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Advancements in Umbilical Cord Biobanking: A Comprehensive Review of Current Trends and Future Prospects

Sahar AlOraibi, Sebastien Taurin, Sfoug Alshammary

Molecular Medicine Department, Princess Al Jawhara Center for Molecular Medicine, Genetics, and Hereditary Diseases, College of Medicine and Health Sciences, Arabian Gulf University, Manama, Bahrain

Correspondence: Sfoug Alshammary, Arabian Gulf University, Building 293, Road 2904, Manama, Bahrain, Tel +973 17237336, Email sfoug1@gmail.com

Abstract: Biobanking has emerged as a transformative concept in advancing the medical field, particularly with the exponential growth of umbilical cord (UC) biobanking in recent decades. UC blood and tissue provide a rich source of primitive hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) for clinical transplantation, offering distinct advantages over alternative adult stem cell sources. However, to fully realize the therapeutic potential of UC-derived stem cells and establish a comprehensive global UC-biobanking network, it is imperative to optimize and standardize UC processing, cryopreservation methods, quality control protocols, and regulatory frameworks, alongside developing effective consent provisions. This review aims to comprehensively explore recent advancements in UC biobanking, focusing on the establishment of rigorous safety and quality control procedures, the standardization of biobanking operations, and the optimization and automation of UC processing and cryopreservation techniques. Additionally, the review examines the expanded clinical applications of UC stem cells, addresses the challenges associated with umbilical cord biobanking and UC-derived stem cell therapies, and discusses the promising role of artificial intelligence (AI) in enhancing various operational aspects of biobanking, streamlining data processing, and improving data analysis accuracy while ensuring compliance with safety and quality standards. By addressing these critical areas, this review seeks to provide insights into the future direction of UC biobanking and its potential to significantly impact regenerative medicine.

Keywords: umbilical cord biobanking, hematopoietic stem cells, mesenchymal stem cells, cryopreservation, artificial intelligence

Introduction

Biobanks have been recognized as one of the "top 10 ideas changing the world" by Time magazine.[1] Biobanking refers to the process of preserving biological specimens and associated data for use in health and/or medical research.[2] In 1991, following the first umbilical cord blood (CB) transplantation in 1988, the first unrelated CB bank was established at the New York Blood Centre by Dr Pablo Rubinstein. Since then, the global landscape has witnessed the rise of public umbilical cord (UC) banks, catering to altruistic UC donations for general registries, private UC banks offering commercial storage for familial use, and hybrid biobanks amalgamating these approaches.[3]

CB has been established as a source of primitive hematopoietic stem cells (HSCs) and pluripotent progenitor cells, alternatively to bone marrow or peripheral blood progenitor stem cells (PBSC). It has been utilized successfully for clinical transplantation to treat a range of hematologic malignancies and disorders, metabolic disorders, immunological defects, bone marrow failures, and other genetic diseases.[4] In comparison to other sources, CB transplantation is associated with a low incidence of acute and chronic graft-versus-host disease (GvHD), is more tolerant to partial human leukocyte antigen (HLA) mismatch between donor and recipient, presents a reduced risk of infectious disease transmission, and does not require an invasive collection method.[4,5]

Over the last few decades, it has been reported that UC tissue is also an ideal source for mesenchymal stem cells (MSCs). UC-derived MSCs (UC-MSCs) showed high similarities with bone marrow-derived MSCs. Compared to adult

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stem cells, UC-MSCs offer great therapeutic potential attributed to their enhanced self-renewal and multilineage differentiation capacity, hypo-immunogenicity, paracrine and immune-modulatory activity, genetic stability, and migratory properties.[6,7] Similarly, to HSCs, MSCs offer a great range of therapeutic potential and applicability. Clinical trials on UC-MSCs and GvHD, multiple sclerosis, cirrhosis, Crohn's disease, osteogenesis imperfecta, and leukemia, have been instituted since.[6]

As clinical applicability has expanded and become more evident, umbilical cord banking has become more widespread.[8] However, there are several limitations encompassing UC tissue and blood banking. Firstly, concerning CB, it is limited in regard to low cell dose per blood unit, which is associated with delayed engraftment and recovery. Double umbilical cord grafts are usually required, with most adults denied routine access to CB.[5,9] Similarly, manufacturing and establishing a therapeutic UC tissue-derived MSC-based product remains a challenge due to poor cell recovery and/or variable quality.[6,7,10] Moreover, the inability to further collect lymphocytes or additional stem cells in case of graft failure or disease relapse, and the risk of undiagnosed hereditary disorders being transmitted to the recipient from the donor hinder the applicability of UC.[5,9] Overall, there is less experience around UC banking and transplantation hindering its potential.[5]

Thus, to enhance the utility of UC, optimization and standardization of procedures, and progression towards better global networking is of the essence. Therefore, it is timely to review the recent advancements within the field, including advancements in safety and quality standards, harmonization and standardization initiatives, sample processing and cryopreservation, and the potential clinical applications of UC-derived stem cells. The review also presents an overview of the current status and challenges of umbilical cord biobanking and explores the future potential of artificial intelligence (AI) to enhance the efficacy and accuracy of UC biobanking procedures, further revolutionizing the field.

The Global Umbilical Cord Blood Banking Landscape: Market Growth and Trends

The number of UC worldwide is multiplying, with the global cord banking market being valued at $1.3 billion in 2020 and is expected to grow to $4.5 billion with a compound annual growth rate (CAGR) of 13.22% from 2020 to 2030.[11] In the early 2000s, only a few dozen cord banks were operational worldwide; since then, it has grown exponentially, with Bioinformant reporting there are more than 450 active banks spread out across 98 different countries, with the majority located in the United States, Italy, and Spain as of 2022.[12,13]

As of 2021, International Cord Blood Association (ICBA) estimates that more than 700,000 units of CB are stored in 160 public banks worldwide, while around 5 million units of CB are stored in more than 200 private or family UC biobanks worldwide.[14,15] While public UC biobanks are accessible at no cost, private banks can cost between $1200 to $3000, coupled with an annual storage fee varying between $100 to $400. The fees are contingent primarily on whether the cord tissue is biobanked alongside the cord blood.[16–18]

