

# World Journal of *Stem Cells*

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## Prospects for the therapeutic development of umbilical cord blood-derived mesenchymal stem cells

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### Abstract

Umbilical cord blood (UCB) is a primitive and abundant source of mesenchymal stem cells (MSCs). UCB-derived MSCs have a broad and efficient therapeutic capacity to treat various diseases and disorders. Despite the high latent self-renewal and differentiation capacity of these cells, the safety, efficacy, and yield of MSCs expanded for *ex vivo* clinical applications remains a concern. However, immunomodulatory effects have emerged in various disease models, exhibiting specific mechanisms of action, such as cell migration and homing, angiogenesis, anti-apoptosis, proliferation, anti-cancer, anti-fibrosis, anti-inflammation and tissue regeneration. Herein, we review the current literature pertaining to the UCB-derived MSC application as potential treatment strategies, and discuss the concerns regarding the safety and mass production issues in future applications.

**Key Words:** Umbilical cord blood; Mesenchymal stem cell; Stem cell therapy; Immunomodulation; Regenerative medicine; Therapeutic cell manufacturing processing

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**Core Tip:** Umbilical cord blood (UCB) is a primitive and rich source of mesenchymal stem cells (MSCs). UCB-derived MSCs have the potential of exerting profound immunomodulatory effects with the secretion of factors and cytokines. However, the safety and yield of UCB-derived MSCs are still a concern. Next-generation stem cell

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therapy is necessary, referring to the mass production of efficient stem cells based on the fundamental technology, to improve whole cell processing.

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## INTRODUCTION

Regenerative medicine is a medical technology specialty whereby tissues and organs, irreparably damaged by injury or disease, are restored through reconstruction or replacement in order to reestablish normal function. A current approach within the field of regenerative medicine is the development of stem cell research. Over the past 50 years, stem cell biology has advanced and focused on finding new sources of stem cells. Understanding the characteristics and the therapeutic potential of stem cells forms the basis for future prospective research in evaluating this field of regenerative medicine for clinical benefit. Mesenchymal stem cells (MSCs), known as mesenchymal stromal cells or medical signaling cells, are multipotent stromal cells that have the potential to differentiate into various cell types<sup>[1]</sup>; thus are attractive candidates for regenerative medicine. Recently, adipose tissue (AT), bone marrow (BM), dental pulp, peripheral blood, menstrual blood, fallopian tube, cord blood, liver, and lung MSCs have gained much attention due to the high proliferation and differentiation capacity of the cells obtained from these sources<sup>[2-4]</sup>.

Human umbilical cord blood (UCB) contain the youngest and most primitive MSCs, and a rich source is obtained at birth<sup>[5]</sup>. The collection of UCB is relatively easy, with no risk to the mother or baby as it does not require invasive procedures for procurement, and is ethically non-controversial. UCB collected after birth can be frozen and banked for future clinical use, without losing viability nor function<sup>[6]</sup>. Moreover, UCB has a low risk of transmitting viral infections and somatic mutations after clinical transplantation<sup>[7]</sup>. Both public and private cord blood banks have been developed to store umbilical cord blood for future use. Currently there are around twenty public cord blood banks worldwide<sup>[8-11]</sup>. The main advantages of UCB-MSC result from their properties in self-renewal, multipotency, hypo-immunogenicity, non-tumorigenicity, and immunomodulation; therefore have a broad therapeutic potential<sup>[12-16]</sup>. Despite the similar spindle-shaped morphology, UCB-derived MSCs have unique and significant advantages over adult source-derived MSCs<sup>[14,17-19]</sup>. UCB-derived MSCs are easier to obtain than BM stem cells, which are the most widely studied and harvested. The MSC proliferation rates and yield per unit volume in UCB is greater than that in BM. Further, transplantation of MSCs derived from UCB results in fewer immune system incompatibilities, such as graft-versus-host disease (GvHD). UCB-derived cells exhibit class I human leukocyte antigen (HLA), showing inherent immunoprivileged properties<sup>[6,20,21]</sup>. A typical UCB unit of approximately 100 mL includes approximately 1000 to 5000 MSCs<sup>[22]</sup>. UCB-derived MSCs are more tolerant of HLA mismatches than those derived from BM<sup>[23,24]</sup>. Additionally, the capability of storing MSCs in a bank allows UCB-derived MSCs to be used "off-the-shelf" for the treatment of various diseases. More than 5 million cord blood samples are stored in private cord blood banks for the treatment of blood and immune system disorders<sup>[11]</sup>. To date, UCB-derived MSCs have been used in around 133 clinical trials (ClinicalTrials.gov). Regardless of the success achieved in MSC clinical trials, manufacturing a therapeutic cell-based product is and will remain a challenge. Herein, we discuss the many concerns surrounding potential and current clinical applications of UCB-derived MSCs. Nonetheless, we foresee that the use of UCB-derived MSCs will continue to increase and diversify within the field of regenerative medicine.



