifugation, a pre-cryopreserved cell deferment is enhanced with mononuclear cells under strict aseptic conditions. The quality of cryopreserved UCB is routinely expressed based on the estimated total nucleated cells (TNCs), the evaluation of CD34+ and CD45+ cells, and cell variability.

3.2. Cryopreservation of Umbilical Cord Blood

In cryopreservation, very low temperatures are used to maintain the structural and functional integrity of cells and tissues; in this period, the aqueous phase classically endures the ice formation phase. Once frozen, the cells and tissues can be stored in a stable state as the low sub-zero temperature achieved is optimal, which is typically at or near the temperature of liquid nitrogen (−196 °

C) [53]. Cryopreservative agents must be used for the cell's survival and to maintain the structural integrity of the cells. An alternative procedure to cryopreservation, is vitrification, in which a solidification of the aqueous system occurs, without the crystallization and growth of ice. Umbilical cord blood is cryopreserved using an automated microprocessor-controlled cell freezer. Over 20 min, an equivalent amount of the cryoprotectant dimethyl sulfoxide (DMSO) is gently and slowly added to the autologous plasma. According to the cryopreservation protocol, the temperature is gradually reduced to −80 °

C under the control of a controlled-rate freezing process. The cells are stored in a specially constructed liquid nitrogen freezer (MVE, Inc., Laguna Beach, CA, USA) at the end of the freezing procedure, which allows for vapor storage at liquid nitrogen temperatures [54][55]. The use of autologous plasma in cryopreservation is crucial for preventing cell exposure to non-self and animal proteins. To maintain a regulated and recorded cryopreservation run for each and every frozen sample, appropriate temperature protocols governing the freezer must be used in accordance with the regulatory bodies' guidelines. Distinctive procedures for UCB cryopreservation have already

been implemented over time. Similarly, liquid- or vapor-phase nitrogen is used to store and process the UCB, in order to conserve the practicality and probability of the cell artifact [40][56].

As per the results of Broxmeyer et al. in [57], UCB preservation has had no significant impact on cell viability and production over the last 20 years. Furthermore, industrialized small-scale automated cryopreservation systems such as the Mini-BioArchive system (Cesca Therapeutics Inc., Rancho Cordova, CA, USA) have provided sufficient cellular products for UCB transplantation [58]. Technically, the banking of UCB uses two kinds of freeze cell products: plasma depletion (PD) or red cell reduction (RCR). The PD techniques remove the plasma cells and hoard all cells, freezing them in 10% dimethyl sulfoxide (DMSO). In the RCR technique, UCB is centrifuged in albumin solution to separate 21 mL of UCB, the majority of which is WBC; four ml of 50% DMSO are added, resulting in 25 mL of frozen cell suspension [59]. Although UCB methodologies are less costly to process, they are costlier to the bank and more difficult to defrost. Even though optimally washed and defrosted platelet-depleted UCB units have more total nucleated cells (TNCs), CD34+ cells, colony-forming units, and advanced cell engraftment amounts than red blood cells; they are used to treat diseases such as thalassemia [56][60].

The addition of DMSO to the UCB before freezing aids in cell protection by controlling the formation of intracellular ice crystals. However, more than 1% of DMSO can harm blood cells for more than 30 min at 37 °

C. As a result, DMSO must be removed after defrosting to reduce adverse effects on transplanted patients [59]. Only about 10% of cord blood banking units have enough cells for use in adult transplants. Barker et al. reported positive results, with approximately 23 recipients receiving a binary partially human leukocyte antigen (HLA), comparable to UCB units [61][62].

4. Public and Private Umbilical Cord Blood Banking

The New York Blood Center opened the first UCB bank in 1993. In Asia, Europe, Oceania, North America, and South America, there are a total of 100 UCB banks. Around 5 million UCB units are in use across the world. A total of 800,000 UCB units are owned by public banks, while private banks own the rest. Across the world, around 35,000 UCBTs were performed till 2019, whereas the United States alone performed 2803 from 2016 to 2020. Under ideal conditions, the biological qualities of UCB units can last for more than 10–20 years. Because UCB is readily available from unrelated donors, the search time is shortened from three to four months for bone marrow and two weeks for peripheral blood [41].