It is worth to note however, that since 2014, the Center for International Blood and Marrow Transplant Research has reported that haploidentical transplants has surpassed CB transplants. As of 2021, less than 500 allogenic HCS transplants were from a CB donor, in comparison to ~2000 haplo-HCS transplants, performed in the United States.[19,20] A similar trend was noted by the European and Chinese Blood and Marrow Transplantation groups.[21] Moreover, a study by Kanate et al indicated that the median graft acquisition charges for UC and haploidentical grafts were $88,000 and $35,000, respectively. The median total 100-day charges, encompassing both outpatient and inpatient costs, were $605,000 for UC transplants and $562,000 for haplo-HCS transplants, suggesting that haplo-HCS transplants are more cost-effective than UCB transplants.[22]

Advancements in Safety, Potency, and Quality Control Standards

The Food and Drug Administration (FDA) mandates a series of safety, purity, potency, and identity tests to assess the clinical suitability of UC samples. Under safety criteria, the UC sample must undergo several checks, including testing for infectious diseases sampled from maternal peripheral blood within a week of UC collection, a sterility test before cryopreservation to ensure the absence of bacterial or fungal growth, and a hemoglobin test to detect homozygous

hemoglobinopathy.[23] Regarding purity and potency, specific requirements include a total nucleated cell (TNC) count of ≥ 5.0×108 TNC/unit of CB hematopoietic progenitor cells (HPC), ≥ 85% viable nucleated cells, and a viable CD34+ HSC cell count of ≥ 1.25×106 CD34+/unit of CB HPC, which is analyzed pre-cryopreservation via flow cytometry. Lastly, for identity confirmation, HLA, blood group, and Rhesus (RH) typing must be reported.[23]

Additionally, the Association for the Advancements of Blood and Biotherapies (AABB) and NetCord-FACT (Foundation for the Accreditation of Cellular Therapy) standards organizations have also recently mandated testing for the presence of granulocyte-macrophage progenitor cells using colony-forming unit (CFU) assays.[24] Recent studies have even suggested assessing CFU of erythroid cells and megakaryocytes to better determine the activity of hematopoietic stem and progenitor cells.[25,26] CFU assays are considered a strong independent predictor of engraftment following UC transplantation and an indicator of potency when selecting CB units for transplantation.[27]

To further ensure the quality of CB sample, a Cord Blood Apgar (CBA) score has been suggested, providing an arbitrary score based on the weighted accumulative score of pre-cryopreservation and post-thaw graft data including TNCs, MNCs, CD34+ cell dose, CFU content, volume, and cell viability, with the addition of CD3+ testing included in the post-thaw testing criteria. This scoring system enables the prediction of neutrophil engraftment following CB transplantation.[24,28] Furthermore, multiparametric immunophenotyping, such as the use CD34+/CD45+/CD90+/CD49f +/CD38-/CD45RA-/7-ADD- as characteristic markers for HSCs, is recommended to further characterize and enumerate the CB cell population. This approach has been observed to provide a more comprehensive assessment of sample quality and increase the likelihood of successful engraftment.[29,30]

To define UC-MSCs, the International Society for Cellular Therapy (ISCT) imposed a minimum criterion which includes immunophenotyping (≥95% positive expression of CD105, CD90, CD73 and ≤2% expression of CD45, CD34, CD14, or CD11b, CD133, CD79α or CD19, HLA-DR), assessing the cells' multilineage differentiation potential (primarily their osteogenic, chondrogenic, and adipogenic potential), as well as their plastic adherence property to culture vessels.[31] Assessing UC-MSCs' ability to form CFU-fibroblasts and adopt the typical fibroblastoid, or cuboidal morphology is further suggested.[32] A viability criterion of ≥90% viable UC-MSCs is also recommended.[6]

Although minimum, testing criteria are established, functionality of UC stem cells is more regularly presumed rather than actually assessed. Routine cell viability procedures do not always correlate with the cells' functionality, as they do not provide a true representation of the fraction of proliferating ("active") stem cells present. Thus, it does not accurately equate to the potency concluded from the preserved UC sample.[24,33] This is especially problematic as clinical outcomes, including the intended response of engraftment, are correlated with the dose/size of the "active" stem cell component, which also initiates the reconstitution process.[24]

Functional assays to test for proliferation, metabolic activity,[33] and/or clonogenic differentiation activity[25] of HSCs have been suggested and observed to correspond more accurately with UC sample potencies.[34] Additionally, a study by Patterson et al indicated that the mononuclear cell (MNC) fraction is a better estimate of the quality and potency of UC-HSCs compared to the TNC fraction.[33] Thus, proposing MNC fraction testing as a more reliable measurement for quality and potency, either independently or in conjunction with TNC testing.[33]

Cryopreservation can potentially impact UC-MSC potency and quality. While some studies report no impairment of paracrine effects post-cryopreservation, others suggest diminished immunomodulatory, angiogenic, and anti-apoptotic functions.[35,36] Given the critical role of paracrine signaling in the therapeutic potency of UC-MSCs, and to better standardize their use in clinical applications, it is therefore recommended to implement measures that ensure the preservation of these functions.[35] Suggested approaches for assessing paracrine function include qRT-PCR, flow cytometry, nanoparticle tracking analysis (NTA), enzyme-linked immunosorbent assay (ELISA), liquid chromatography-mass spectrometry (LC-MS), and proteomics-based profiling.[37–39] The ISCT also calls for more predictive potency assays, including immune plasticity testing using interferon gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), interleukin-1α (IL-1α), and/or interleukin-1β (IL-1β) as priming agents, mixed lymphocyte reaction using either purified immune effector cells or PBMCs, as well as immunophenotyping. Additionally, multiple complementary assays that measure various product attributes related to quality, consistency, and stability, coupled with biological assays (immunochemical, molecular, and biochemical), are recommended.[40]

The health status of a donor can also influence the functionality and therapeutic potency of UC-MSCs.[41–44] Donor-dependent variations can lead to variable clinical outcomes, thereby negatively impacting their clinical translatability.[45] To mitigate these effects, specific therapeutic purpose-based assays, and pre-treatment with IFN-y and TNF-a may be employed to enhance treatment efficacy and address donor-related variability.[45]

