REVIEW ARTICLE

Advancements in Polymeric Biomaterials For In Vitro Expansion of Hematopoietic Stem Cells: A Scoping Review

Muhammad Azamuddin Ismail[1], Mohd Fuad Rahmat Sam[1,*]

[1]Department of Biomedical Science, Kulliyyah of Allied Health Sciences, International Islamic University Malaysia, Pahang, Malaysia

ABSTRACT

Background: A thorough source of HSPCs with a reduced risk of graft host disease (GVHD) is umbilical cord blood (UCB). Nevertheless, compared to peripheral blood or bone marrow stem cells, hematopoietic stem cells (HSCs) isolated from single cord blood are less common and require longer to settle in the bone marrow before they may begin generating blood cells. Earlier clinical trials were conducted to ensure bone marrow (BM) sustainability through the application of various natural and synthetic polymeric techniques. Usage of polymeric biomaterials can be seen as alternative to stabilise stem cell-based therapies currently. Therefore, this article aims to evaluate the data progress and compile the evidence of current advances of polymeric biomaterial for in vitro expansion of HSCs. **Methods:** Articles were found through four electronic search engines which were PubMed, Scopus, ScienceDirect and SpringerLink. The highlighted keywords utilised in this study to assist the research framework. The article selection followed Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. Articles were included if they met the following criteria: (1) full text articles between 2019 until 2023; (2) specific keywords must have in the research articles; (3) published in English; (4) qualitative or quantitative study. Studies were excluded if they were review articles, chapter books, discussion papers or did not match with study objectives to achieve high quality of scoping review. **Results:** A total of 5,208 records were initially identified from the selected databases. After removing duplicates, a total of 5194 articles were screened, and 52 full-text articles were evaluated. There were 37 articles that did not match with the inclusion and exclusion criteria and had been excluded because the paper involved review paper and did not discuss the usage of biomaterials for expansion of HSCs. Lastly, only 15 articles were selected for scoping review analysis. **Conclusion:** The findings reveal that cultured polymeric biomaterials have had a significant impact on the stability and integrity of HSCs. Besides, the selected polymeric biomaterials can improve crosstalk or cell-cell interaction through laboratory settings. From this review, it can be concluded that the approach used by researchers truly aids the clinical institution to overcome the deficiency in stem cell therapies.

Keywords:
biomaterials; polymers; in vitro expansion; hematopoietic stem cells; bone marrow

Article history:
Received: 30 October 2025
Accepted: 28 January 2026

INTRODUCTION

Over the years, haematological disease has increased in human populations and become a burden towards clinical institution. According to World Health Organization (WHO), they stated that anaemia is one of common blood disorder worldwide and caused 50 million years of healthy life lost due to disability in 2019. Multipotential hematopoietic stem cells (HSCs) as a core of the immune system play a significant role in haematopoiesis. The bone marrow (BM) niche naturally supports human HSCs to undergo expansion, differentiation, and self-renewal for numerous cell types (Lucas, 2017). The uniqueness of BM that can produce diverse types of cell lineage has become a spotlight for researchers to establish stem cell-based therapies. The therapies can be performed via in vivo, ex vivo and in vitro method. This application aims to provide an efficient clinical test by augmenting the number of HSCs without impacting cell viability (Petaroudi et al., 2022). The current approaches in expanding HSCs were developed through in vitro technique in recent years by using recombinant cytokines, co-culture methods and small molecules (Bozhilov et al., 2023). However, it is quite challenging to maintain HSCs in vitro as the stem cell survival depends on interactions between cells and paracrine cues from BM microenvironment (Manzo et al., 2022).

The advances of biomaterials nowadays can be seen as contributors towards expansion of HSCs either naturally or synthetic. Petaroudi et al., (2022) mentioned that natural and synthetic polymers made of proteins, polysaccharides, amino acids, apatite and decellularized extracellular matrices have potential in hematopoietic stem and progenitor cells (HSPCs) expansion. Katagiri et al., (2021)

*Corresponding author.
E-mail address: mfuad_rahmat@iium.edu.my

suggested that chondroitin sulphate (CS), a glycosaminoglycan improve crosstalk interactions between hematopoietic cells and the BM niche after perform experiment towards CS N-acetylgalactosaminyltransferase-1 (T1) knockout mice and wild-type mice. Moreover, potential for HSPCs maintenance and expansion has been demonstrated by both static and dynamic culture conditions in a perfused 3D polyethylene glycol (PEG) hydrogel-based bone marrow and on-a-chip 3D co-culture technique, based on a hydroxyapatite coated zirconium oxide scaffold (Petaroudi et al., 2022). This review aims to summarize and critically evaluate current advances in polymeric biomaterials for the in vitro expansion of hematopoietic stem cells.