Private banks are profit organizations that provide services to store UCBs for individual use. These organizations incur storage fees but do not guarantee that the UCB from a person is useful to treat a specific disease condition of the same person (autologous UCB transfusion) or a family member [63]. The fundamental goal of private banks is to retain the high-quality UCB units used to transplant hematopoietic stem cells as regenerative medicine. Several technologies have emerged to increase the number of HSCs and to speed up engraftment. At the same time, the public UCB banks provide free services to store blood for individuals who meet the requirements for donation. These banks are typically supported or funded by federal or private companies, allowing them to provide free

collection and storage services. Personal engaged storage is not permitted in public UCB banks. The UCB in public banks is available for all patients to transplant, which is known as allogenic UCB transfusion, and it is not limited to a family or an individual [63].

The benefits and drawbacks of public versus private UCB banks vary, depending on the patient's needs, which may differ. The concept of autologous and allogenic UCB should be discussed. Because stored blood contains the same genetic material, UCB stem cells collected from newborns cannot be used to treat cancers or other genetic disorders in the same individual. However, researchers and healthcare professionals must provide accurate information to parents about the goals and indications of UCB banking, as this is one of the most important ethical concerns [64]. Public UCB banking is widely recommended for obtaining umbilical cord blood for transplantation, therapeutic use, and other medically validated indications. Public banks typically encourage allogenic donations, which are similar to blood collection in various blood banks [63].

The following are the public cord banks in India.

- Jeevan Stem Cell Bank was founded in 1995 and is supported by the Tamil Nadu government. These banks primarily treat leukemia, thalassemia, and other hematological disorders.
- The Reliance Dhirubhai Ambani Life Sciences Center in Thane, Maharashtra, is supported by Reliance Life Sciences Pvt. Ltd. Free UCB; collection and storage services are provided.
- The School of Tropical Medicine (STM) established Kolkata's first public cord blood bank.
- StemCyte Inc., Apollo Hospital Enterprises Ltd., and Cadila Pharmaceuticals Ltd. founded StemCyte India. The bank provides collection, processing, testing, and storage services for private and public umbilical cord blood units, and therapeutic applications.
- LifeCell was established in 2004 in technological collaboration with cryo-cell international. The primary goal of this bank was to assist patients in receiving lifesaving stem cell transplants to increase their chances of receiving the same stem cells.

5. Ethical Concerns in UCB Banking

Legal aspects and regulatory norms are of prime importance in the practice of UCB banking. They include obtaining informed consent, medical suggestions, proprietorship, entitlements connection to medical welfare, uses pertaining to allogenic versus autologous, legal outlines, public and private banks, budgetary systems, entrée and society, quality assurance, tracing and tracking systems, associated cost, publicizing, patenting, the protection of individual data, and maintaining confidentiality; and relations between receivers, patients, physicians, and UCB banks. Another emerging issue is the debate on donations and self-preservation at UCB banks. To address this issue, various governmental and non-government bodies have drafted rules and regulations to meet and resolve

maximum concerns [65][66]. An additional apprehension with UCB is that it should not alter routine obstetric or newborn care practices, such as delayed umbilical cord cutting and clamping, except for some of the rarest medical conditions. The time of clamping and cutting the cord became a point of disagreement for UCB collection for some obstetricians [65].

Recommendations of Professional Organizations Regarding UCB

According to the American College of Obstetricians and Gynecologists (ACOG), pregnant women should be given unbiased information about UCB. According to ACOG statistics, the estimated need for UCB transplantation to a baby or a relative is about 1 in 2700. As a result, ACOG recommends UCB only if a family member has a history of or is currently undergoing stem cell treatment, and not for future anticipated uses. According to the American Academy of Pediatrics (AAP), UCB should be regarded as free biologic insurance. It also observes that many private UCB banks are unfounded. It advises storing UCB only in public banks for general public use. The AAP recommends private UCB only if any family members are currently receiving stem cell treatment or if a diagnosis for stem cell treatment is required. Lamaze International (2010) also prohibits the advertising of cord blood collection practices, particularly by private UCB banks.