An exhaustive family medical history, as well as genetic disease testing pre-cryopreservation are necessary in UC biobanking practices to ensure the biosafety of UC samples and is crucial to reduce the risk of transmitting genetic disorders through transplantation.[23,46–48] To further demonstrate the importance of genetic testing, in a study that included 3168 CB samples, 1 in 200 tested healthy individuals were found to carry a deleterious mitochondrial DNA mutation, albeit at low mutant heteroplasmy, providing an estimate of 0.00107% live births harboring a de novo mutation not detected in the mother's blood.[49] Moreover, there are varying findings regarding the cytogenetic stability of UC cells post-cryopreservation. While a karyotyping analysis in a study by Zhang et al of UC-MSCs following cryopreservation showed no numerical or structural abnormalities were present,[50] a study by Duarte et al has demonstrated the occurrence of structural aberrations and/or paracentric inversion in some UC-MSCs samples post cryopreservation.[46] As these abnormalities may have carcinogenic potential, routine chromosomal characterization post-cryopreservation has been proposed for quality control within UC biobanks.[46]

When considering UC biobanking, factors such as the mode of collection (in utero vs ex utero), delivery method, type of pregnancy (single or multiple), and gestational age should be taken into account, as these factors can also affect UC sample quality.[51–54] Studies have shown that in utero CB collection and vaginal delivery yield higher CB volumes and higher counts of TNC, $CD34^+$ cells, monocytes, and granulocytes compared to ex utero collection and cesarean section deliveries, respectively.[51,54] Multiple pregnancies and lower placental and/or birth weights have been linked to reduced CB volume, CFUs, and cell counts, suggesting these factors be considered as obstetric criteria for UC biobanking.[51–53] Interestingly, gender also plays a role, with male neonates' cord blood containing higher concentrations of CD34+ cells, while female neonates' samples tend to be richer in TNCs.[55] While maternal factors such as age and race generally do not affect cell counts, smoking during pregnancy has been associated with reduced CD34+ cell counts in female donors.[53]

Regarding UC-MSCs, maternal age, delivery mode, and gestational age have been observed to impact yield, differentiation and proliferative capacity, immunomodulatory properties, and/or gene expression, thereby affecting their therapeutic potential.[56–59] Studies have associated younger maternal age, higher gestational age and neonatal birth weight with higher UC-MSC yield.[56,58] Additionally, gestational conditions like preeclampsia, acute fetal distress, and gestational diabetes mellitus may also affect the maturation and differentiation potential of HSCs and MSCs.[60,61] Incorporating these factors into the selection criteria for UC biobanking could improve the efficiency of UC biobanks, ensuring higher sample quality while reducing processing costs, a critical factor in the expansion of biobanking initiatives.[53]

Advancements in Harmonization, Standardization, and Ethical Frameworks in Umbilical Cord Biobanking

To sustain and develop biobanks, including UC biobanks, harmonization and standardization of shared protocols concerning the procurement, collection, processing, quality assessment, and storage of samples are pivotal. As well as harmonization of material and information exchange, administrative and operational management of biobanks, alongside regulatory, and ethical procedures which include informed consent, confidentiality, and pseudo-anonymization.[62] Initiatives have emerged to address the harmonization and standardization of procedures, including the Biobanking and Biomolecular Resources Research Infrastructure-European Research Infrastructure Consortium (BBMRI-ERIC),[63] of European and Middle Eastern Society for Biopreservation and Biobanking (ESBB),[64] International Society for Stem Cell Research (ISSCR), and International Stem Cell Banking Initiative (ISCBI) which recently considered UC-derived cells. Specifically, ISCBI, their mission is to establish a scientific and ethical framework governing international stem cell banking and research followed and thus create a global biobanking network.[1] A number of global biobanks that offer UC banking are now represented in ISCBI, including the UK, Singapore, and Australian Stem Cell Banks. Similarly, the International Society for Biological and Environmental Repositories (ISBER), a global biobanking organization was

established to promote opportunities for networking and bio-sharing by harmonizing approaches in regard to biobanking policies and related processes.[64,65] These efforts will better promote stem cell research and clinical delivery, despite the multiformity of repositories.[66]

Secondly, for both research and clinical purposes, traceability and identifiability are of important basis. Impediment of obtaining patient information due to complete anonymization hinders the utility of the preserved samples. Concerns of re-identifiability and traceability, as a possible threat to privacy, obstruct the potential of biobanking. Therefore, there has been a move towards aggregating data and positing it into either public/ open access databases or into controlled access databases.[1] An example is DataSHIELD which is an open-source database that privacy-preserves biomedical and social data.[67,68] The basic premise of DataSHIELD is that researchers employ a central computer that utilizes authorized R-functions to create an impromptu pooled analysis summary without disclosing individual study site statistics, ensuring privacy and confidentiality in biobanking where patients' information remains sensitive.[67–69]

There are also established international standards, such as the ISO 20387:2018 which covers the general requirement for biobanking including defining the required quality standards for a biological sample of an intended use, and the requirements for validation and verification.[70] The ISO 20387:2018 is set to improve access to biological specimens and their associated data, harmonize and standardize procedures to advance the exchange and global availability of bio-banked material, and foster the reproducibility of relevant biomedical research. It may also be used as a tool to attest for conformity, advantageous for accreditation purposes.[70] Biobanks on an international scale has implemented these standards and have been subsequently accredited. There is also the more recent establishment of ISO/DTS 22859, which complements the ISO 20387:2018 and provides more specific requirements related to human mesenchymal stromal cells derived from UC tissue for added credibility to a UC biobank.[70]

Lastly, the potential secondary use of a sample and corresponding data within a biobank cannot be previsied. This has led to the establishment of a consent provision referred to as broad consent. This allows for a wider utility of samples while maintaining a respectful degree of participants' autonomy.[71] Upon establishing a National Cord Blood Stem Cell Bank Program, the US committee provided a list of criteria for applicable informed consent. This criteria addresses obtaining informed consent prior to labor and delivery and only after providing adequate information on the different types of UC banking, the imposition of clear policies on who must provide consent while considering paternal objections, the delivery of an abnormality to the donor if discovered during assessment, disclosure of all potential clinical and research uses in the case of public bank donation and that donation will cease the donor's ability to request a direction for the utilization of the sample.[72,73]