MATERIALS AND METHODS

Study Design

The study design that had been chosen for this study was the scoping review method. Scoping studies are a technique for thoroughly mapping evidence from various study designs. This scoping review has been widely used by researchers because they can compare and analyse all the information and data that are related to the selected study or topic. There are researchers that have done their study on the current advances of biomaterials strategies for in vitro expansion of HSCs. Nowadays, this approach can be seen evolving years to years to treat various blood malignancies. Therefore, this scoping review gathers and studies the data or information from relevant papers by exploring and mapping the biomaterials that contribute to expansion of HSCs.

Search Strategy

This scoping review emphasises a relevant scientific publication since it has potential to contribute related information needed. The topic discussed in this research project reflects the fundamentals of science. Therefore, a list of reliable electronic databases such as PubMed, Scopus, Science Direct and Springer Link had been used in this study. The selected journal or article gave ideas within this study and created various outcomes. The precise parameters also been used during the search process to achieve the objectives of the study and answer the research questions. Thus, utilisation of highlighted keywords in this study would be “biomaterials”, “polymers”, “in vitro expansion”, “hematopoietic stem cells”, “bone marrow” and other related words that can assist the research framework. Additionally, the AND and OR which are Boolean operators were used in the keyword search to help discover specific publications and make sure the studies chosen were associated with the research.

Inclusion and Exclusion Criteria

To produce a latest and high quality of scoping review study, there are several criteria that need to be assessed. Inclusion and exclusion criteria are the important parts to determine the article reliability to meet the purpose of the research and consistency in analysing data for scoping review. Hence, several parameters such as pre-review, develop protocol, conduct literature research and manage citations are chosen and considered to select relevant articles for this study. All articles that are not relevant to this study were excluded. In this study, the inclusion and exclusion criteria are shown in Table 1.

Selection Procedures

The selection procedure was based on the Preferred Reporting Item for Systematic Review and Meta-Analyses (PRISMA) guideline (Page et al., 2021). PubMed, Scopus, SpringerLink and ScienceDirect online databases were used to compile all relevant publications, which were then all screened for articles published between 2019 and 2023. The elimination of duplicate articles from various databases was the next step. The chosen papers were then subjected to title and abstract screening in order to find any studies that did not pertain to the study's goals. The remaining papers' full-text articles were then all obtained. Next, remaining articles were read and examined in depth to identify the information regarding the current advances of biomaterials strategies for in vitro expansion of hematopoietic stem cells. During the screening process, any articles that did not match the inclusion and exclusion criteria will be excluded. The selection procedures are displayed in the PRISMA 2020 flow diagram show in Figure 1.

Data Extraction

Data extraction from selected studies involved tabulating relevant information, including author names, year of publication, type of polymeric biomaterials, source of cells, other cells involved in expansion, media culture, rate of expansion, days of culture and mechanism of action. This tabulated data provides a comprehensive overview of factors that influence the in vitro expansion of HSCs.

Table 1: Criteria for Inclusion and Exclusion

Inclusion	Exclusion
Research articles or journal that had been published must be written in English.	Article that does not match with study objectives.
Full text articles must between 2019 until 2023.	Any chapter books, review paper, systematic review or discussion papers.
Research articles whether qualitative or quantitative. Specific keywords must have in the research article.	

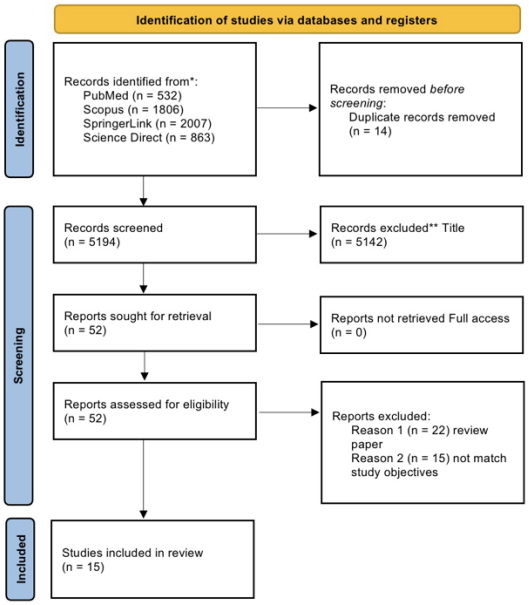

Figure 1: PRISMA flow diagram

RESULTS AND DISCUSSIONS

Based on the searching efforts, a total of 5208 potential articles were identified from the selected databases which are PubMed, Scopus, SpringerLink and ScienceDirect. 14 articles have been removed due to duplicates with similar titles and abstracts. The 5194 articles that left were further assessed for titled and abstract screening. From title and abstract screening, 5142 number of articles had been eliminated because the article did not match the objective of this study which is discussing current advances of biomaterials strategies for in vitro expansion of HSCs and did not consist of the specific keywords in the title and abstract either in the paper. The remaining 52 articles were further screened as all were available to view in full text access. All remaining articles were retrieved and screened for inclusion and exclusion criteria. There were 37 articles that did not match with the inclusion and exclusion criteria and had been excluded because the paper involved review paper and article that did not discuss the usage of biomaterials for expansion of HSCs. Lastly, only 15 articles were selected for scoping review analysis. Table 2 display a list of the titles of the retrieved full-text journal articles.