References

1. Zakrzewski, W.; Dobrzyński, M.; Szymonowicz, M.; Rybak, Z. Stem cells: Past, present, and future. Stem Cell Res. Ther. 2019, 10, 1–22.
2. Burns, C.E.; Zon, L.I. Portrait of a stem cell. Dev. Cell 2002, 3, 612–613.
3. Preston, S.; Alison, M.; Forbes, S.; Direkze, N.; Poulsom, R.; Wright, N. The new stem cell biology: Something for everyone. Mol. Pathol. 2003, 56, 86.
4. Cai, J.; Weiss, M.L.; Rao, M.S. In search of “stemness”. Exp. Hematol. 2004, 32, 585–598.
5. McGuckin, C.P.; Forraz, N. Umbilical cord blood stem cells-an ethical source for regenerative medicine. Med. Law 2008, 27, 147.
6. Vazin, T.; Freed, W.J. Human embryonic stem cells: Derivation, culture, and differentiation: A review. Restor. Neurol. Neurosci. 2010, 28, 589–603.
7. Meshorer, E. What are embryonic stem cells and how can they help us? Front. Young Minds 2020, 8, 32.
8. Murata, M.; Kawabe, K.; Hatta, T.; Maeda, S.; Fujita, M. Current status of umbilical cord blood storage and provision to private biobanks by institutions handling childbirth in Japan. BMC Med. Ethics 2022, 23, 92.

9. Gupta, A.O.; Wagner, J.E. Umbilical cord blood transplants: Current status and evolving therapies. Front. Pediatr. 2020, 8, 570282.
10. Khaddour, K.; Hana, C.K.; Mewawalla, P. Hematopoietic stem cell transplantation. In StatPearls ; StatPearls Publishing: Tampa, FL, USA, 2021.
11. Pascutti, M.; Erkelens, M.; Nolte, M. Impact of viral infections on hematopoiesis: From beneficial to detrimental effects on bone marrow output. Front Immunol. 2016, 7, 364.
12. Theunissen, K.; Verfaillie, C.M. A multifactorial analysis of umbilical cord blood, adult bone marrow and mobilized peripheral blood progenitors using the improved ML-IC assay. Exp. Hematol. 2005, 33, 165–172.
13. Hildbrand, P.; Cirulli, V.; Prinsen, R.C.; Smith, K.A.; Torbett, B.E.; Salomon, D.R.; Crisa, L. The role of angiopoietins in the development of endothelial cells from cord blood CD34+ progenitors. Blood 2004, 104, 2010–2019.
14. Gluckman, E. Milestones in umbilical cord blood transplantation. Blood Rev. 2011, 25, 255–259.
15. Liao, Y.; Geyer, M.B.; Yang, A.J.; Cairo, M.S. Cord blood transplantation and stem cell regenerative potential. Exp. Hematol. 2011, 39, 393–412.
16. Götherström, C.; Ringdén, O.; Tammik, C.; Zetterberg, E.; Westgren, M.; Le Blanc, K. Immunologic properties of human fetal mesenchymal stem cells. Am. J. Obstet. Gynecol. 2004, 190, 239–245.
17. North, T.E.; Goessling, W.; Walkley, C.R.; Lengerke, C.; Kopani, K.R.; Lord, A.M.; Weber, G.J.; Bowman, T.V.; Jang, I.H.; Grosser, T.; et al. Prostaglandin E2 regulates vertebrate haematopoietic stem cell homeostasis. Nature 2007, 447, 1007–1011.
18. Flynn, P.; Yingling, J.; Shoemaker, D. Converging technologies to enable induced pluripotent stem cells in drug discovery. Regen. Med. 2010, 5, 489–491.
19. Malgieri, A.; Kantzari, E.; Patrizi, M.P.; Gambardella, S. Bone marrow and umbilical cord blood human mesenchymal stem cells: State of the art. Int. J. Clin. Exp. Med. 2010, 3, 248.
20. Garbuzova-Davis, S.; Rodrigues, M.C.; Mirtyl, S.; Turner, S.; Mitha, S.; Sodhi, J.; Suthakaran, S.; Eve, D.J.; Sanberg, C.D.; Kuzmin-Nichols, N.; et al. Multiple intravenous administrations of human umbilical cord blood cells benefit in a mouse model of ALS. PLoS ONE 2012, 7, e31254.
21. Dominici, M.; Le Blanc, K.; Mueller, I.; Slaper-Cortenbach, I.; Marini, F.; Krause, D.; Deans, R.; Keating, A.; Prockop, D.; Horwitz, E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 2006, 8, 315–317.
22. Williams, K.J.; Picou, A.A.; Kish, S.L.; Giraldo, A.M.; Godke, R.A.; Bondioli, K.R. Isolation and characterization of porcine adipose tissue-derived adult stem cells. Cells Tissues Organs 2008,

188, 251–258.