Automation and Cryopreservation Advances in Umbilical Cord Blood Banking

To refine the cryopreservation process of CB, volume reduction protocols are employed prior to freezing. Volume reduction maximizes storage space and, importantly, mitigates the risk of toxicity post-transplantation, a consequence of infusing excessive amounts of dimethyl sulfoxide (DMSO) and hemolyzed products.[74] Several approaches can be utilized, including manual processing techniques such as hydroxy-ethyl starch (HES) or PrepaCyte®-CB, as well as automated processing techniques like AXP® and Sepax®.[74]

The manual HES-protocol is an industry-standard CB processing method widely used within the blood banking industry. HES binds to red blood cells (RBCs) and aids in their agglutination, creating a density gradient between blood components, resulting in RBC separation from white blood cells (WBCs) and platelets during centrifugation, forming a buffy coat.[75] Prominent umbilical cord biobanks, such as LifeBank USA, Viacord, and Americord, solely utilize the HES-protocol.[76]

The PrepaCyte®-CB system is an advancement succeeding the traditional HES-protocol. It's an FDA 510K Current Good Manufacturing Practice (cGMP) approved product designed to aggregate and sediment 99% of erythrocytes while retaining non-erythroid subsets in the plasma without chemical bonding agents.[27,76–78] This translates to higher hematopoietic stem cell recovery. Cryopreservation bags can be attached to the PrepaCyte®-CB to catch the HSCs

fraction for storage. A study showed that PrepaCyte®-CB had a TNC and CD34+ recovery rate of ~72% and ~79%, respectively, following cryopreservation.[77]

Another recent development is the AXP® System, a fully automated system designed to lower CB processing costs and reduce the need for human intervention.[79,80] It's a closed, sterile system compliant with cGMP, and employs an optical detection system to separate whole blood components.[76,81] During the two-step centrifugation cycles, MNCs, TNCs, and CD34+ cells are transferred into the attached freezing bag, while RBCs and plasma are retained in separate bags in case of further processing needs. The second-generation AXP® II system was launch in 2018, alongside the XpressTRAK® software for data processing and storage[81,82]. A study observed a total recovery rate of ~77% of TNC, ~99% of CD34+, and an 88% RBC depletion, following processing using the AXP® system, while maintaining high cell viability (~90%).[83] This processing system is used within the New York Cord Blood Center.[76]

Following the AXP® system, the Sepax® was launched. The system is similar to the AXP® System in its approach to reducing volume and depleting RBCs, Sepax® gained FACT and AABB accreditation, and FDA clearance.[79,83,84] A study by Souri et al, reported a TNC recovery rate of 74.2% after volume reduction of CB sample using the Sepax® system, and a ~90% CD34+ cell recovery and cell viability.[85] Despite it currently being used in Cyroviva CB Biobank and Caricord,[79,84] this product has been discontinued from the market following the launch of the Sepax® 2 system which retains the same fundamental scientific technology of the original Sepax® system.[86]

Following the volume reduction step, the process of CB cryopreservation involves controlled-rate freezing (CRF) at a rate of 1°C per minute to reach −80°C, using specialized devices.[74,87] Subsequently, the samples are transferred to either −150°C vapor phase or −196°C liquid phase nitrogen tanks for long-term storage.[87,88] This process has also been automated through the development of the BioArchive® system, which integrates a controlled-rate freezer and an automated liquid nitrogen tank in one closed-system. This system allows for minimal exposure to transient warming events, and the individual storage and retrieval of CB units without disturbing the other cryopreserved units.[89,90] The system employs barcoding and a robotic arm with an integrated barcode reader to retrieve samples and a sample management software to maintain records of the cryopreserved CB units.[89] A comparative analysis study demonstrated significant improvements in CB units cryopreserved using the BioArchive® system.[90] These units exhibited higher viability in terms of mononuclear cells (78.2% ± 6.8% vs 81.7% ± 7.2%; conventional vs automated) and CD34+ cells (90.6% ± 6.9% vs 94.7% ± 3.5%; conventional vs automated), as well as enhanced colony-forming unit-granulocyte /macrophage (CFU-GM) counts ($7.1 \times 10^5 \pm 5.9 \times 10^5$ vs $12.3 \times 10^5 \pm 12.0 \times 10^5$; conventional vs automated). No significant difference in TNC recovery rates were noted between the conventional and BioArchive® automated system. In summary, CB units cryopreserved using the BioArchive® system exhibited superior quality compared to conventionally cryopreserved units.[90]

Isolation Methods and Challenges in Umbilical Cord Tissue-Derived Mesenchymal Stem Cell Culture

UC-derived MSCs predominantly reside in the subendothelial layer, perivascular region, and Wharton Jelly (WJ).[91] The isolation of MSCs from UC tissue employs two primary methods: the explant and enzymatic digestion methods.[7] In the explant approach, the tissue is manually digested into small fragments (usually 1–2 mm^2) and seeded into a culture vessel, allowing cells to migrate from the tissue explants into the culture medium and adhere to the vessel surface. The culture medium is changed every 3–7 days over the course of 2–4 weeks.[7,92] Conversely, the enzymatic digestion method uses solutions like collagenase, hyaluronidase, and/or dispase II to isolate cells.[7] Biobanks utilizing the explant method isolate MSCs after cryopreservation and thawing, while those employing the enzymatic digestion method isolate cells and then cryopreserve the cellular isolate. Cryopreservation of UC tissue follows a similar process to that of CB.[93]

Standard protocols for isolating and culturing MSCs however, often involve xeno-derived nutrient supplements such as fetal bovine serum (FBS) or fetal calf serum (FCS). This raises concerns about xenogenic immune reactions and viral/prion disease transmission, prompting exploration of alternatives like allogenic human AB serum,[94] autologous cord blood serum (CBS),[95] and platelet lysates (PL).[96] Studies, including one by Venugopal et al, found no significant differences in various UC-derived MSC characteristics, including colony forming potential, immunophenotype profile,

multilineage differentiation capacity, replicative senescence, and the overall expression profile of UC-MSCs when cultured in supplemented allogenic human AB serum compared to FBS.[94] Similarly, when cultured in CBS or PL, UC-MSCs demonstrated typical characteristics.[92,96]