Table 2: Evidence Table Based on Findings for In Vitro Expansion of HSCs

Authors (year)	Polymeric biomaterials	Source of cells	Other cells involved	Media culture	Rate of expansion	Days of culture	Mechanism
Igarashi et al. (2023)	Polyvinyl alcohol (PVA)-based	HSCs	N/A	O_2 concentration	N/A	28	Optimizing O_2 concentrations, limit the buildup of progenitors and mature hematopoietic cells, thereby improving HSC culture selectivity
Li et al. (2023)	Biomimetic Microniche	HSCs	MNCs	StemSpan™ SFEM II	6.2-folds	7	Generates a suitable cytokine milieu and supplies the appropriate physical scaffolding
Liang et al. (2023)	3D porous gelatin microscaffolds	HSPCs	MSCs	IMDM	N/A	7	Mimicking the structural and mechanical properties (pore size and stiffness)
Manzo et al. (2022)	Alginate-based hydrogel	HSCs	MNCs, MSCs	MyeloCult™ H5100	N/A	21	Resembling BM architecture to improve HSC survival and proliferation, reproduce in

							vitro complex biological same as in vivo cross-talks between stem cells
Marx-Blumel et al. (2021)	3D PDMS scaffold	$CD34^+$ cells	N/A	Stemline® II Hematopoietic Stem Cell Expansion Medium (Sigma Aldrich	N/A	14	Activate key molecular signalling pathways to amplify the numbers of undifferentiated HSCs ex vivo effectively
Miyoshi et al. (2021)	Porous polyvinyl formal resin, Type I collagen	HPCs HSCs	Fetal liver cell, Stromal cells (OP9 and C3H10T1/2)	DMEM	13.9-folds	14	Enhance cell-cell interactions to produce stable performance
Nurhayati et al. (2021)	Alginate-chitosan coating	$CD34^+$ cells	N/A	StemSpan™ SFEM II	94.4 ± 0.4% from 1000 cells	8	The capsules restrict cell growth of MSCs, the $CD34^+$ have enough nutrient/oxygen to release paracrine factor
Sudo et al. (2021)	Hydrolysed polyvinyl acetate	HSCs	N/A	IMDM	1×10^4 $CD34^+$ to 5×10^4 $CD34^+$	7	Support proliferation and expansion of mouse long-term (LT)-HSCs, did not compromise HSC activity after active cell division
Kefallinou et al. (2020)	PDMS and Type I collagen	HSCs	MSCs	Gibco™ MEM α	4.0×10^4 cells/ mL to 8.8×10^5 cells/ mL	8	Resemble the natural in vivo bone marrow microenvironment
Lin et al. (2020)	Wharton's jelly	$CD34^+$ cells	MSCs	DMEM	$0.74 \pm 0.10 \times 10^6$	7	Acts as natural scaffold ex vivo expansion of UCB $CD34^+$ cells and helping to keep them primitive
Miyoshi et al. (2020)	Porous polyvinyl formal resin, Type I collagen coating	HSPCs	Stromal cells	DMEM	6.6-folds to 8.0-folds	14	Support the stimulating factors and cell-cell contact
Zhou et al. (2020)	Alginate-gelatin hydrogel	HSPCs	MSCs	StemSpan™ SFEM II	16.66-folds	14	Mimic the natural conditions for HSPC growth
Arabkari et al.	Polyethersulfone nanofiber	$CD34^+$ cells	MNCs	StemSpan™ SFEM II	9.17 ± 1.06-folds	7	Enhance cell-cell interaction and

(2019)	scaffolds						growth zone
Bai et al. (2019)	3D zwitterionic hydrogel (Polycarboxybetaine acrylamide)	HSPCs	N/A	StemSpan™ SFEM II	73-folds	24	Maintain the HSPCs repopulating ability likes in vivo
Severn et al. (2019)	Porous PolyHIPE foam scaffolds	HSPCs	Neutrophil, Macrophage, MSCs	IMDM	2.85×10^6	28	Mimic the honeycomb architecture of human bone marrow

Comparison of Various Parameters for In Vitro Expansion

Selected articles that have been discussed in this study proved that polymeric biomaterials have ability to support expansion of HSCs. Either natural or synthetic, this approach had shown an effective mechanism in diagnostic settings to treat patients with haematological disorder through HSCs transplantation. Several methods can be seen to create a three-dimensional architecture hydrogel, in which cells can be encapsulated, fibrous scaffolds, 3D printing, or porous materials. Therefore, the chosen parameters which are selection of polymeric biomaterials, selection of main cells, selection of other cells, selection of culture media, rate of expansion, days of culture and optimizing conditions for HSCs expansion could be discuss in depth to identify scientific evidence of current advances of biomaterial strategies for in vitro expansion of HSCs.