23. Liao, H.T.; Chen, C.T. Osteogenic potential: Comparison between bone marrow and adipose-derived mesenchymal stem cells. World J. Stem Cells 2014, 6, 288.
24. Wang, J.; Cai, X.; Wang, Z.; Xu, Q.; Li, K.; Hua, C. Isolation and identification of exosomes from human adipose-derived mesenchymal stem cells. Chin. J. Tissue Eng. Res. 2019, 23, 2651.
25. Cotten, C.M.; Murtha, A.P.; Goldberg, R.N.; Grotegut, C.A.; Smith, P.B.; Goldstein, R.F.; Fisher, K.A.; Gustafson, K.E.; Waters-Pick, B.; Swamy, G.K.; et al. Feasibility of autologous cord blood cells for infants with hypoxic-ischemic encephalopathy. J. Pediatr. 2014, 164, 973–979.
26. Vendrame, M.; Gemma, C.; Mesquita, D.D.; Collier, L.; Bickford, P.C.; Sanberg, C.D.; Sanberg, P.R.; Pennypacker, K.R.; Willing, A.E. Anti-inflammatory effects of human cord blood cells in a rat model of stroke. Stem Cells Dev. 2005, 14, 595–604.
27. Harris, D.T.; Badowski, M.; Ahmad, N.; Gaballa, M.A. The potential of cord blood stem cells for use in regenerative medicine. Expert Opin. Biol. Ther. 2007, 7, 1311–1322.
28. Taguchi, A.; Soma, T.; Tanaka, H.; Kanda, T.; Nishimura, H.; Yoshikawa, H.; Tsukamoto, Y.; Iso, H.; Fujimori, Y.; Stern, D.M.; et al. Administration of CD34+ cells after stroke enhances neurogenesis via angiogenesisin a mouse model. J. Clin. Investig. 2004, 114, 330–338.
29. Nikfarjam, S.; Rezaie, J.; Zolbanin, N.M.; Jafari, R. Mesenchymal stem cell derived-exosomes: A modern approach in translational medicine. J. Transl. Med. 2020, 18, 449.
30. Kim, Y.J.; mi Yoo, S.; Park, H.H.; Lim, H.J.; Kim, Y.L.; Lee, S.; Seo, K.W.; Kang, K.S. Exosomes derived from human umbilical cord blood mesenchymal stem cells stimulates rejuvenation of human skin. Biochem. Biophys. Res. Commun. 2017, 493, 1102–1108.
31. Harris, D.; He, X.; Badowski, M.; Nicols, J. Regenerative medicine of the eye: A short review. In Stem Cell Repair and Regeneration; Imperial College Press: London, UK, 2008; Volume 3, pp. 211–225.
32. Laughlin, M.J.; Barker, J.; Bambach, B.; Koc, O.N.; Rizzieri, D.A.; Wagner, J.E.; Gerson, S.L.; Lazarus, H.M.; Cairo, M.; Stevens, C.E.; et al. Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors. N. Engl. J. Med. 2001, 344, 1815–1822.
33. Moodley, Y.; Atienza, D.; Manuelpillai, U.; Samuel, C.S.; Tchongue, J.; Ilancheran, S.; Boyd, R.; Trounson, A. Human umbilical cord mesenchymal stem cells reduce fibrosis of bleomycin-induced lung injury. Am. J. Pathol. 2009, 175, 303–313.
34. Undale, A.H.; Westendorf, J.J.; Yaszemski, M.J.; Khosla, S. Mesenchymal stem cells for bone repair and metabolic bone diseases. In Mayo Clinic Proceedings; Elsevier: Amsterdam, The Netherlands, 2009; Volume 84, pp. 893–902.