A drawback of utilizing human serum poses challenges for the standardization of the cell manufacturing process.[97] To address this, serum-free, xeno-free media can be employed. Commercially available options include Stem Pro MSC SFM® (Invitrogen), TheraPeakTM MSCGM-CD (Lonza), MesenCult®-XF medium (Stem Cell Technologies), StemGro® hMSC medium (Corning), CellGro® Serum-free MSC medium (CellGenix), and StemMACS TM MSC Expansion Media Kit XF (Miltenyi Biotec).[97,98] Alternatively, the development of chemically defined media like S&XFM-CD, retaining UC-MSC characteristics, provides further avenues for exploration.[97]

The Expanding Applications of Umbilical Cord-Derived Stem Cells

Hematopoietic stem cells from UC units have gained FDA approval for treating approximately 80 different diseases. These include solid tumors in pediatric patients, both acute and chronic leukemia, lymphomas, myelodysplastic syndromes, non-malignant hematological diseases like sickle cell anemia, aplastic anemia, thalassemia, as well as inherited immune and metabolic disorders.[99]

Beyond the FDA-approved clinical applications of UC stem cells, UC-derived MSCs have more recently been explored for various conditions[100] (Figure 1), including cardiovascular, neurological, musculoskeletal, metabolic, and developmental disorders, as well as infectious diseases and wound healing.

In cardiovascular conditions, the use of UC-MSCs has demonstrated an increase in left ventricular ejection fraction (LVEF), overall improvements in the clinical parameters of the New York Heart Association functional class, and/or a decrease in mortality among heart failure patients (NCT01739777),[101–103] Additionally, for cases of myocardial infarction, the administration of UC-MSCs has led to a significant reduction in the size of the infarct along with an increase in LVEF[104,105] Clinical improvements have also been reported in patients with cardiomyopathy and Buerger's disease following CB and UC-MSC transplantation.[106–108]

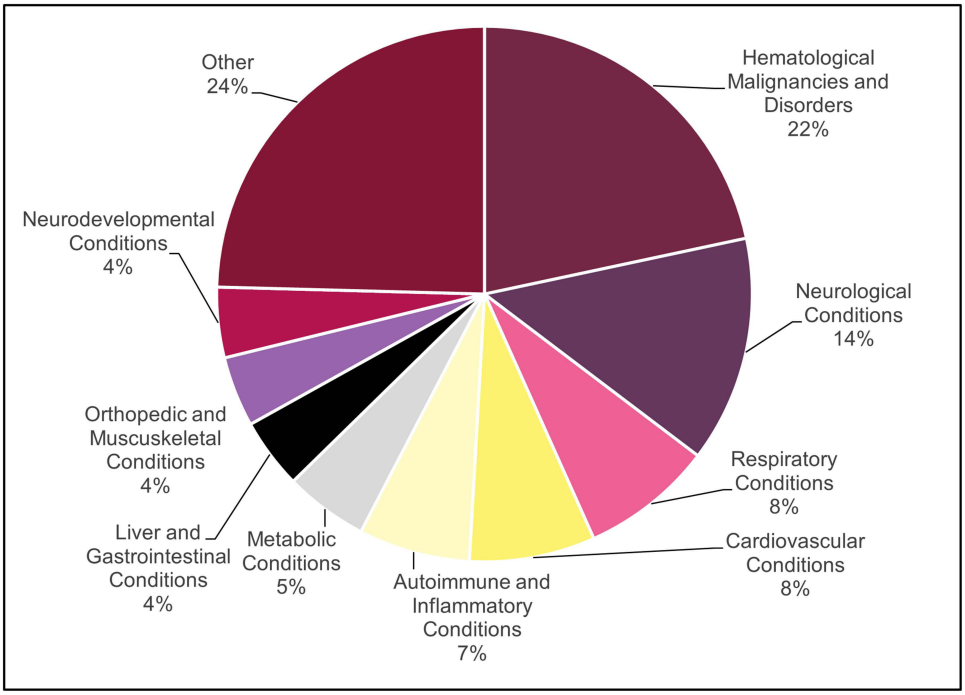

Figure 1 Proportion of the clinical conditions investigating umbilical cord-derived mesenchymal stem cell therapy: Data was sourced from ClinicalTrials.gov, spanning August 2013 to September 2023.

UC-MSCs have also demonstrated favorable clinical outcomes in neurological conditions. After intrathecal and/or intravenous administration of UC-MSCs, improvements in neurological, motor, and sensory functions, as well as bowel and bladder control, have been noted in patients with spinal cord injuries across different clinical trials,[100,109–112] Furthermore, in preclinical trials, the development of neural stem cells from UC-derived MSCs alleviated diabetic retinopathy-associated neurodegeneration in rats and showed promising outcomes in a traumatic optic neuropathy mouse model,[106,113,114] A recent clinical trial (NCT03004976) also demonstrated a clinically favorable application of UC transplantation in patients with ischemic stroke.[115] Stem cell therapy may also hold promise for neurodegenerative disorders such as Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease (AD), and Amyotrophic lateral sclerosis (ALS). Preclinical trials have shown that UC-MSCs, with their high differentiation potential, are ideal for dopaminergic neural cell replacement therapy, effectively treating PD patients.[116] Similarly, in preclinical rodent studies, UC-MSCs exhibited therapeutic potential in reducing the neuropathological deficits associated with HD.[117] Moreover, a Phase 1 clinical trial (NCT03172117) indicated that the administration of UC-MSC units reduced the levels of AD biomarkers, and suggesting that repeated administration might be even more effective.[118] As for ALS, both in vivo and clinical studies demonstrated the efficacy of UC-MSCs in ameliorating muscle atrophy, improving the rate of neuromuscular degeneration, and increasing the median survival time by two-fold, respectively[119,120] Furthermore, clinical trials (NCT01988584) (NCT03473301) on cerebral palsy have noted that administering UC-MSCs led to a reduction in radial diffusivity in the corticospinal tract, improved gross motor function, and better scores in adaptive behavior and pediatric evaluation of disability inventory.[121,122]

