

# Umbilical cord blood stem cells as a beneficial option in cell-based therapy and regenerative medicine

## Abstract

Stem cells are unique cells obtained from a broad range of tissues with different features related to proliferation capability and differentiation capacity. As one of the most important stem cell types in medicine today, umbilical cord blood-derived stem cells (UCB-SCs) are a more practical choice than embryonic stem cells because their use does not involve ethical issues. For example, these cells are a powerful tool used in cell-based therapy and regenerative medicine to treat cancer and neurological, autoimmune, cardiovascular, and blood diseases. In this article, we perform a mini review of umbilical cord blood-derived stem cells as an effector option in cell-based therapy and regenerative medicine.

**Keywords:** umbilical cord blood-derived stem cells, umbilical cord blood-derived mscs, umbilical cord blood-derived hscs, regenerative medicine, cell-based therapy

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**Abbreviations:** UCB-SCs, umbilical cord blood-derived stem cells; HSCs, hematopoietic stem cells; MSCs, mesenchymal stem cells; UCB-MSCs, umbilical cord blood-derived mesenchymal stem cells; UCB-MSCs, umbilical cord blood-derived mscs; hUCB-MSCs, human umbilical cord blood-derived mscs; GvHD, graft-versus-host disease; HIV, human immunodeficiency virus

## Introduction

### Umbilical cord blood

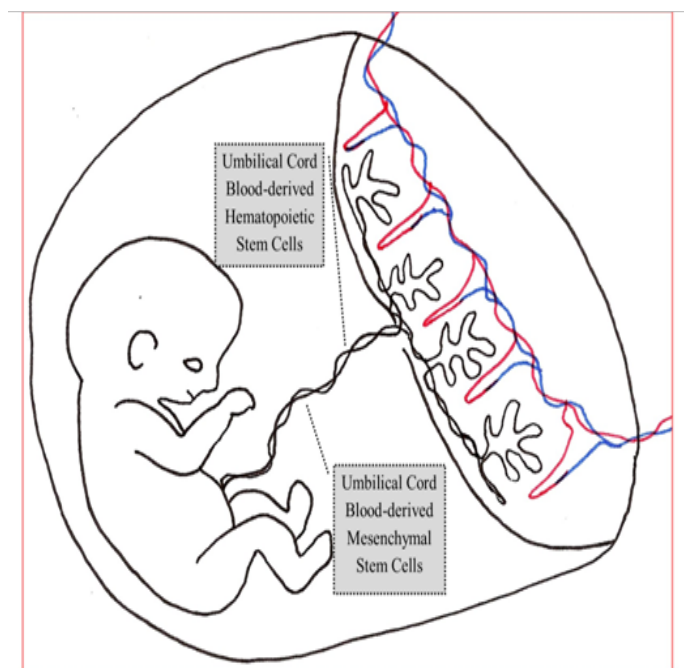
Umbilical cord blood used to be regarded as waste material after childbirth.<sup>1</sup> In the last decades, however, it has been found to contain valuable biomaterials such as stem cells.<sup>2-5</sup> These potentially lifesaving cells in umbilical cord blood are called hematopoietic stem cells (HSCs).<sup>6,7</sup> This blood contains mesenchymal stem cells (MSCs) as well<sup>8-10</sup> (Figure 1).

