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Reviews

Cell-Based Therapy Using Umbilical Cord Blood for Novel Indications in Regenerative Therapy and Immune Modulation: An Updated Systematic Scoping Review of the Literature

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Cell-based therapy using umbilical cord blood (UCB) is being used increasingly in novel applications. To balance heightened public expectations and ensure appropriateness of emerging cell-based treatment choices, regular evidence-based assessment of novel UCB-derived therapies is needed. We performed a systematic search of the literature and identified 57 studies (814 patients) for analysis. Sixteen of these studies (353 patients) included a control group for comparison. The most commonly reported novel indication for therapy was neurologic diseases (25 studies, 476 patients), including studies of cerebral palsy (12 studies, 276 patients). Other indications included diabetes mellitus (9 studies, 149 patients), cardiac and vascular diseases (7 studies, 24 patients), and hepatic diseases (4 studies, 106 patients). Most studies administered total nucleated cells, mononuclear cells, or CD34-selected cells (31 studies, 513 patients), whereas 20 studies described the use of UCB-derived mesenchymal stromal cells. The majority of reports (46 studies, 627 patients) described cellular products obtained from allogeneic sources, whereas 11 studies (187 patients) used autologous products. We identified 3 indications where multiple prospective controlled studies have been published: 4 of 4 studies reported clinical benefit in cerebral palsy, 1 of 3 studies reported benefit for cirrhosis, and 1 of 3 studies reported biochemical response in type 1 diabetes), although heterogeneity among the studies precluded meaningful pooled analysis of results. We anticipate a more clear understanding of the clinical benefit for specific indications once more controlled studies are reported. Patients should continue to be enrolled on registered clinical trials for novel therapies. Blood establishments, transplantation centers, and regulatory bodies need to prepare for greater clinical demand.

INTRODUCTION

Although used mainly for transplantation of hematopoietic stem cells in the treatment of blood disorders, cell-based therapies using umbilical cord blood (UCB) are now being used increasingly for novel applications in nonhematopoietic diseases and as a form of cellular regenerative therapy or immune modulation. Indeed, new types of cellular products are emerging using UCB cells as a starting material, including mesenchymal stromal cells, endothelial progenitors, and neural progenitors [1]. We provided an initial scoping review of published studies and ongoing trials in 2013 and described the use of UCB for the treatment of neurologic diseases (eg, spinal cord injury, stroke, traumatic brain injury), diabetes mellitus and other autoimmune conditions, cardiac and vascular diseases, gastrointestinal diseases, and dermatologic diseases [2]. Given the rapid pace of progress in this area, we conducted an updated scoping review and analysis to provide more current insight into the use of UCB for emerging novel indications. In particular, we sought to understand whether increasing numbers of studies were including prospective control groups that would allow for an assessment of efficacy. In the face of increasing hype and elevated public expectations regarding the potential uses of UCB therapy, there is an urgent need to perform regular evidence-based assessments of emerging applications to inform cord blood banking establishments, transplantation centers, and patients, and to avoid the inappropriate use of unproven therapies [3-5].

METHODS

Searching for Relevant Published Trials

We searched for studies that described the use of human UCB to treat patients for nonconventional indications that addressed regenerative therapy

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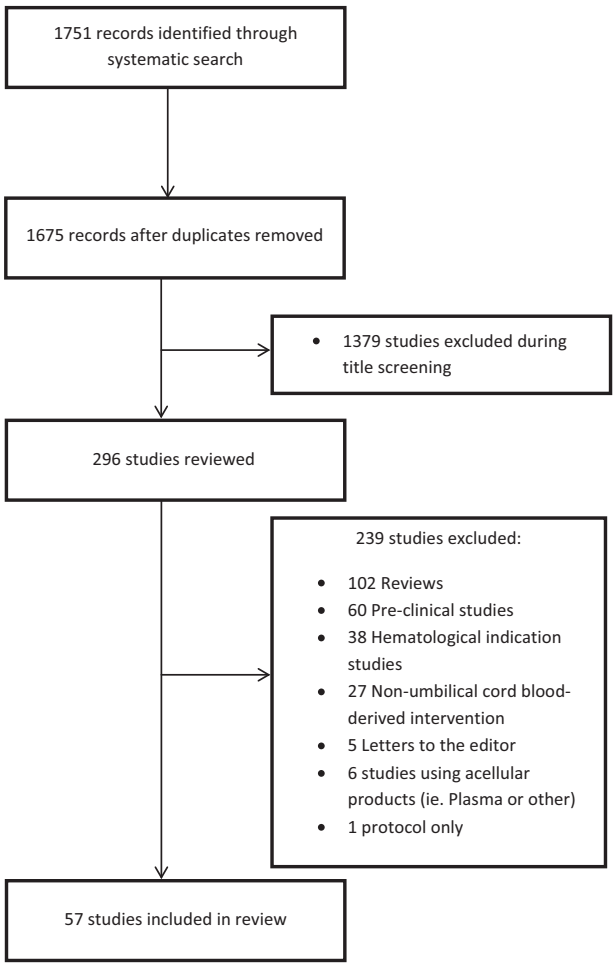