## CHARACTERISTICS OF UCB-MSCS

### **Surface markers and self-renewal**

According to the International Society for Cellular Therapy guidelines, multipotent human MSCs show fibroblastic morphology with adherent properties during culture conditions. In addition, they express positive ( $\geq 95\%$ ) immunophenotypic markers CD105, CD73, and CD90, as well as negative expression ( $\leq 2\%$ ) of CD11b, CD14, CD19, CD34, CD45, CD79, and HLA-DR<sup>[25]</sup>. Several studies support the finding that MSCs derived from both UCB and BM express the same surface markers and differentiation capacity. However, MSCs derived from UCB have a faster population doubling time and higher fibroblast colony-forming units frequency (CFUF) in comparison to MSCs derived from BM<sup>[14,18,26]</sup>. Despite the similar cell surface immunophenotypes, the higher proliferation rate increases the potential therapeutic value. MSCs are heterogeneous populations of cells, and the diversity of the existing tissue sources adds to its complexity. The origin of the tissue can affect the secretion of MSC factors. Donor age is a critical factor affecting MSC efficacy. MSCs obtained from neonatal tissues show a longer lifespan than those obtained from adult tissues, such as adipose tissue and BM. Interestingly, UCB-derived MSCs are reported to have the lowest CFUF frequency but can be cultured for the longest period and show the highest proliferation capacity<sup>[14,18,27]</sup>.

### **Senescence and apoptosis**

The optimal MSC characteristics for clinical selection and application are slow senescence and low apoptosis rates. The function of MSCs appear to decrease with age; therefore, understanding the MSC aging process is critical for the development of therapeutic interventions to enhance the repair processes. Earlier passages of cultured MSCs are reported to have better colony efficiency<sup>[28,29]</sup>. Comparative analysis showed significantly higher CD146 expression in UCB-derived MSCs, compared to BM- and umbilical cord (UC)-MSCs<sup>[30]</sup>. Suppression of CD146 accelerates cellular senescence in MSCs, correlating with studies that showed high levels of CD146 expression delayed the cellular senescence of UCB-derived MSCs compared to other source-derived MSCs<sup>[31]</sup>. CD106 expression was weakly positive in UCB-derived MSCs, whereas umbilical cord vein - and umbilical cord Wharton's jelly - MSC lacked cell surface CD106 expression<sup>[18,30,32]</sup>. Furthermore, a significantly higher expression of HLA-ABC on the cell surface of UCB-derived MSCs was shown, compared to umbilical cord tissue-derived MSCs<sup>[33]</sup>. Comparative studies on the cellular senescence of BM-, AT, and UCB-derived MSCs demonstrated that MSCs derived from UCB had significantly lower expressions of senescence markers p53, p21, and p16. Dramatically increased senescence-associated  $\beta$ -galactosidase expression in BM- and AT-derived MSCs was observed in UCB-derived MSCs at the same passage<sup>[14]</sup>. Telomere lengths shorten after each division cycle, undergoing cellular senescence<sup>[34-37]</sup>. UCB-derived MSCs have demonstrated greater telomerase activity and longer telomere length, associated with shorter doubling time, than adult tissue-derived MSCs<sup>[38]</sup>. A higher proportion of UCB-derived MSCs in the quiescent state (G0/G1) was observed, compared to BM-derived MSCs, which possess shorter cell cycles. Taken together, the longer telomere activities and higher expression of senescence-related genes in UCB-derived MSCs results in a higher proliferative potential, maintaining the self-renewal abilities of stem cells compared to other source-derived stem cells<sup>[39,40]</sup>.

## MECHANISMS OF ACTION

### **Homing and migration**

In cell-based therapies, homing and migration of MSCs to sites of injury and tumors is a critical mechanism for delivering trophic signals<sup>[41,42]</sup>. Chemoattraction to inflammation sites facilitates trafficking of MSCs, adhesion, and infiltration to injured site. Accumulated chemokines and cytokines, platelet-derived growth factor, vascular endothelial growth factor (VEGF), stromal cell-derived factor (SDF)-1, and inflammatory cytokines, stimulate the mobilization of MSCs<sup>[41,43,44]</sup>. Chemokine receptors, C-X-C chemokine receptor type 1 (CXCR1) and CXCR4, expressed on UCB-derived MSCs are attracted to the accumulation of chemokines and cytokines at target sites<sup>[45-47]</sup>. Previous independent reports demonstrated that secretion of SDF-1 by UCB-derived MSCs plays a pivotal role in mobilization and homing *via* protein kinase B (PKB/Akt), extracellular signal-regulated kinase (ERK), and p38 signaling

pathways<sup>[48]</sup>. Subsequent adhesion of UCB-derived MSCs is brought about by adhesion molecules, vascular cell adhesion molecule, CD62, and integrins<sup>[18,44,49]</sup>. MSCs finally infiltrate into the site aided by enzymatic proteins, matrix metalloproteinase (MMP)-2 and MT1-MMP<sup>[43]</sup>.

### Tissue regeneration

Although MSCs appear to have similar potential for differentiation, significant differences have also been observed. Many studies have provided insights into the distinct differentiation capacities of UCB-derived MSCs, compared to BM- or adipocyte-derived MSCs<sup>[14,32]</sup>. Induction of osteogenesis in UCB-derived MSCs demonstrated higher increases in Alizarin Red S and developed alkaline phosphatase activity than other adult tissue-derived MSCs, respectively<sup>[17]</sup>. Gene expression profiles showed that UCB-derived MSCs had osteogenic key transcription factors, *Runx2* and *Osterix*, similar to BM-derived MSCs<sup>[50]</sup>. *Runx2* expression peaked at 3-7 d in induced BM-derived MSCs, far ahead of UCB-derived MSCs<sup>[51]</sup>. Significant increase in *Runx2* gene expression in UCB-derived MSCs has been reported in polyglycolic acid scaffolds<sup>[52]</sup>. Similarly, the arginine-glycine-aspartic acid on 3-dimensional polyurethane scaffolds and GHK peptides (Gly-His-Lys) on oxidized alginate hydrogel scaffolds have bolstered attempts to harness the osteogenic differentiation potential of UCB-derived MSCs, expressing enhanced alkaline phosphatase activity and osteogenic gene markers<sup>[53,54]</sup>. In addition, osteo-induction efficiency of UCB-derived MSCs was analyzed and assessed by metabolomics analysis of osteogenic differentiation. This revealed that UCB-derived MSCs showed sensitivity to osteogenic agents<sup>[55]</sup>. UCB-derived MSCs from bone defects promoted new bone formation in osteoporotic models, similar to non-osteoporotic bone regeneration<sup>[56,57]</sup>.