### Umbilical cord blood-stem cells benefits and features

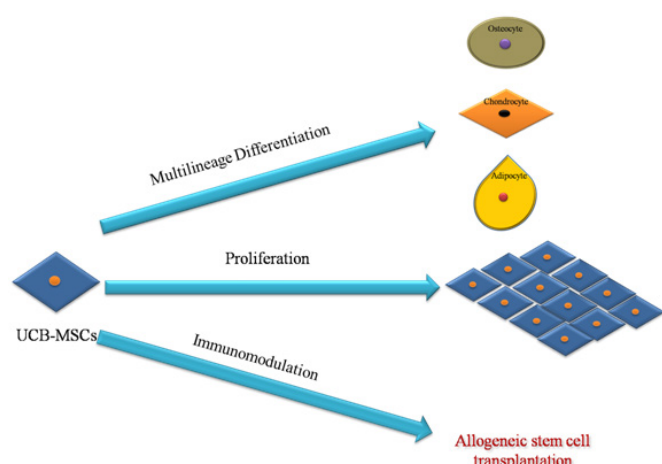
Both of the abovementioned stem cells derived from umbilical cord blood could be used to repair and restore damaged tissues and treat diseases such as cancer, blood and neurological disorders, and immune deficiencies because of their tremendous proliferation and differentiation potential and great regenerative capacity.<sup>11-26</sup> In addition, these candidate cells have a great paracrine mechanism on other cells.<sup>27</sup> This biological mechanism could increase stem cells' regenerative capacity.<sup>27</sup>

Besides these biological mechanisms, umbilical cord blood-derived MSCs (UCB-MSCs) have few immunological properties because they naturally express little class I MHC and lack HLA-DR and both CD80 and CD86 proteins.<sup>28-32</sup> A number of studies have shown that UCB-MSCs have initial immunomodulatory effect and are compatible with safety systems.<sup>28-32</sup> These mechanisms are unknown, but evidence shows that paracrine factors secreted by these candidate cells could be involved in this process.<sup>28-30</sup> UCB-MSCs immunomodulatory

effects on the immune system provide by the number of paracrine factors.<sup>27-30</sup> These factors not only inhibit T-cell proliferation but also often increase anti-inflammatory cytokine secretions.<sup>28-30</sup> Owing to this regulatory effect, UCB-MSCs regulate immune responses with anti-inflammatory effects and expand production.<sup>30</sup> Consequently, the use of these candidate cells in the allogeneic form could be suggested as an immunologically safe treatment in the field of regenerative medicine<sup>30</sup> (Figure 2).

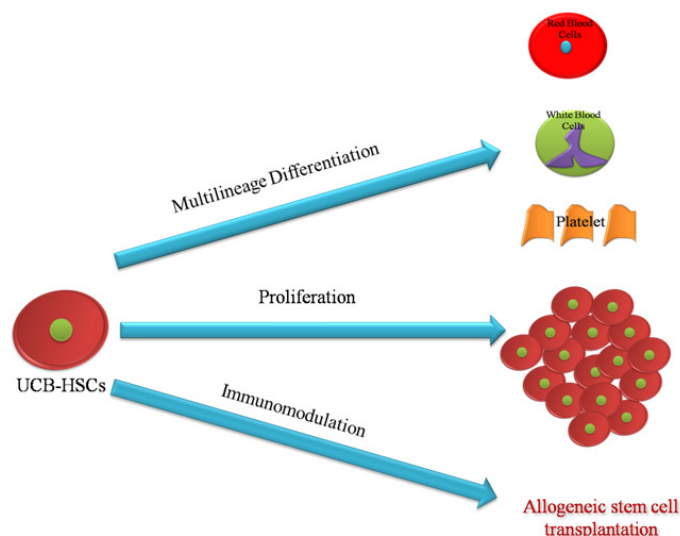


**Figure 1** This figure schematically demonstrates the different types of stem cells from umbilical cord blood.



**Figure 2** This figure schematically demonstrates the unique properties of umbilical cord blood-derived mesenchymal stem cells for regenerative medicine approach.

Similar to MSCs derived from bone marrow, UCB-MSCs can differentiate into multilineage cells (e.g., adipocyte, chondrocyte and osteocyte) at induced differentiation conditions *in vitro* (Figure 2).<sup>28</sup> In addition to UCB-MSCs, hematopoietic stem cells are other stem cells derived from umbilical cord blood that can generate red blood cells, white blood cells, and platelets<sup>33</sup> (Figure 3). Furthermore, UCB-HSC could be differentiated into hematological cells and non-hematological cells in physiologic and pathological condition, respectively.<sup>34</sup>



**Figure 3** This figure schematically demonstrates the unique properties of umbilical cord blood-derived hematopoietic stem cells for regenerative medicine approach.