Figure 1. Results of our systematic literature search.

or modulation of immune disorders (Figure 1). A systematic scoping review of the literature was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [6] using MEDLINE and EMBASE (1950 to June 1, 2016), using a previously published search strategy [2]. We also identified any additional literature using Google Scholar and checking bibliographies of included studies.

Information Analysis

All duplicates, editorials and opinion articles, review articles, and studies involving animals and articles that did not involve human UCB were removed. The screening and selection of articles for inclusion and analysis was performed in duplicate (by M.R. and J.A.). All relevant studies were categorized based on disease process (eg, cardiovascular, diabetes, hepatic). Each article was then analyzed for the following parameters: specific disease treated, patient age, geographic region of intervention, relationship of patient to donor of banked cord blood unit (allogeneic or autologous), route of administration of cells, cell product administered, and adverse event reporting. These parameters were then tabulated and described.

RESULTS

Our search strategy initially identified 1751 articles. After duplicates were removed, 1675 articles were screened for relevance, and 296 studies underwent full text review. Of these, 239 were excluded for the following reasons: 102 reviews, 60 preclinical studies, 38 studies in which UCB was given for a standard hematologic indication, 27 studies in which a product not derived from UCB was administered, 5 letters to the editor, and 1 study protocol and 6 studies reported on acellular cord blood-derived products (4 studies using UCB serum, 1 using platelet-derived gel, and 1 using UCB mesenchymal stem cell microvesicles) [7-12]. A total of 57 studies comprising 814 patients were included for final analysis. A total of 16 studies comprising 353 patients were controlled.

The most commonly reported novel indication for therapy was neurologic diseases (25 studies, 476 patients) [13-37]. Cerebral palsy was the disease most frequently studied among this subgroup (12 studies, 276 patients) [13-24]. Other commonly studied indications included diabetes mellitus (9 studies, 149 patients) [38-46], cardiac and vascular diseases (7 studies, 24 patients) [47-53], and hepatic diseases (4 studies, 106 patients) [54-57]. The complete list of disorders studied is provided in Table 1. Of the 57 studies, 43 (75% enrolling 516 patients) reported possible benefit to patients. Thirty-four studies (60%) reported on the presence or absence of adverse events. Of these, 25 studies reported no adverse events, and 9 studies reported minor and/or serious adverse events, which are summarized in Table 2. Postinfusion headaches, fever, nausea/vomiting, and urticaria were reported in multiple patients in several studies; more serious neurologic adverse events, including seizures, subdural and subarachnoid hemorrhage, and intracranial hypotension, occurred less frequently and were associated with interventions for neurologic disorders. Two of 6 patients receiving allogeneic cells for cartilage hair hypoplasia developed acute graft-versus-host disease. Systematic patient-specific data extraction

Table 1
Clinical Studies of Regenerative Therapy or Immune Modulation Using UCB-Derived Cell Transplantation

Disorder [Reference(s)]	Published (Patients), n	Controlled Studies (Patients), n	Studies Reporting Possible Benefit (Patients), n
Neurologic [13-37]	25 (476)*	6 (171)	16 (270)
Cerebral palsy [13-24]	12 (276)	4 (141)	9 (201)
Degenerative conditions [25]	1 (114)	0	0
Traumatic brain injury [26-28]	3 (29)	1 (20)	2 (23)
Stroke [29,30]	2 (14)	0	1 (4)
Spinal cord injury [31-35]	5 (41)	1 (10)	5 (41)
Diabetes mellitus [38-46]	9 (149)	4 (53)	6 (108)
Type 1 [38-42]	5 (68)	3 (29)	3 (27)
Type 2 [43-46]	4 (81)	1 (24)	4 (81)
Cardiac and vascular [47-53]	7 (24)*	1 (12)	7 (24)
Myocardial infarction [47,48]	2 (13)	1 (12)	2 (13)
Hepatic/gastrointestinal [54-57]	4 (106)	4 (106)	2 (55)
Liver cirrhosis [54-56]	3 (81)	3 (81)	1 (30)
Hepatitis B [57]	1 (25)	1 (25)	1 (25)
Muscle/cartilage disorders [58-62]	5 (21)*	1 (11)	5 (21)
Muscular dystrophy [58-60]	3 (15)	1 (11)	2 (12)
Other [63-69]	7 (38)*	0 (0)	7 (38)
Systemic lupus erythematosus [63]	1 (16)	0	1 (16)
Total	57 (814)	16 (353)	43 (516)