While comparing the therapeutic potentials of other adult tissue- and UCB-derived MSCs, a similar pattern in the extent and level of chondrogenic differentiation capacity was demonstrated<sup>[58,59]</sup>. Moreover, similar increases in proteoglycans were detected by safranin O staining<sup>[14]</sup>. Chondrogenic differentiation of UCB-derived MSCs has been shown by collagen type 2a1 (COL2a1) antibody staining<sup>[60]</sup>. Except for cartilage oligomeric matrix protein, chondrogenesis-related gene markers, *SOX9*, *Runx2*, *AGC1*, and *COL10a1* were not significantly different between BM- and UCB-derived MSCs, as shown by microarray analysis<sup>[15]</sup>. Using UCB-derived MSCs 3D culture systems, increased levels of mature chondrocyte-specific markers, COL2a1, COL2b, and ACAN were detected<sup>[61,62]</sup>. In rabbit and rat models, cartilage repair was observed after transplantation of UCB-derived MSCs with hyaluronic acid hydrogel composites<sup>[63-65]</sup>. Additionally, hypoxia triggered the chondrogenesis of UCB-derived MSCs in the presence of bone morphogenetic protein (BMP)-2 and transforming growth factor (TGF)- $\beta$ 1<sup>[66]</sup>.

Interestingly, several studies demonstrated that UCB-derived MSCs showed low levels of adipogenic differentiation capacity, in contrast to BM- and AT-derived MSCs<sup>[14,17,18,67]</sup>. It is difficult to induce adipogenic differentiation in UCB-derived MSCs, to reveal the production of fat droplets, identified by Oil red O staining<sup>[68,69]</sup>. However, microarray results revealed the up-regulation of adipogenesis-related genes, such as *LPL* and *PPAR $\gamma$* , in UCB-MSC, which was corroborated by quantitative RT-PCR analysis<sup>[70]</sup>. Additionally, calcium induction increased the adipogenic differentiation capacity of UCB-derived MSCs *via* Wnt5a/ $\beta$ -catenin signaling pathways<sup>[71,72]</sup>.

UCB-derived MSCs can also differentiate into neural-like cells. Similar developmental and functional characteristics to neurons were observed in neuronal differentiated UCB-derived MSCs, which expressed neuronal transcription factors mammalian achaete scute homolog-1, distal-less homeobox 1 (DLX1), and DLX2, and is reported to develop into human cortical GABAergic neurons<sup>[73]</sup>. Neuronal differentiation of UCB-derived MSCs, showing glial fibrillary acidic protein (GFAP) and nestin gene expression, was demonstrated together with a combination of chemical and growth factors during neuronal induction<sup>[74]</sup>. Disialoganglioside 2 proteins regulate neuronal differentiation of UCB-derived MSCs<sup>[75]</sup>. After transplanting UCB-derived MSCs intravenously into the animal brain area, only a small portion of MSCs remained, and expressed the neuronal markers neuron-specific nuclear protein, microtubule-associated protein-2, GFAP and class III beta-tubulin<sup>[76,77]</sup>. Brain-derived neurotrophic factor (BDNF) mediates and activates the mitogen-activated protein kinases/ERK and PI3K/Akt-dependent signaling pathways to stimulate the neural differentiation of UCB-derived MSCs<sup>[78]</sup>. Inducing the differentiation of UCB-derived MSCs with antioxidants, tropical factors, and stimulated microgravity microenvironments, resulted in the differentiation of neuronal-like cells, such as oligodendrocytes, neurons and astrocytes<sup>[79-81]</sup>.

UCB-derived MSCs can also differentiate into cells of the cardiomyocyte lineage.



Myocardial proteins with or without application of oscillating pressure augmented cardiac-specific genes, *α-MHC*, *Cx43*, *cTNT*, and *ANP*. Consistent with *in vitro* data, the transplantation of UCB-derived MSCs into acute myocardial infarction models, lead to improved cardiac function and expression of cardiomyocyte-specific markers after 8 wk<sup>[82]</sup>. VEGF, which induces angiogenesis, was also engineered into UCB-derived MSCs to control the VEGF level and applied to a rat myocardial infarction (MI) model. The VEGF-inducible MSCs showed significant improvement in left ventricle ejection fraction. Fractional shortening with decreased MI size, fibrosis, and increased muscle thickness protected the cardiomyocytes from MI damage<sup>[83]</sup>. TGF-β1, a key anti-fibrosis factor can be secreted by UCB-derived MSCs and acts upon the tissue by improving both muscle and skin regeneration after cleft repair<sup>[84]</sup>. VEGF, IL-10, and tumor necrosis factor-stimulated gene (TSG)-6 secreted by UCB-MSCs also affects wound healing in a severe burn model in rats<sup>[85]</sup>.