UCB-MSCs holds the ability of genes expression associated with embryonic stem cells, and, through this feature, they differ from adult stem cells.<sup>35</sup> Additionally, these cells show more proliferation than adult stem cells.<sup>35</sup> As a result, these cells prefer the culture condition related to embryonic stem cells as compared to adult stem cells.<sup>35</sup>

Due to UCB-HSC' great therapeutic capacity in the field of cell-based therapy, many private/commercial and public cord blood banks have been established worldwide.<sup>34</sup> UCB-HSC are collected,

processed, and cryo-reserved in cord blood banks.<sup>34</sup> For the use of cryo-reserved UCB-HSC in cord blood banks, it is important to assess several factors.<sup>34</sup> HLA matching is one of the most important factors measured for UCB-HSC transplantation.<sup>34</sup> In addition to HLA matching, the dose or content of some cells, including CD34+ cells or colony-forming cells, are required to determine the hematopoietic recovery after UCB stem cell transplantation.<sup>34</sup> Furthermore, the total nucleated cell count are of critical importance for UCB stem cell transplantation.<sup>34</sup>

### Applications of umbilical cord blood-stem cells in research study

An animal-based study showed that the human umbilical cord's mesenchymal stem cells may be useful in treatments for alleviating the symptoms of preeclampsia.<sup>36</sup> In this study, human umbilical cord cells were collected, extracted, and cultured.<sup>36</sup> The results of these experiments demonstrated that umbilical cord blood's mesenchymal stem cells have the ability to affect preeclampsia symptoms in the mice.<sup>36</sup> Additionally, the blood pressure reduced and fetal weight symptoms associated with the disease increased after treatment.<sup>36</sup> Finally, the outcomes of this study demonstrated that the transfer of UCB-MSC may be useful for the treatment of preeclampsia.<sup>36</sup>

Treatment using UCB-MSCs has shown promise for treating diabetes mellitus in a rat model, particularly in regard to the vitreous humor and the blood-retinal barrier.<sup>37</sup> Furthermore, it has been demonstrated that MSCs derived from human umbilical cord blood (hUCB-MSCs) may have a positive effect on murine experimental colitis.<sup>38</sup>

Three experiments carried out on two dimensional conditions have illustrated that UCB-HSC could have better maintained under specific condition, such as hypoxic condition.<sup>39-41</sup> However, some studies described that 3D culture systems could be used in proliferation and differentiation of UCB stem cells for tissue engineering applications.<sup>42-44</sup>

Therefore, during various experiments, HSC stem cells were proliferated and expanded on a variety of three-dimensional (3D) conditions, including electrospun polyethersulfone nanofibers, 3D collagen gels, PCL, PLGA, fibrin, collagen, hydroxyapatite ceramic scaffolds, macroporous PEG hydrogels and so on.<sup>42-45</sup>

In an *in vitro* study, chondrogenic differentiation ability of human UCB-MSCs was evaluated in four different scaffolds during 4 weeks.<sup>46</sup> Considering the obtained outcome in this study, it was identified that human fibroblast-derived matrix (hFDM) had the best effect on the cell differentiation and mesenchymal condensation *in vitro*.<sup>46</sup>

An *in vitro* experiment also confirmed that the UCB-MSCs could be induced to differentiate toward osteoblast lineage on 2D and 3D environment.<sup>47</sup> In this study, the osteogenic differentiation of UCB-MSCs was accelerated on both 2D and 3D environment by single and dual growth factors delivery using nanoparticles-in-microcapsules.<sup>47</sup>