* Other indications: amyotrophic lateral sclerosis [36] (1 study, 1 patient); multiple sclerosis [37] (1 study, 1 patient); hypoplastic left heart syndrome [49] (1 study, 1 patient); dilated cardiomyopathy [50] (1 study, 1 patient); diabetic erectile dysfunction [51] (1 study, 7 patients); critical limb ischemia [52] (1 study, 1 patient); basilar artery dissection [53] (1 study, 1 patient); cartilage hair hypoplasia [61] (1 study, 6 patients); articular cartilage damage [62] (not stated); optic nerve hypoplasia [64] (1 study, 2 patients); Leber hereditary optic neuropathy [65] (1 study, 1 patient); wound repair [66] (1 study, 2 patients); chronic discogenic back pain [67] (1 study, 2 patients); bronchopulmonary dysplasia [68] (1 study, 9 patients); and bone nonunion [69] (1 study, 6 patients).

Table 2
Adverse Events Reported by Studies Using UCB-Derived Cells

Reference	Indication	Total Patients, N	Adverse Events Reported, n/N
[17]	Cerebral palsy	47	Fever (20/47), vomiting (10/47), seizures (3/47), headache (3/47), dermatitis (2/47), constipation (1/47)
[19]	Cerebral palsy	20	Nausea (3/20), urticaria (2/20)
[25]	Degenerative conditions	114	Headache (3/114), fever (1/114)
[26]	Traumatic brain injury	20	Intracranial hypotension (4/20)
[32]	Spinal cord injury	10	Neuralgia (1/10)
[35]	Spinal cord injury	28	Neuropathic pain (1/28), subdural hematoma (1/28), subarachnoid hemorrhage (1/28)
[43]	Type 2 diabetes mellitus	18	Fever (4/18)
[55]	Liver cirrhosis	38	New malignancy (1/38)
[61]	Cartilage hair hypoplasia	6	Acute graft-versus-host disease (2/6)

UCB indicates umbilical cord blood.

was not possible owing to the heterogeneity of studies and lack of detail in reporting clinical outcomes. Many studies remain in abstract form, with little or no reporting on adverse events.

The lack of control groups in most studies significantly hampered determination of efficacy; however, 16 studies (353 treated patients) included control groups, and there are multiple published reports of controlled studies for 3 indications for treatment: cerebral palsy (4 studies, 141 treated patients) [13,15,20,21], type 1 diabetes (3 studies, 29 treated patients) [39-41] and liver cirrhosis (3 studies, 81 treated patients) [54-56] (see Table 3). The other controlled studies addressed traumatic brain injury (1 study, 20 treated patients) [26], type 2 diabetes (1 study, 24 treated patients) [46], myocardial infarction (1 study, 12 treated patients) [47], hepatitis B (1 study, 25 treated patients) [57], optic nerve hypoplasia (1 study, 2 treated patients) [64], and Duchenne muscular dystrophy (1 study, 11 treated patients) [47]. Although no clinical benefit was reported for ischemic cardiomyopathy or optic nerve hypoplasia, some benefit was reported for some or all of the studies for the other indications.