### Immunomodulation

The differentiation capacity of UCB-derived MSCs suggests that umbilical cord blood is a highly appropriate cell source for regenerative purposes. Additionally, the main advantage of UCB-derived MSCs in injured tissue regeneration is immunomodulation (Figure 1). It is well known that MSCs release growth factors and cytokines along with extracellular vesicles to modulate immune responses. Among different origin-derived MSCs, UCB-derived MSCs showed higher immune modulatory effects by both direct immune cell contact and secretion factors<sup>[86]</sup>. Secreted factors from UCB-derived MSCs affect angiogenic properties in animal models. UCB-derived MSCs possess unique paracrine properties that can affect angiogenesis, as confirmed by the formation of vascular tubular structures<sup>[87]</sup>. Thrombospondin-2 secreted by UCB-derived MSCs also induced chondrogenic differentiation<sup>[88,89]</sup>. Growth/differentiation factor -15 secretion from UCB-derived MSCs is reported to induce hippocampal neurogenesis and synaptic activity in an Alzheimer's disease mouse model<sup>[90]</sup>. Secreted proteins, decorin and progranulin, from UCB-derived MSCs induced anti-apoptotic and anti-neurotoxic activity of amyloid-β42, which is involved in the pathogenesis of Alzheimer's disease<sup>[91]</sup>. Intercellular adhesion molecule (ICAM)-1 secreted by UCB-derived MSCs also reduced amyloid β plaques in Alzheimer's disease mouse model<sup>[92]</sup>. Another group also demonstrated that cortical neurogenesis was enhanced by sequential induction of UCB-derived MSCs<sup>[93]</sup>. GDNF, BDNF, and VEGF secreted by UCB-derived MSCs significantly increased the neurogenic and neurorescue effects in an ischemic stroke rat model<sup>[94]</sup>. In monocrotaline-induced pulmonary artery hypertension, the secretory factors, ICAM-1 and MMP-2, from UCB-derived MSCs inhibited immune reactions<sup>[95]</sup>. Monocyte chemoattractant protein (MCP)-1 secreted by UCB-derived MSCs downregulated BMI-1 proteins to control senescence<sup>[96]</sup>. Notwithstanding the immunosuppressive effect of MSCs, it was recently shown that UCB-derived MSCs can be used in cancer therapy. Tumor necrosis factor-related apoptosis-inducing ligand-secreting UCB-derived MSCs delivered the gene to treat intracranial glioma<sup>[97]</sup>. Similar to BM-derived MSCs, TSG-6 secreted by UCB-MSCs controlled the anti-inflammatory reaction by inhibiting the activation of P38 and JNK signaling<sup>[98,99]</sup>.

Another aspect of immunomodulation is triggered by direct contact of immune cells with UCB-derived MSCs. Macrophage polarization-mediated paracrine factors from UCB-derived MSCs were determined using bronchopulmonary dysplasia (BPD) model. Decorin secreted by MSCs attenuated the anti-inflammatory reaction of macrophages, polarized toward an anti-inflammatory phenotype *via* CD44. Knockdown of decorin on UCB-derived MSCs showed less recovery of lung alveolarization in BPD model<sup>[100]</sup>. Similarly, UCB-derived MSCs also released pentraxin-related protein (PTX3), while interacting with macrophages in hyperoxic lung injury rat model. PTX3 secretion induced increased cell survival levels, lung alveolarization, and Dectin-1 Levels along with anti-inflammatory cytokine release in macrophages of the BPD model<sup>[101]</sup>. Decorin-overexpressing UCB-derived MSCs revealed decreased levels of inflammatory cytokines, MCP-1, MCP-3, MIP-2, and eotaxin by targeting pro-fibrotic factors and T-regulatory cells<sup>[102]</sup>. UCB-derived MSCs pretreated with IFN-γ suppressed the functional activity of mature dendritic cells, stimulating T-lymphocyte proliferation after direct contact<sup>[103]</sup>.

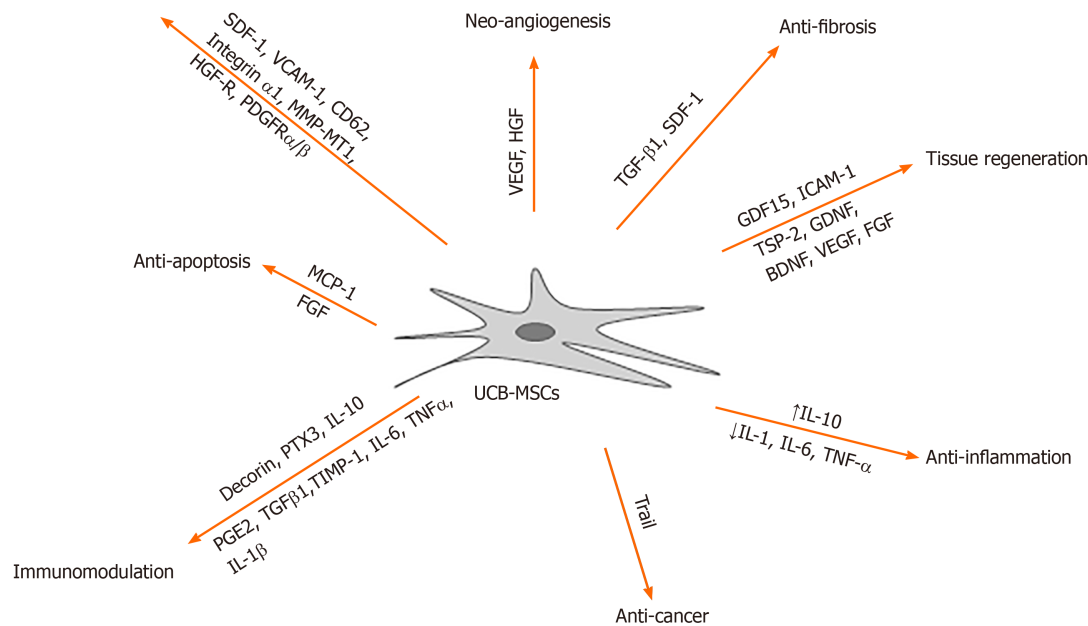
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## CURRENT APPROACH FOR THERAPEUTIC EFFECTS