Thirdly, it has been observed that UC-MSCs possess a high osteogenic and chondrogenic differentiation potential.[123] Studies have demonstrated that UC-MSCs enhance bone formation parameters and promote bone regeneration in ovariectomized and osteoporotic animal models by elevating collagen levels and promoting osteoblast formation,[124–126] Regarding osteoarthritis, a study revealed that UC-derived MSCs resulted in enhanced cartilage repair in rat models.[127] Furthermore, novel suppressive effect of UC-MSCs on T follicular helper cell proliferation and differentiation has been observed in mice models, suggesting their potential to prevent the progression of rheumatoid arthritis (RA),[123,128] Similarly, in clinical studies (ChiCTR-ONC-16008770) (NCT01547091) (NCT02221258), UC-MSC treatment for RA has led to improved serological indices and immune balance as manifested by significantly lower C-reaction protein levels (CRP), erythrocyte sedimentation rate (ESR), anti-cyclic citrullinated peptide (anti-CCP), and rheumatoid factor (RF), interleukin- 6 (IL-6), and TNF-α, and an increase in interleukin-10 (IL-10) and the Treg/T helper 17 (Th17) cell ratio. The studies also reported a significant decrease in the Health Assessment Questionnaire (HAQ) and the 28-joint Disease Activity (DAS28) scores, which are used to determine disease status, further indicating the efficacy of UC-MSC therapy in RA.[129–131]

UC-derived MSCs have also been investigated for their role in modulating GvHD. In a clinical trial (ChiCTR-IOR -15006330), UC-MSCs exhibited prophylactic effect against GvHD following HLA-haploidentical stem cell transplantation, resulting in an accumulative incidence rate of chronic GvHD of 27.4% compared to 49% in the MSC and control group, respectively.[132] Notably, increased CD27+ memory B lymphocytes following UC-MSC infusions and decreased natural killer (NK) and T helper 2 (TH2) cells which are responsible for the fibroproliferative changes accompanying GvHD, were associated with a lower incidence of chronic GvHD.[132] Similarly, UC-MSCs proved effective in treating grade II to IV steroid-refractory GvHD, attributed to their high proliferative potential and suppressive effects on T-cells and NK proliferation,[133,134] Moreover, an in vivo study noted that UC-MSCs demonstrated prophylactic effect on GvHD by upregulating the CXCL1 expression, and therefore, enriching the myeloid-derived suppressor cells which present an immunoregulatory role following allogenic HSCs transplantation.[135] Co-transfusion of UC-MSCs with HSCs in severe aplastic anemia patients post-HSC transplantation also resulted in no chronic GvHD, as well as full donor chimerism and rapid hematopoietic engraftment,[136,137] Similarly, UC-MSCs reduced GvHD and enhanced engraftment in hematological malignancy patients undergoing haploidentical-HSCT with myeloablative conditioning.[138]

UC-derived MSCs are also being investigated as a potential treatment for diabetes. Their high differentiation potential and low immunogenicity make them an ideal therapy. In clinical trials (ChiCTR2200057370), UC-MSCs have been associated with improved pancreatic islet function, regulated glycemia, and reduced dosages of hypoglycemic agents in type 2 diabetes (T2D) patients[139,140] In vivo, UC-MSCs have also been observed to ameliorate insulin resistance in T2D

rat models by interfering with the inflammatory processes that induce insulin resistance.[141] UC-MSCs may also be differentiated into insulin-producing cells (IPC) and be utilized as cell therapy for type 1 diabetes (T1D). It has been observed that differentiated IPCs from UC-MSCs lowered fasting glucose and improved glucose tolerance test results in T1D mice.[142]

Following the onset of the recent pandemic, patients with severe COVID-19 infection have been treated with UC-MSCs as well. Across several trials (ChiCTR2000031494) (NCT04339660)/ (ChiCTR2000029990) (IRCT20200217046526N2) (NCT04355728), UC-MSC transfusion led to a significant reduction in inflammatory cytokines, as well as improvements in lymphocyte count, survival rates, and recovery times.[143–146]

Not least of all, UC-MSCs have also been observed to possess wound healing properties. In an in vivo and clinical trial study, UC-MSCs accelerated the healing process and induced efficient skin regeneration in chronic diabetic ulcers and burns, respectively.[147,148]

Challenges of Umbilical Cord Biobanking and Umbilical Cord-Derived Stem Cell Therapies

Although UC biobanking holds significant potential for UC-derived stem cell therapies, several limitations and challenges remain. Firstly, the risk of microbial contamination remains a concern during the procurement of CB and tissue. This is due to the inherently non-sterile nature of birth environments.[149] Extended transit and incubation times between collection and processing can further exacerbate this risk, compromising the safety, as well as possibly the cellular composition and thereby, the quality of UC samples,[149,150] Additionally, while UC tissue is often treated with antibiotics prior to transportation to mitigate the risk of contamination, the use of certain antibiotics may trigger allergic reactions, which presents another layer of complexity in ensuring biosafety and gaining regulatory approvals.[149]

The FDA has also highlighted another safety concern regarding the potential risks associated with stem cell therapies. These include the possibility of stem cells differentiating into undesired cell types or undergoing malignant transformation, potentially leading to tumor development.[151]

Moreover, more challenges arise from the need to culture UC-MSCs, as they are not considered minimally manipulated components and would require ex vivo expansion. Firstly, the choice of culture media can greatly impact the functionality of the cells. And while the alternative chemically defined media reduces variability between batches, they often require the use of exogenous proteins to ensure cell attachment, which introduces additional risks[149,152] Additionally, the variations in processing techniques, cell quantity and/or bioactivity, approaches to characterize samples and assess quality parameters, as well as inter-donor variability of UC-MSCs, complicate the standardization of the manufacturing process and the development of UC-MSC-based advanced medicinal products. These challenges hinder the process of gaining marketing authorization and limit the clinical potential of UC-MSCs.[10]