Pooling of data and performance of meta-analysis for the studies of cerebral palsy, type 1 diabetes, and cirrhosis was not performed owing to the marked heterogeneity among the studies. Specifically, among the studies in patients with cerebral palsy, 1 study used autologous cord blood cells, and 2 studies used allogeneic cells and also administered different growth factors (murine neural growth factor and erythropoietin). Moreover, only 1 of the studies was published in a peer-reviewed journal, limiting confirmation of many aspects related to methodology, assessment of homogeneity, and reporting of outcomes. Importantly, all 4 studies of cerebral palsy reported benefit from the infusion of UCB cells using a range of functional assessment tools, imaging, and biochemical analyses. Two of the 3 studies in type I diabetes involved transplantation with autologous cells and did not report any significant changes in biochemical markers, such as serum C-peptide or insulin requirements [39,41] and the third study used allogeneic UCB cells cocultured with autologous lymphocytes and reported an increase in serum C-peptide and reduced insulin requirements compared with controls [40]. All 3 studies addressing treatment of patients with liver cirrhosis used allogeneic UCB-derived mesenchymal stromal cells (MSCs). Only 1 study reported a benefit in the group receiving cells (30 patients) [55], whereas the other studies enrolling a total of 51 patients did not report any difference in outcomes compared with placebo and/or standard care [54,56]. Importantly, details regarding the derivation of MSCs, cell dose, and number of cell administrations could not be verified, because the publications were only in abstract form and/or published in Chinese.

Most studies administered total nucleated cells (TNCs), mononuclear cells, or CD34-selected cells (31 studies, 513 patients) (Table 4). These were most frequently administered intravenously (18 studies, 294 patients), intrathecally (5 studies, 79 patients), or both (2 studies, 115 patients). Other routes of administration were intracardiac injection, intramuscular injection, intrapancreatic transplantation, and injection into the corpus cavernosum. A total of 20 studies administered UCB-derived MSCs. MSCs were most frequently administered intravenously (10 studies, 156 patients) or

Table 3
Prospective Controlled Studies Using UCB-Derived Cells

Study	Cell Source	Cell Product	Experimental Group, n	Control Group, n	Control Treatment
Cerebral palsy					
[9]	Autologous	Bulk UCB	*	*	Placebo
[12]	Allogeneic	bulk UCB	17	17	Placebo
[41]	Allogeneic	UCB MSCs + mNGF	30	30	mNGF and PT
				30	Placebo
[43]	Allogeneic	Bulk UCB + EPO	31	32	EPO only
				35	Placebo
Liver cirrhosis					
[40]	Allogeneic	UCB MSCs	30	15	Placebo
[36]	Allogeneic	UCB MSCs	38	16	Placebo
[17]	Allogeneic	UCB MSCs and BM stem cells	13	19	Regular care
Type I diabetes mellitus					
[39]	Allogeneic	Lymph auto coculture with bulk UCB	12	3	Lymph auto only
[44]	Autologous	Bulk UCB (+DHA and vitamin D)	10	5	Placebo
[25]	Autologous	Bulk UCB	7	10	No treatment

UCB indicates unbilical cord blood; MSCs, mesenchymal stem cells; mNGF, murine neural growth factor; PT, physiotherapy; EPO, erythropoietin; BM, bone marrow; DHA, docosahexanoic acid.

* This study reported 63 total patients, without specifying how many are experimental or control.

Table 4
Cell Products Derived from UCB Used in Treatment of Nonhematopoietic Diseases

Cell Type Administered	Studies (Patients), n
TNCs, MNCs, or CD34-selected cells	31 (513)
Intravenous	18 (294)
Intrathecal	5 (79)
Intracardiac	3 (14)
Intramuscular	1 (1)
Intrapancreatic transplant	1 (3)
Intravenous and intrathecal	2 (115)
Intracavernosal injection	1 (7)
MSCs or cultured adherent cells	20 (234)
Intravenous	10 (156)
Intrathecal	5 (52)
Intravenous and intramuscular	1 (11)
Intradisc	1 (2)
Intratracheal transplantation	1 (9)
Intrarterial injection via catheter	1 (4)
Intrarticular graft	1 (not stated)
Other	6 (67)
CD34-selected cells and UBC MSCs	2 (2)
Fibrin-platelet glue with CD34-selected cells	1 (2)
Autologous lymphocytes, cocultured with allogeneic UCB cells	3 (63)
Cell source	
Allogeneic	46 (627)
Autologous	11 (187)

UCB indicates umbilical cord blood; TNCs, total nucleated cells; MNCs, mononuclear cells; MSCs, mesenchymal stromal cells.

intrathecally (5 studies, 52 patients). Other routes of MSC administration were intracardiac injection, intradisc injection, intratracheal transplantation, intra-arterial injection via catheter, and intrarticular graft injection (Table 4). The majority of reports (46 studies, 627 patients) described a cellular product obtained from an allogeneic source. We identified 11 studies (187 patients) that used a cellular product derived from an autologous source.