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### *New culture conditions of UCB-MSCs for cellular therapy benefits*

Recent applications of stem cells have been presented as potential therapeutic



**Figure 1 Mechanisms of action mediated by umbilical cord blood-derived mesenchymal stem cells.** SDF: Stromal cell-derived factor; VCAM: Vascular cell adhesion molecule; MMP: Matrix metalloproteinase; HGF: Hepatocyte growth factor; PDGF: Platelet-derived growth factor; MCP: Monocyte chemoattractant protein; FGF: Fibroblast growth factor; PTX: Pentraxin-related protein; TGF: Transforming growth factor; TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand; GDF: Growth/differentiation factor; ICAM: Intercellular adhesion molecule; BDNF: Brain-derived neurotrophic factor; VEGF: Vascular endothelial growth factor; FGF: Fibroblast growth factor; UCB: Umbilical cord blood; MSC: Mesenchymal stem cell.

strategies for incurable diseases. However, unsolved issues still remain regarding early senescence during cell culture and low treatment efficacy after transplantation. To apply UCB-derived MSCs to clinical settings, several conditions need to be verified. Firstly, acquiring a large number of MSCs, is related to improved proliferation and delayed senescence. Secondly, a highly efficient cell culture condition is needed to enhance the therapeutic efficacy of MSCs. The current verified and developed culture conditions are described in Table 1.

The preexisting cell culture is mostly based on normoxia conditions (20%). However, recent culture conditions have changed to favor a hypoxic state with 1 to 5% oxygen, similar to oxygen deficiency of the body in a biotic environment. Hypoxia improved cell proliferation, neurogenic gene expression, and stem cell capacity of UCB-derived MSCs. In particular, apoptosis and enhanced angiogenesis of MSCs promote therapeutic efficacy in a mouse hindlimb ischemia model<sup>[77,104-106]</sup>. The classic characteristics of MSCs are adherence to cell monolayers in two-dimensional cell cultures. Recent reports have shown that three-dimensional cell culture techniques, including aggregation, microcarrier formation, spheroid formation, and sponge form, increase cell viability, stem cell potential, and differentiation capacity on osteogenesis, adipogenesis, chondrogenesis, and neurogenesis of UCB-derived MSCs. Moreover, the therapeutic efficacy of UCB-derived MSCs is improved in several disease-related animal models<sup>[61,65,107,108]</sup>. In an MI animal model, the therapeutic benefits of MSCs formed by spherical bullets were affected by the increased secretion of various paracrine factors<sup>[109]</sup>. With spherical bullets or aggregation formation of UCB-derived MSCs, high levels of paracrine factors are stimulated by increased protein interactions between SOD2 or E-cadherin<sup>[61,109]</sup>.

Another aspect to consider regarding cell collection, is the size of MSCs. Cell size may compromise the therapeutic efficacy of UCB-derived MSCs. A small size ranging between 7 to 10  $\mu$ m showed a high MSCs proliferation rate, referred to as recycling stem cells or rapid stem cells<sup>[110,111]</sup>. UCB-derived MSCs from neonatal tissue are small in size compared to other adult tissues, such as BM and adipose tissue<sup>[112]</sup>. The efficacy of small stem cells isolated from UCB-derived MSCs to have high proliferative rates, enhanced stem cell capacity, and delayed senescence has been confirmed. In an animal model of emphysema, the therapeutic efficacy of small cells on UCB-derived MSCs has been proven<sup>[112]</sup>.

Additional reports on the improvement of the stem cell capacity have been confirmed after pretreatment with cobalt chloride (CoCl<sub>2</sub>). The anti-inflammatory function of UCB-derived MSCs increased with CoCl<sub>2</sub> via the ERK-HIF-1 $\alpha$ -MicroRNA-