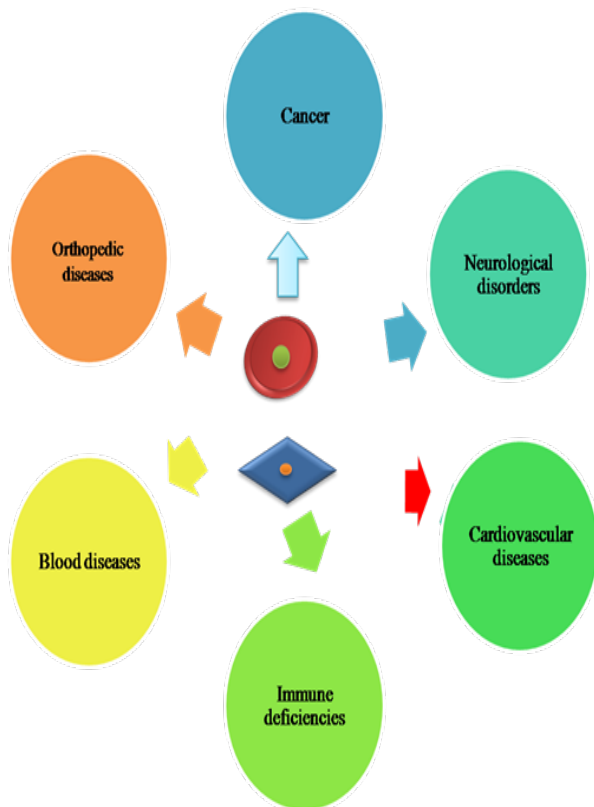
### Umbilical cord blood-stem cell in the clinical study

Most of the clinical trials related to UCB-MSCs are in phases I and II, in which the safety and efficacy of treatment is determined.<sup>48</sup> The efficacy of treatment for all studies based on UCB-MSCs has shown no serious adverse events or side effects.<sup>1</sup>

Recently, stem cells derived from umbilical cord blood have been

clinically transplanted into patients with severe thalassemia and some types of cancer, including malignant and non-malignant disorders.<sup>49–51</sup> Thus far, it appears that, worldwide, more than 600,000 transplants have been performed using stem cells obtained from umbilical cord blood.<sup>7</sup> It is important to mention that most completed or ongoing clinical trials are still in the early phases (phase I and II).<sup>48</sup> As a result, the outcomes of these studies are not yet clear.

According to data obtained from ClinicalTrials.gov, more than 180 clinical trials have demonstrated the widespread use of umbilical cord blood stem cells for the treatment of diseases.<sup>48</sup> These clinical studies are verified based on the beneficial results of the most recent studies. One of the most important clinical trials focuses on neurological disorders such as autism, cerebral palsy, spinal cord damage, hearing loss and hypoxic ischemic encephalopathy, as well as autoimmune medical conditions including multiple sclerosis, lupus, diabetes mellitus, Crohn's disease, graft-versus-host disease (GvHD), and rheumatoid arthritis (Figure 4).<sup>51</sup> Cardiovascular diseases such as congenital heart disease, ischemic stroke, and myocardial infarction have also been treated using these candidate cells (Figure 4).<sup>51</sup> Additionally, inherited disorders such as human immunodeficiency virus (HIV), thalassemia, sickle cell disease, and severe combined immunodeficiency can be treated by UCB-MSCs.<sup>51</sup> In addition to these diseases, UCB-MSCs also were used for treat orthopedic problems, including articular cartilage defects and knee articular cartilage injury.<sup>51</sup>



**Figure 4** This figure schematically demonstrates the application of umbilical cord blood stem cells for regenerative medicine approach.

## Conclusion

The future holds great promise for the use of umbilical cord blood stem cells. In the transplantation discipline, collection of data from

clinical trials will continue to improve knowledge, thereby assisting to enhance survival rates. Recent medical progress have illustrated that these candidate cells could be used to treat the similar disease as the hematopoietic stem cells available in bone marrow but without some of the drawbacks of these type of transplant. These candidate cells are currently used to treat approximately 80 diseases including cancer, immune deficiencies, cardiovascular diseases, neurological disorders, and blood diseases.

## Acknowledgements

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## Conflict of interest

The author declares no conflict of interest.

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