Furthermore, the use of specialized assays to assess the quality and potency of stem cells for clinical use is both resource-intensive and costly. This financial burden, coupled with the expense of culturing cells under cGMP conditions for large-scale clinical production, further impedes the development and commercialization of UC-derived stem cell therapies,[40,44,153] It must also be noted that cryopreservation practices for MSCs commonly involve the use of cryoprotectants, mainly DMSO, which carry risks of cellular and infusion-related toxicity[44,149]

Therefore, due to the challenges and high costs, advancements of UC biobanking and UC-derived cellular therapies have been hindered, and alternative approaches such as haploidentical-HCT have recently expanded.[154]

The Potential of Artificial Intelligence for Umbilical Cord Biobanking

The implementation of AI in biobanks is still in its infancy but holds the promise of progressively integrating into various aspects of cord blood biobanking. AI-based systems, which include machine-learning and/or natural language processing methods, can be designed to understand and explain the contents of consent forms and manage web-based communications with biobank participants. If a participant was to withdraw, an AI system could destroy any associated data and notify biobank's administrators to dispose of the corresponding biological specimen. Moreover, if an AI system was linked to an automated sample storage system, it can re-locate bio-samples to utilize vacant spaces within the storage

system more efficiently. AI may also be used to develop standard operating procedures (SOPs) tailored to specific biosample uses, as well as to appropriately identify or match a biospecimen to a specific study,[155,156] Additionally, AI can also institute a biospecimen collection plan for prospective biomedical research based on its analysis of the biobank's distribution and inventory status, as well as research trends.[156]

A research team has created innovative machine-learning techniques to spot outliers, or potential errors, in data or questionnaires linked to a biological sample. They employed two specific methods for this purpose. The first, known as "kurPCA", merges Principal Component Analysis (PCA) and kurtosis to identify these errors. The second method, "RAMP" (Regression Adjustment Method for Systematic Missing Pattern), is used to detect errors and simplify the data cleaning process, which would otherwise demand a substantial amount of manual effort. These methods improve the precision and efficiency of data analysis.[157]

Deep learning and machine learning techniques have been created to estimate HLA genotypes, a process that is particularly relevant to UC biobanking as regulatory bodies require HLA-typing. This imputation process is generally quicker and more cost-effective than lab-based HLA genotyping methods such as direct sequencing, allele-specific amplification, or hybridization, making it particularly beneficial for large-scale datasets. Dilthey et al developed a framework, HLA*IMP, which uses genotypic data from various genome-wide single nucleotide polymorphism (SNP) datasets to impute classical HLA alleles with an accuracy of 92–98%, comparable to lab-based HLA-typing techniques.[158] An advancement to the HLA*IMP, the HLA*IMP:02, was designed to use SNP data from diverse population and ethnicity settings to account for genotypic heterogeneity, achieving an imputation accuracy of 90–97% across European and non-European panels.[159] The HLA Genotype Imputation and Attribute Bagging (HIBAG) software program was later developed, surpassing HLA*IMP in accuracy performance. Additionally, DEEP*HLA, a convolutional neural network (CNN), was created to estimate low-frequency and rare HLA-alleles with high accuracy and the shortest processing time, making it ideal for biobank-scale data.[160]

AI can be used to assist in the diagnostic screening of infectious diseases from maternal blood samples, a required safety test for UC samples. A recent study explored the use of a stacked ensemble, which combines traditional parametric (logistic regression) and non-parametric machine learning methods (random forest and gradient boosting trees), to effectively screen for the hepatitis C virus (HCV), which is often under-diagnosed. This method achieved a precision rate of 97%, which is 66% more precise than conventional logistic regression.[160] Additionally, AI can be used in cytogenetics for karyotyping analysis to further ensure sample safety. For instance, Ikaros, a karyotyping software based on deep neural networks, can accurately analyze chromosomes, and reduce processing times.[161] Furthermore, ChromoEnhancer, a novel AI-based method, uses CycleGAN (Generative Adversarial Networks) to enhance images of neoplastic karyograms, aiding in the accurate detection of hidden chromosomal abnormalities. While it was specifically developed for neoplastic karyotyping, external cross-study validation could potentially expand its use and further enhance UC biobanking.[162]

If an umbilical cord biobank also serves as a genomic data provider, the use of "sure independence screening" (SIS), a statistical machine learning method, could be beneficial. SIS can be used in SNP analysis for genome-wide association studies (GWAS) and in analyzing genome-wide gene-gene interactions.[163] Narita et al incorporated the SIS algorithm into a software program called "EPISIS", which successfully identified functional and epistatic interactions between genetic components linked to a severe form of Stevens-Johnson Syndrome. EPISIS is capable of conducting significant gene-gene interaction analysis in biobanks.[163] Other machine learning methods, including neural networks, lasso regression, support vector machines (SVM), and random forest, can effectively predict phenotypes and identify genetic risk factors for specific diseases or conditions,[164,165] A more recent development is "ExPecto", a scalable deep learning approach that can accurately predict common or rare variants within disease or trait-associated loci based on sequence data.[166]

AI may also be utilized to aid quality assessment of UC-MSCs, which is especially important due to their significant heterogeneity, and streamlining the biobanking and cell therapy process. A study by Marklein et al, used a machine learning approach called visual stochastic neighbor embedding (viSNE), to accurately identify IFN-γ-stimulated morphological subpopulations of MSCs.[167] These subpopulations, which were otherwise unidentifiable using single or multiple morphological analysis, were identified at a single-cell resolution, and strongly corresponded with their

immunosuppressive capacity.[167] This can help better identify the functionality of MSCs population, and consequently their therapeutic potential.[167] Another study demonstrated that CNN, such as VVG16, ResNet50V2, DenseNet121, can accurately distinguish between high and low functioning MSC lines using live-cell microscopy imaging and variable efficacy markers, potentially eliminating the need for costly experimental analyses while still ensuring therapeutic efficacy as per clinical conditions.[168] Furthermore, a study by Mota et al developed a machine learning algorithm that can determine the viability of MSCs according to their morphological phenotype and characterize them as either self-replicating or slowly replicating cells.[169] Slowly replicating cells have impaired differentiation capabilities, and therefore impaired therapeutic potential.[169] AI may also be incorporated to identify MSCs based on their differentiation potential, providing a non-invasive cell quality assessment.[170]