**Table 1 New culture condition of umbilical cord blood-derived mesenchymal stem cells**

Subject	Conditions	Title	Year
Hypoxia	5 %	Effects of hypoxia on proliferation of human cord blood-derived mesenchymal stem cells.	2016
	1 %	Protein profiling and angiogenic effect of hypoxia-cultured man umbilical cord blood-derived mesenchymal stem cells in hindlimb ischemia.	2017
	2.5 %	The effect of hypoxia preconditioning on the neural and stemness genes expression profiling in human umbilical cord blood mesenchymal stem cells.	2017
	1 %	Hypoxia preconditioning increases survival and pro-angiogenic capacity of human cord blood mesenchymal stromal cells <i>in vitro</i> .	2015
3D	Spheroid	Up-regulation of superoxide dismutase 2 in 3D spheroid formation promotes therapeutic potency of human umbilical cord blood-derived mesenchymal stem cells.	2020
	Spheroid	effect on multipotency and phenotypic transition of unrestricted somatic stem cells from human umbilical cord blood after treatment with epigenetic agents	2016
	Collagen sponge	Chondrogenic commitment of human umbilical cord blood-derived mesenchymal stem cells in collagen matrices for cartilage engineering.	2016
	Collagen constructs	Enhanced survival and neurite network formation of human umbilical cord blood neuronal progenitors in three-dimensional collagen constructs.	2013
	Spheroid	Spherical bullet formation <i>via</i> E-cadherin promotes therapeutic potency of MSCs derived from human umbilical cord blood for myocardial infarction.	2012
Small size	8 $\mu\text{m}$ size $\leq$	A small-sized population of human umbilical cord blood-derived mesenchymal stem cells shows high stemness properties and therapeutic benefit.	2020
CoCl <sub>2</sub>	100 $\mu\text{mol/L}$	Cobalt Chloride Enhances the Anti-Inflammatory Potency of Human Umbilical Cord Blood-Derived Mesenchymal Stem Cells through the ERK-HIF-1 $\alpha$ -MicroRNA-146a-Mediated Signaling Pathway	2018
Combine condition	Ca <sup>2+</sup> (1.8 mmol/L) and hypoxia (3%)	Optimization of culture conditions for rapid clinical-scale expansion of human umbilical cord blood-derived mesenchymal stem cells.	2017
	Size (10 $\mu\text{m}$ $\leq$ ) and Ca <sup>2+</sup> (1.8 mmol/L) and hypoxia (3%)	Small hypoxia-primed mesenchymal stem cells attenuate graft-versus-host disease.	2018
	Hypoxia (5%) and 3D (collagen sponge)	Hypoxia is a critical parameter for chondrogenic differentiation of human umbilical cord blood mesenchymal stem cells in Type I/III collagen sponges	2017
	IL-1 $\beta$ (5 ng/mL) and IFN $\gamma$ (20 ng/mL)	Preconditioning with interleukin-1 beta and interferon-gamma enhances the efficacy of human umbilical cord blood-derived mesenchymal stem cells-based therapy <i>via</i> enhancing prostaglandin E2 secretion and indoleamine 2,3-dioxygenase activity in dextran sulfate sodium-induced colitis.	2019
Gene overexpression	HGF and VEGF (TALEN)	Coronary stents with inducible VEGF/HGF secreting UCB-MSCs reduced restenosis and increased reendothelialization in a swine model.	2018
	LEF-1 (adenoviral)	Transplantation of hMSCs genome edited with <i>lef1</i> improves cardio-protective effects in myocardial infarction.	2020
	LIGHT (lentiviral)	Gene therapy of gastric cancer using LIGHT-secreting human umbilical cord blood-derived mesenchymal stem cells.	2013
	BMP-2 (lentiviral)	Lentiviral gene therapy for bone repair using human umbilical cord blood-derived mesenchymal stem cells.	2019
	BMP-2 (non-viral)	Transfection of hBMP-2 into mesenchymal stem cells derived from human umbilical cord blood and bone marrow induces cell differentiation into chondrocytes.	2014
	FGF-20 (adenoviral)	The effect of MSCs derived from the human umbilical cord transduced by fibroblast growth factor-20 on Parkinson's disease	2016

ERK: Extracellular signal-regulated kinase; HIF: Hypoxia-inducible factor; VEGF: Vascular endothelial growth factor; HGF: Hepatocyte growth factor; TALEN: Transcription activator-like effector nuclease; UCB: Umbilical cord blood; MSC: Mesenchymal stem cell; LEF: Lymphoid enhancer-binding factor; LIGHT: TNFSF14 (tumor necrosis factor superfamily member 14); BMP: Bone morphogenetic protein; FGF: Fibroblast growth factor.

146 signaling pathway in an animal model of asthma<sup>[113]</sup>. Recent studies have generated a synergic effect by combining hypoxic conditions and calcium treatment to improve the stem cell capacity. UCB-derived MSCs showed increased cell viability through ERK signaling, and improved beneficial effects by increasing anti-inflammatory processes in an animal emphysema model<sup>[114]</sup>. Stable culture conditions were demonstrated with small stem cells isolated from UCB-derived MSCs with

calcium treatment and hypoxia. Small MSCs primed with hypoxia and calcium improved stem cell capacity and immunomodulatory function *in vitro*, as well as the therapeutic effectiveness against organ failure in a GvHD animal model using key regulator, polo-like kinase 1<sup>[115]</sup>. In addition, UCB-derived MSC culture with collagen sponge under hypoxic conditions enhanced chondrogenic differentiation capacity<sup>[66]</sup>. *In vitro* pre-conditioning of UCB-derived MSCs with inflammatory cytokines, IL-1 $\beta$  and IFN- $\gamma$ , suppressed inflammation, and increased the gene expression of *PGE2*; while the therapeutic effect of MSCs had increased in colitis and cerebral ischemia models<sup>[116,117]</sup>.

Various culture conditions have been verified by past research and technical approaches to obtain low-cost cell therapy products. Emerging studies evaluating new culture conditions need to be expanded consistently to develop successful stem cell therapies for intractable diseases.

Gene editing techniques have been applied to stem cell therapy to improve stem cell efficacy. In particular, most studies on UCB-derived MSCs have used gene overexpression to achieve the desired therapeutic effects (Table 1). UCB-derived MSCs overexpressed with VEGF/hepatocyte growth factor (HGF) using the transcription activator-like effector nuclease (TALEN) system, showed high proliferative rates, cell viability, angiogenesis, and progress in coronary restenosis in a swine model with stent material<sup>[118]</sup>. Additionally, TALEN-mediated HGF editing in UCB-derived MSCs promoted angiogenesis to improve the tube-formation ability and anti-apoptotic responses to oxidative stress<sup>[119]</sup>. Overexpression of lymphoid enhancer-binding factor 1 in UCB-derived MSCs using an adenoviral vector increased proliferation and anti-apoptotic effects by improving the cardioprotective effect in an animal model of MI<sup>[120]</sup>. In addition, TNFSF14 (LIGHT, tumor necrosis factor superfamily member 14) - overexpressed UCB-derived MSCs using a lentiviral system demonstrated suppressed growth and augmented apoptosis of tumors in a gastric cancer model<sup>[121]</sup>. Similarly, BMP-2 overexpression in UCB-derived MSCs using a lentiviral system, showed high osteogenic differentiation, which was confirmed in an animal model with bone repair<sup>[122]</sup>. Additionally, non-viral BMP-2 overexpressed in UCB-derived MSCs demonstrated increased chondrogenic marker, ColII, and induced chondrocyte differentiation in a disease model<sup>[123]</sup>. Overexpression of SRY-related high-mobility group box 9 (SOX9), a cartilage-specific transcription factor, enhanced the chondrogenic differentiation of UCB-derived MSCs<sup>[124]</sup>. Adenoviral transduction of FGF-20 in Parkinson's disease (PD) promotes the degradation of the proinflammatory cytokine NF- $\kappa$ B, expressed in nigrostriatal dopaminergic regions in PD patients<sup>[125]</sup>. In future stem cell approaches, modified therapy must focus on fundamental treatment of the disease; therefore specific target-based modifications will be needed. However, the development of desired gene-edited stem cells will increase the price and safety considerations in manufacturing and quality control processes. The concerns regarding stem cell gene editing warrants further assessments for obtaining viable solutions.