Gathering details on the cell dosages used in the studies was hampered by heterogeneity in reporting. Thirty-four studies (60%) reported information concerning cell dose, with some studies reporting TNC dose administered and others reporting $CD34^+$ cell dose. Cell doses were reported as a total number of cells administered, as dose of cells per infusion or injection, or as dose of cells/kg of patient mass. Of note, however, 15 studies reported multiple administrations of cell therapy, and 23 described a single administration (19 studies did not specify). Only 31 studies explicitly stated whether fresh or cryopreserved cells were used for administration, with 16 reporting administration of cryopreserved cells and 15 reporting the use of fresh cells.

In terms of geographic location, China was the country with the most published studies (26 studies, 492 patients).

Table 5
Geographic Regions Where Studies Were Performed

Geographic Region	Published (Patients), n	2012, n	Change, n
China	26 (492)	8 (261)	18 (231)
United States	13 (166)	4 (32)	9 (134)
Republic of Korea	8 (82)	4 (13)	4 (69)
Europe and United Kingdom	5 (24)	2 (3)	3 (21)
India	2 (35)	0 (0)	2 (35)
Turkey	1 (7)	0 (0)	1 (7)
Russia	1 (6)	1 (6)	0
Thailand	1 (2)	1 (2)	0
Total	57 (814)	20 (317)	37 (497)

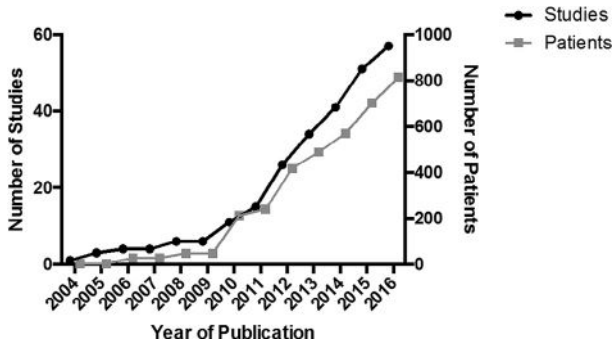

Figure 2. Cumulative number of published clinical studies (and total patients) using UCB-derived cells for novel indications in regenerative therapy or immune modulation.

China also accounted for the greatest number of new reports published since our last review (18 studies, 244 patients). Additional publications were also identified from groups within the United States (9 studies, 134 patients), Republic of Korea (4 studies, 69 patients), Europe and the United Kingdom (3 studies, 21 patients), India (2 studies, 35 patients), and Turkey (1 studies, 7 patients) (Table 5).

There has been a continuous increase in the number of published studies (8 to 10 per year since 2010) and also in the number of patients reported in these studies (approximately 100 patients per year since 2010) (Figure 2). The rate of increase in publications is most pronounced for neurologic disorders (3 per year since 2010). The rate of new publications for other indications is slower and may be leveling off (Figure 3).

DISCUSSION

In our updated systematic review of published studies on the use of UCB for novel indications in regenerative therapy and immune modulation, we have identified an acceleration of clinical activity in recent years, with increased numbers of studies and patients undergoing UCB-derived cell-based therapy. In particular, we observed marked increases in the number of studies addressing neurologic disorders, type I diabetes, and cardiovascular diseases. Moreover, we identified 3 indications for which multiple prospective controlled studies have been published: cerebral palsy, cirrhosis, and type 1 diabetes. Although heterogeneity among the studies precludes meaningful pooled analysis of results, we anticipate that a clearer understanding of the clinical benefits and safety profile for these indications will emerge in the near future. In the meantime, the use of UCB for nonconventional indications remains within the domain of clinical research, and all patients should be enrolled on registered clinical trials. The appropriateness of UCB-derived cell-based treatments is gaining clarity and blood establishments, transplantation centers, and regulatory bodies will soon need to prepare for greater clinical demand in this area.

It is most encouraging that an increasing number of published studies are including prospective control groups to assess the efficacy associated with the use of UCB cell-based products. Although heterogeneity in study parameters precluded meaningful pooling of the data for meta-analysis at this time, we anticipate that meta-analysis will be possible after more studies have been published.