Moreover, data mining approaches, including decision trees, artificial neural networks (ANN) and SVM, can potentially be used to develop a prediction model based on attribute selection (such as diagnosis, age, gender, and conditioning protocol during transplantation) for treatment-related morbidity and/or mortality post-allogenic HSCT, thereby aiding in donor and patient selection for treatment and improving treatment outcome.[171] A study observed ANNs sensitivity in predicting acute GvHD post HSC transplantation to be 83.3%, and 90.1% in predicting the absence of patients developing acute GvHD.[172] Furthermore, data mining approaches have been shown to not only detect the list of significant and globally selected set of variables to select HSC donors for AML patients, but also identify novel variables that may be of importance for the selection criteria.[173] This can potentially further aid UC biobanks, in terms of donor selection, given their large incorporation of biological data.[171]

AI is not widely adopted yet in UC biobanking, and its definite potential remains to be fully established. Investigating and further validating appropriate AI algorithms in relation to UC biobanking more specifically, is essential to expand the applicability of AI into the field.[174]

Conclusion and Future Directions

Umbilical cord biobanking has expanded remarkably over the past few decades, with projections indicating exponential growth. Initially focused primarily on sourcing CB-derived HSCs to treat a range of hematological malignancies, as well as non-malignant hematological, genetic, and immunological disorders, the field has more recently ventured into investigating the therapeutic applicability and potential of MSCs within UC tissue for use in cardiovascular, neurological, neurodevelopmental, musculoskeletal, and autoimmune conditions.

Despite its notoriety, optimizing UC biobanking has presented challenges, including limited cell doses, poor recovery rates, variable quality, and restricted accessibility. To overcome these obstacles, it is imperative to optimize and standardize volume reduction and cryopreservation procedures. Additionally, there is a pressing need for the standardization and harmonization of various other aspects including characterization, quality control, regulatory compliance, and ethical procedures. These efforts are mandated by regulatory bodies and biobanking programs to ensure the potency, safety, and appropriate identifiability of samples while upholding donor autonomy.

On a broader scale, efforts to harmonize procedures and protocols, inspired by initiatives like ISCBI, ISBER, and the ISO have been prompted to enhance the global UC biobanking network and improve clinical availability.

Furthermore, the incorporation of state-of-the-art of AI technologies, including machine learning, natural language processing, and deep learning, holds the promise of improving data management, biobanking operations, sample identification, diagnostic screening, and quality control. Additionally, these technologies can improve the quality and therapeutic efficacy assessments of UC-derived MSCs and facilitate the development of predictive models for HSCT-related outcomes, aiding in donor and patient selection and ultimately improving treatment results. While this integration represents a promising frontier in UC biobanking, further investigation is essential to advance its applicability within the field.

In conclusion, further endeavors should be directed toward optimizing UC biobanking practices, addressing existing challenges, and embracing technological advancements to unlock the full clinical and therapeutic potential of the field in cell therapy and regenerative medicine. By doing so, UC biobanking can contribute to expanding treatment options and enhancing medical outcomes.

Abbreviations

AABB, Association for the Advancement of Blood and Biotherapies; AD, Alzheimer's disease; AI, artificial intelligence; ALS, Amyotrophic lateral sclerosis; ANN, artificial neural networks; Anti-CCP, anti-cyclic citrullinated peptide; BBMRI-ERIC, Biobanking and Biomolecular Resources Research Infrastructure-European Research Infrastructure Consortium; CAGR, compound annual growth rate; CB, cord blood; CBA, Cord Blood Apgar; CBS, cord blood serum; CFU, colony-forming unit; CFU-GM, colony-forming unit granulocyte/macrophage; cGMP, current Good Manufacturing Practice; CNN, convolutional neural network; CRF, controlled-rate freezing; CRP, C-reactive protein; CycleGAN, Cycle Generative Adversarial Networks; DAS28, 28-joint Disease Activity; DMSO, dimethyl sulfoxide; ELISA, enzyme-linked immunosorbent assay; ESBB, European and Middle Eastern Society for Biopreservation and Biobanking; ESR, erythrocyte sedimentation rate; FACT, Foundation for the Accreditation of Cellular Therapies; FBS, fetal bovine serum; FCS, fetal calf serum; FDA, Food and Drug Administration; GvHD, graft-versus-host disease; GWAS, genome-wide association studies; HAQ, Health Assessment Questionnaire; HCV, hepatitis C virus; HD, Huntington's disease; HES, hydroxy-ethyl starch; HIBAG, HLA Genotype Imputation and Attribute Bagging; HLA, human leukocyte antigen; HPC, hematopoietic progenitor cells; HSC, hematopoietic stem cells; ICBA, International Cord Blood Association; IFN-γ, interferon gamma; IL-10, interleukin 10; IL-1α, interleukin-1α; IL-1β, interleukin-1β; IPC, insulin-producing cells; ISBER, International Society for Biological and Environmental Repositories; ISCBI, International Stem Cell Banking Initiative; ISCT, International Society for Cellular Therapy; ISSCR, International Society for Stem Cell Research; LC-MS, liquid chromatography-mass spectrometry; LVEF, left ventricular ejection fraction; MNC, mononuclear cell fraction; MSC, mesenchymal stem cell; NK, natural killer; NTA, nanoparticle tracking analysis; PBSC, peripheral blood progenitor stem cells; PCA, Principal Component Analysis; PD, Parkinson's disease; PL, platelet lysates; RA, rheumatoid arthritis; RAMP, Regression Adjustment Method for Systematic Missing Pattern; RBC, red blood cell; RF, rheumatoid factor; RH, rhesus; SIS, sure independence screening; SNP, single nucleotide polymorphism; SOP, standard operating procedures; SVM, support vector machines; T1D, type 1 diabetes; T2D, type 2 diabetes; TH17, T helper 17; TH2, T helper 2; TNC, total nucleated cell; TNF-α, tumor necrosis factor-alpha; UC, umbilical cord; UC-MSC, umbilical cord-derived MSC; viSNE, visual stochastic neighbor embedding; WBC, white blood cell; WJ, Wharton Jelly.

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