## CONCERNS

### Safety of UCB-MSC treatments

Stem cell therapy is based on adequate availability due to the innate biological characteristics of stem cells, such as self-renewal, differentiation, and motility potential. However, these biological characteristics of stem cells can affect safety issues. The most representative problem is the possibility of inducing tumorigenicity, brought on by chromosomal abnormalities. MSCs, mostly used in stem cell therapy, have a relatively low risk of potential tumorigenicity compared to multipotent stem cells. Emerging studies have demonstrated that tumor formation cannot be avoided due to stem cell characteristics and external conditions<sup>[126]</sup>. Analytical techniques for testing tumorigenicity are based on *in vivo* experiments. Additional *in vitro* tests with karyotyping and molecular and cellular genetic analysis (fluorescence in situ hybridization, chromosomal comparative genomic hybridization, single nucleotide polymorphism *et al*) need to be used for genetic stability analysis. Karyotyping analysis demonstrated that UCB-derived MSCs did not have any abnormalities on chromosome until passage 15<sup>[112]</sup>. In addition, the carcinogenicity evaluation of UCB-derived MSCs confirmed that tumors were not induced *in vitro* and that tumor formation *in vivo* was not observed at 13 wk after a single injection of UCB-derived MSCs administered subcutaneously in the internal organs of BALB/c-nude mice<sup>[127]</sup>.

As per the expectation and demand for stem cell therapy in regenerative medicine, the application of various administration routes, such as spinal cord, subcutaneous,

intramuscular, and intravenous injection, had increased, followed by confirmation of biological distribution. The Food and Drug Administration recommended that data for biological distribution, mobility, and residual period were needed and retained on the aspect of safety probability. In particular, the confirmation of cell fate after injection is important in order to analyze the mode of action of cell therapy and to decide whether the activation of cell engraftment is necessary and critical. Direct single injection of cells into the topical site of the disease, by intraparenchymal, intratracheal, intramyocardial, and intra-articular routes, demonstrated the residue of cells from 3 to 10 wk<sup>[65,92,109,128]</sup>. Therapeutic efficacy was observed before the verification of cell distribution, confirming anti-apoptosis, anti-fibrosis, anti-inflammation, and tissue regeneration. The cells injected intravenously in lung disease models, emphysema, and asthma have remained for 7 d<sup>[96,112]</sup>. The residual cells in the bladder were observed until day 7 after injection for the treatment of cystitis<sup>[129]</sup>. From the above studies, intravenous administration showed rapid extinction of cells compared to direct injection at the disease site. Intravenous injection also revealed therapeutic efficacy with anti-inflammation, anti-apoptosis, anti-fibrosis, and angiogenesis. Collectively, the results indicate the stability of injected UCB-derived MSCs in various diseases.

### **Heterogeneity**

Heterogeneity remains a critical problem, not only for gaining a general understanding of the mechanism by which MSCs maintain their growth rate and undergo differentiation toward specific lineage potentials, but also with respect to achieving better outcomes in therapeutic applications<sup>[130]</sup>. It is mainly affected by growth media, two-dimensional adherence to plastic culture dishes, and sub-culturing methods; therefore, these processes were repeated until an adequate number of MSCs were obtained for large-scale expansion *in vitro*<sup>[131]</sup>. In this context, researchers have tried to establish a standard set of criteria for attaining more homogenous populations of MSCs. Firstly, for clearer cell origins, studies have attempted to clone UCB-MSCs derived from single cells by limiting dilution assays. Single cell-derived clones were identified by evaluating MSC features including growth, surface marker, stemness, and multi-lineage potential. As a result, one clone showed a faster growth rate and higher differentiation potential than the original populations. However, other clone cells showed weak growth ability and differentiation potential compared to the original cells, except for one clone that had superior data<sup>[132]</sup>. Further, this processing draws attention to the selection criteria as a possible marker related to the excellent MSC clones. Secondly, several protocols have been developed to isolate more homogeneous cells using several specific antigens such as CD143, CD146, and CD271<sup>[16,133,134]</sup>; however, none of these processing methods have gained wide acceptance, and a unique single marker has not been identified to date. Moreover, to obtain primitive homogeneous, multi or pluripotent stem cells have been introduced with different names in adult hematopoietic tissues, for example, unrestricted somatic stem cells<sup>[135]</sup>, depending on the isolation strategy, *ex vivo* expansion protocol, and markers employed for their identification; however, these factors remain unclear and are a major obstacle for heterogeneity. Despite such an attempt, there is still no defined culture protocol to overcome MSC heterogeneity.