With regard to the use of MSCs for the treatment of liver cirrhosis, scrutiny of the methods described in forthcoming full publications will be necessary to assess how MSCs were generated. Heterogeneity in MSC manufacturing underscores

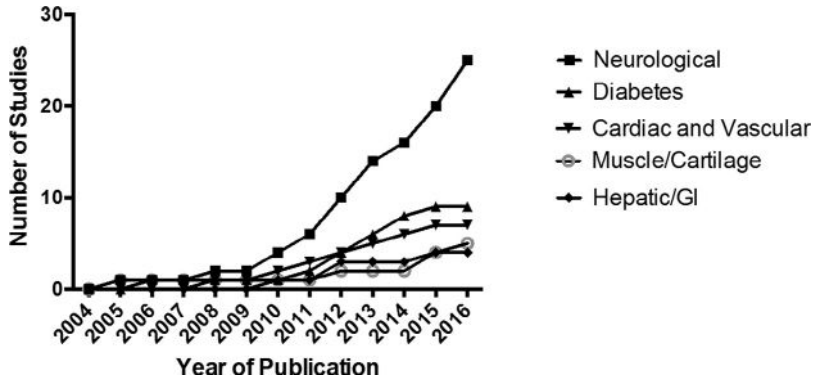

Figure 3. Cumulative number of published clinical studies using UCB-derived cells for novel indications by category of indication for treatment.

much of the clinical confusion regarding MSC therapy in other fields, such as graft-versus-host disease [70].

A quantitative meta-analysis of studies with sufficient homogeneity will allow the grading of specific indications as "proven" or "not proven yet" to facilitate evidence-based decision making with regard to the responsible and more routine use of UCB blood to treat specific diseases. Criteria for assessing whether UCB cell-based therapy is proven or unproven remains in evolution, although a recent publication from the International Society for Cellular Therapy advanced key principles aimed at defining unproven therapies [3]. Key elements of the criteria for proven therapies include the presence of a clear scientific rationale related to the expected potential benefit, understanding of the biological mechanism that supports its clinical application, sufficient data from preclinical or early clinical studies demonstrating safety of the approach, clearly described methods to assess product quality and/or manufacturing consistency, informed consent by the patient and donor, acceptable methods of administration, and the use of prospective control groups in studies assessing clinical efficacy. Although feasibility has been demonstrated for a number of diseases, significant work remains before we can assess whether UCB-derived cell-based therapy is proven for any indication.

A key challenge facing the field of regenerative therapy is excessive hype in the public domain, which may be fueled by discussion and representations in the mass media [5]. Moreover, infrastructure for UCB banking is expensive and is currently being reevaluated in many jurisdictions owing to the declining use of UCB in recent years. Certain jurisdictions appear to be investing more significantly than others, as reflected in the continuing increase in publication of studies arising from China, United States, Korea, and Europe. Jurisdictions with different models of health care delivery may develop different patterns of care depending on their capacity for UCB banking and conducting clinical trials in cell-based therapy.

The most common cell type used in the studies reported to date remains minimally manipulated cells, such as TNCs and CD34-selected cells. The use of cultured products, such as UCB-derived MSCs, is also being widely studied, and infrastructure and regulatory guidance surrounding MSC product development is likely to increase. However, no new cell types were described in the studies published since our first review, and none are anticipated in the near future. More diversity regarding routes of delivery was observed, however, highlighting the need for close scrutiny regarding safety issues. Allogeneic sources of UCB cells still dominate the study landscape to date, underscoring the important role of public UCB banks in cell-based regenerative therapy [71]. Although the majority of preclinical and early-phase clinical studies in cell-based regenerative medicine have been conducted in academic centers, blood establishments, including UCB banks, will have an expanding role as larger clinical trials develop and as experimental therapies become adopted as more proven and effective treatments [4]. Whether blood operators will be involved in manufacturing specialized cell types or performing manipulations of UCB or stem cell products remains unclear, but regardless, they will remain a critical partner in procuring donor cells, processing and storing cellular products, and overseeing regulatory adherence, and are well positioned to facilitate optimal donor selection for cell-based applications in regenerative medicine.

Our study has some limitations that should be acknowledged. As with any systematic review, it is possible that we have overlooked some publications or studies. Moreover, we have included abstracts, and a more refined understanding of the field will be possible only after peer-reviewed publication of the completed studies. The heterogeneity among studies precludes a meta-analysis, although we anticipate greater potential for pooled estimates of efficacy once more publications are available.

Although the prospect of cell-based therapy using UCB remains highly attractive and holds promise for the future, the amplified public expectations regarding UCB therapy underscores the need for rational, transparent, and evidence-based expert guidance for the benefit and protection of donors, patients, and the public.

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