35. Chorath, K.; Willis, M.; Morton-Gonzaba, N.; Moreira, A. Mesenchymal stem cells for sensorineural hearing loss: A systematic review of preclinical studies. Mol. Biol. Rep. 2020, 47, 4723–4736.
36. Sierra-Sánchez, Á.; Montero-Vilchez, T.; Quiñones-Vico, M.I.; Sanchez-Diaz, M.; Arias-Santiago, S. Current advanced therapies based on human mesenchymal stem cells for skin diseases. Front. Cell Dev. Biol. 2021, 9, 643125.
37. Broxmeyer, H.E.; Douglas, G.W.; Hangoc, G.; Cooper, S.; Bard, J.; English, D.; Arny, M.; Thomas, L.; Boyse, E.A. Human umbilical cord blood as a potential source of transplantable hematopoietic stem/progenitor cells. Proc. Natl. Acad. Sci. USA 1989, 86, 3828–3832.
38. Kielpinski, G.; Prinzi, S.; Duguid, J.; Du Moulin, G. Roadmap to approval: Use of an automated sterility test method as a lot release test for Carticel®, autologous cultured chondrocytes. Cytotherapy 2005, 7, 531–541.
39. Harris, D.; Schumacher, M.; Rychlik, S.; Booth, A.; Acevedo, A.; Rubinstein, P.; Bard, J.; Boyse, E. Collection, separation and cryopreservation of umbilical cord blood for use in transplantation. Bone Marrow Transplant. 1994, 13, 135–143.
40. M-Reboredo, N.; Díaz, A.; Castro, A.; Villaescusa, R. Collection, processing and cryopreservation of umbilical cord blood for unrelated transplantation. Bone Marrow Transplant. 2000, 26, 1263–1270.
41. Mousavi, S.H.; Zarrabi, M.; Abroun, S.; Ahmadipanah, M.; Abbaspanah, B. Umbilical cord blood quality and quantity: Collection up to transplantation. Asian J. Transfus. Sci. 2019, 13, 79.
42. Fung, M.K.; Eder, A.; Spitalnik, S.L.; Westhoff, C.M. Technical Manual; AABB: Bethesda, MD, USA, 2017.
43. Solves, P.; Moraga, R.; Saucedo, E.; Perales, A.; Soler, M.; Larrea, L.; Mirabet, V.; Planelles, D.; Carbonell-Uberos, F.; Monleon, J.; et al. Comparison between two strategies for umbilical cord blood collection. Bone Marrow Transplant. 2003, 31, 269–273.
44. Tamburini, A.; Malerba, C.; Picardi, A.; Amadori, S.; Calugi, A. Placental/umbilical cord blood: Experience of St. Eugenio Hospital collection center. Transplant. Proc. 2005, 37, 2670–2672.
45. Nakagawa, R.; Watanabe, T.; Kawano, Y.; Kanai, S.; Suzuya, H.; Kaneko, M.; Watanabe, H.; Okamoto, Y.; Kuroda, Y.; Nakayama, T.; et al. Analysis of maternal and neonatal factors that influence the nucleated and CD34+ cell yield for cord blood banking. Transfusion 2004, 44, 262–267.
46. Jan, R.H.; Wen, S.H.; Shyr, M.H.; Chiang, B.L. Impact of maternal and neonatal factors on CD34+ cell count, total nucleated cells, and volume of cord blood. Pediatr. Transplant. 2008, 12, 868–873.