### **Low yield**

Despite the many advantages of UCB-MSCs, their utility remains controversial due to their low isolation efficiency. Many groups have reported that UCB has a 65%-90% maximum isolation efficiency in various culture protocols, including the depletion of lymphocytes and monocytes from mononuclear cells before cell seeding, delivery time, volume, addition of cytokines supplements or platelet lysate to the medium, density gradient purification, or cultivation of cells under hypoxia<sup>[12,18,136-139]</sup>. This could also help improve the utility of UCB-MSCs as a therapeutic resource. Further studies should be performed to validate these methods for clinical use.

### **Current good manufacturing practices for development**

For advanced therapy development using UCB-derived MSCs, standard operation procedures are necessary, as well as the reliable application into Good Manufacturing Practice procedures. The current established and developed MSC therapy has limitations in commercialization and market expansion because of the high cost caused by the manufacturing process and quality control with conventional static monolayer culture. Therefore, cost reduction from improving the efficacy of cells is essential to develop the next-generation stem cell therapies, based on fundamental technologies over conventional culture. Consequently, evaluation of optimized and



innovative manufacturing processes is needed (Figure 2).

The study of therapeutic manufacturing focuses on the workflow process for selecting the outstanding upstream cells. However, various commercialization products have been introduced to academic researchers as well as to industrial companies, in accordance with the higher interest in downstream areas to develop the product. Stem cell therapy is affected not only by the skill of the workforce but also by the massification and automation of equipment to guarantee consistent products. The adhesive characteristics of MSCs make it difficult to expand cells for mass production, making it difficult to develop a bioreactor. However, many companies have developed related and combined bioreactors for the extensive production of stem cells<sup>[129,140,141]</sup>. This system demonstrated that the scale-up of a stem cell batch in a single progression reduced the cost for production, followed by an increase in the level of quality control with regards to the development of automated systems in manufacturing cell cultures<sup>[142]</sup>. A bioreactor is defined as a culture system where the organism is controlled and regulated to produce the specific material or cells, by removing the unnecessary metabolic products while culturing the cells and continuously maintaining the proper levels of nutrients and growth factors. For this reason, the selection of the bioreactor, which is appropriate for specific cells, is important in the final manufacturing process to complete the efficient scale-up applied while maintaining the characteristics of cells based on the technical equipment.

Recently developed manufacturing bioreactors, which are fully closed, controllable, and have scalable culture systems, have been used to monitor and control the metabolic state in real time including, dissolved oxygen, glucose, ammonia, pH, and lactate<sup>[143-145]</sup>. As the collection of large cell quantities takes a long time using manual methods, a reduction in collection times using automated equipment, increases the efficacy and consistency of the quality control. Current commercialized stem cell therapy-based products are temperature sensitive, resulting in a short expiration period. The development of frozen preservation techniques and the appropriate storage of these cell products are important for their viable export overseas. The preservative solution in basic culture media or saline solution, is not appropriate for maintaining long-term cell viability. Several frozen preservative solutions have recently been developed, such as serum-free, Xeno-free media and DMSO. However, these result in a low stability of cells with a low cell recovery rate. Therefore, the development of an efficient preservation system needs to be complemented<sup>[146-149]</sup>. Ideally, a division system has been developed for the automated manufacturing of frozen storage of bulk cultured cells, allowing improvements in the accuracy, repetition, time consumption, and number of workers needed compared to the current manual workspace.

## CONCLUSION

Stem cell therapy is an outstanding method for regenerative medicine. With significant advantages, such as self-renewal, differentiation capacity, and immunomodulation, the use of stem cells is appropriate for the treatment of several disorders and diseases. UCB is a primitive and rich source of MSCs. UCB-derived MSCs have the potential of exerting profound immunomodulatory effects with the secretion of factors and cytokines. However, the safety and yield of UCB-derived MSCs are still a concern. Next-generation stem cell therapy is necessary, referring to the mass production of efficient stem cells based on the fundamental technology, to improve whole cell processing. This will solve problems of limited product expansions caused by short expired periods and high production costs. In accordance with the advanced process, a manufacturing system is needed to produce quantity in order to reduce production costs, as well as enhancing yield output, and delivering consistent quality by automated production processes. Overall, advanced manufacturing systems will improve and trigger the commercialization and globalization of stem cell therapy.

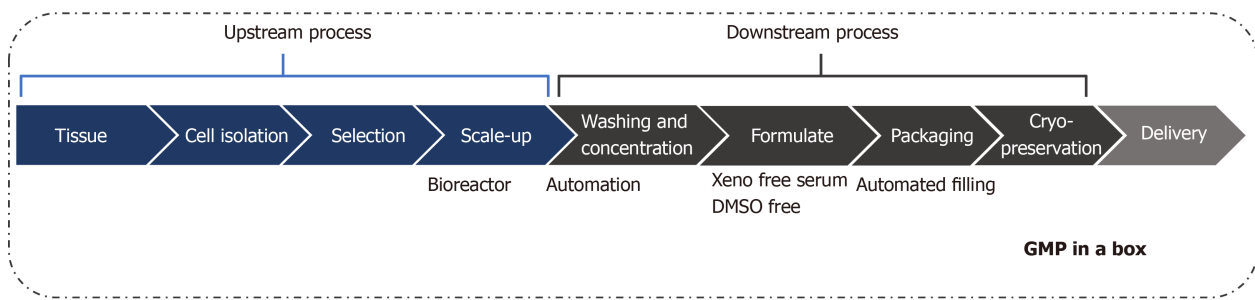


Figure 2 Workflow for therapeutic cell manufacturing processing.

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