47. Bassiouny, M.; El-Chennawi, F.; Mansour, A.; Yahia, S.; Darwish, A. Optimal method for collection of umbilical cord blood: An E gyptian trial for a public cord blood bank. Transfusion 2015, 55, 1263–1268.
48. Harris, D.T. Cord blood banking for transplantation. Can. J. Clin. Med. 1997, 4, 4–12.
49. Solves, P.; Mirabet, V.; Blanquer, A.; Delgado-Rosas, F.; Planelles, D.; Andrade, M.; Carbonell-Uberos, F.; Soler, M.A.; Roig, R. A new automatic device for routine cord blood banking: Critical analysis of different volume reduction methodologies. Cytotherapy 2009, 11, 1101–1107.
50. Solves, P.; Mirabet, V.; Roig, R. Volume reduction in routine cord blood banking. Curr. Stem Cell Res. Ther. 2010, 5, 362–366.
51. Akel, S.; Regan, D.; Wall, D.; Petz, L.; McCullough, J. Current thawing and infusion practice of cryopreserved cord blood: The impact on graft quality, recipient safety, and transplantation outcomes. Transfusion 2014, 54, 2997–3009.
52. Roura, S.; Pujal, J.M.; Gálvez-Montón, C.; Bayes-Genis, A. The role and potential of umbilical cord blood in an era of new therapies: A review. Stem Cell Res. Ther. 2015, 6, 123.
53. Hunt, C.J. Cryopreservation: Vitrification and controlled rate cooling. Stem Cell Bank. 2017, 1590, 41–77.
54. Lane, T.; Plunkett, M.; Buenviaje, J.; Law, P.; Wu, L.; Patterson, H. Recovery of leukocytes in cord blood units after cryopreservation by controlled rate freeze in DMSO and storage in vapor phase liquid nitrogen. In Proceedings of the Blood; The American Society of Hematology: Washington, DC, USA, 2001; Volume 98, p. 180A.
55. Lysak, D.; Brychtová, M.; Leba, M.; Čedíková, M.; Georgiev, D.; Jindra, P.; Vlas, T.; Holubova, M. Long-Term Cryopreservation Does Not Affect Quality of Peripheral Blood Stem Cell Grafts: A Comparative Study of Native, Short-Term and Long-Term Cryopreserved Haematopoietic Stem Cells. Cell Transplant. 2021, 30, 09636897211036004.
56. Rubinstein, P.; Dobrila, L.; Rosenfield, R.E.; Adamson, J.W.; Migliaccio, G.; Migliaccio, A.R.; Taylor, P.E.; Stevens, C.E. Processing and cryopreservation of placental/umbilical cord blood for unrelated bone marrow reconstitution. Proc. Natl. Acad. Sci. USA 1995, 92, 10119–10122.
57. Broxmeyer, H.E.; Lee, M.R.; Hangoc, G.; Cooper, S.; Prasain, N.; Kim, Y.J.; Mallett, C.; Ye, Z.; Witting, S.; Cornetta, K.; et al. Hematopoietic stem/progenitor cells, generation of induced pluripotent stem cells, and isolation of endothelial progenitors from 21-to 23.5-year cryopreserved cord blood. Blood J. Am. Soc. Hematol. 2011, 117, 4773–4777.
58. Miura, J.; Minegishi, M.; Itoh, T.; Kitaura, T.; Fukawa, N.; Takahashi, H.; Suzuki, A.; Kudo, Y.; Narita, A.; Sato, Y.; et al. Quality evaluation of umbilical cord blood progenitor cells cryopreserved with a small-scale automated liquid nitrogen system. Cryobiology 2008, 57, 178–181.

59. Young, W. Plasma-depleted versus red cell-reduced umbilical cord blood. Cell Transplant. 2014, 23, 407–415.
60. Chow, R.; Lin, A.; Tonai, R.; Bolanos, R.; Connor, C.; Mendoza, A.; Heminger, R.; Chow, M.; Ho, E.; Kang, J.; et al. Cell recovery comparison between plasma depletion/reduction-and red cell reduction-processing of umbilical cord blood. Cytotherapy 2011, 13, 1105–1119.
61. Barker, J.N.; Weisdorf, D.J.; DeFor, T.E.; Blazar, B.R.; McGlave, P.B.; Miller, J.S.; Verfaillie, C.M.; Wagner, J.E. Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy. Blood 2005, 105, 1343–1347.
62. Scaradavou, A.; Brunstein, C.G.; Eapen, M.; Le-Rademacher, J.; Barker, J.N.; Chao, N.; Cutler, C.; Delaney, C.; Kan, F.; Isola, L.; et al. Double unit grafts successfully extend the application of umbilical cord blood transplantation in adults with acute leukemia. Blood J. Am. Soc. Hematol. 2013, 121, 752–758.
63. Murdoch, B.; Marcon, A.R.; Caulfield, T. The law and problematic marketing by private umbilical cord blood banks. BMC Med. Ethics 2020, 21, 52.
64. Shearer, W.T.; Lubin, B.H.; Cairo, M.S.; Notarangelo, L.D.; Hord, J.; Crouch, G.; Hale, G.; Harper, J.; Lipton, J.; Rogers, Z.; et al. Cord blood banking for potential future transplantation. Pediatrics 2017, 140, e20172695.
65. Gerdfaramarzi, M.S.; Bazmi, S.; Kiani, M.; Afshar, L.; Fadavi, M.; Enjoo, S.A. Ethical challenges of cord blood banks: A scoping review. J. Med. Life 2022, 15, 735.
66. Petrini, C. Umbilical cord blood collection, storage and use: Ethical issues. Blood Transfus. 2010, 8, 139.