Selection of Polymeric Biomaterials

Polymeric biomaterials have been widely used as cell scaffolds because of its beneficial characteristics, which include excellent biocompatibility, biodegradability, and tuneable physical and chemical properties (Hong et al., 2022). Not only that but expanding HSCs through in vitro usually affordable compared to in vivo method that require animal culture. By constructing a 3D scaffold, it became the most effective tool for simulating biological microenvironments that necessary for stem cell augmentation and proliferation. All studies used polymers to expand HSCs. This is because polymers have potential to provide scaffold for HSCs likely in natural human body. This condition gave HSCs interested to expand despite outside the natural environment. Mostly, the studies used synthetic polymers such as PVA, PDMS, PES and modified zwitterionic as the scaffold (Marx-Blümel et al., 2021; Sudo et al., 2021; Bai et al., 2019). Unlike Nurhayati et al., (2021) and Zhou et al., (2020), they used natural polymers which are alginate-chitosan and alginate-gelatin, respectively. These natural polymers show no effect on gene expression, surface marker integrity, or cell viability. Clearly, polymers-based design has significant applications in tissue engineering and beyond. The 3D zwitterionic hydrogel design by Bai et al., (2019) show a reliable expansion which is 73-folds. The establishment of hydrogels in three-dimensional gave a better resemble BM niche by producing a hypoxic gradient that is seen naturally in the marrow (Liu et al., 2022). Despite that, Wang & Sugimura, (2023) mentioned that it is critically important to comprehend the molecular mechanisms and physio-chemical parameters of the bone marrow niches to reconstruct and duplicate the HSC proliferation in bone marrow.

Selection of Main Cells

Along this study, six out of fifteen used HSCs thus indicates the major stem cell sources for cells-based therapy that have shown good efficacy. HSCs commonly reside in several area such as peripheral blood (PB), bone marrow (BM) and umbilical cord blood (UCB). HSCs provide benefits such as increased tolerance to variations in the human leukocyte antigen (HLA) and reduced burden of donor (Sakurai, 2023). It is also having primary benefits over other stem cells like quick sample availability, low risk of infection transmission, and relatively simple procurement process (Derakhshani et al., 2019). In contrast, there were also five studies focus on usage of HSPCs as their source of cell. The interaction of HSPCs with the ECM seems also could mimic porous architecture of cancellous bone, which harbours the niche-harbouring red BM (Chatterjee et al., 2021). In addition, four studies used CD34+ cells as their source to undergoes expansion. This surface marker easily obtains from human BM as it presents both in HSCs and HSPCs.

Selection of Feeder Cells

Eight out of fifteen studies chose MSCs or known as stromal cells as their main option for co-culture with HSCs. According to conventional methods, HSCs often need a feeder cell layer to sustain quiescence and pluripotency. In fact, MSCs and HSCs are naturally resided in BM niche to maintain their physiological behaviour. Biologically, MSCs are dynamic, they develop into a variety of lineages that further make up the niche needed for the preservation of HSCs. Chatterjee et al., (2021) also claimed that clinical

studies have shown that co-culturing human HSPCs ex vivo with MSCs boosted their expansion without compromising their stemness and greatly enhanced patient engraftment after transplantation. Thus, it is crucial to make sure that the co-culturing process align with in vivo environment thus it can give positive results. Apart from that, there were also four studies chose white blood cells such as macrophage, neutrophil and MNCs as the feeder cells to aid expansion of HSCs. According to Li et al., (2023), the culture of HSCs and MNCs demonstrate positive outcome for xenograft assay as the expansion remain HSCs morphology and viability. This suggested that potential application in xenograft experiment could retain the cultured cells. Interestingly, five out of fifteen studies conduct their culture without adding any cells. Despite that, there were still an expansion of HSCs if the paracrine signalling occurs among the cells. The HSCs can communicate with one another through paracrine signalling, in which signalling molecules are released and bind to nearby cells to activate them.

Selection of Culture Media

Throughout the review, five out fifteen studies show that the main media which is StemSpan™ SFEM II used to expand in vitro HSCs. StemSpan™ SFEM II support the expansion of normal or leukemic human HSPCs or their lineage-specific differentiation when added with hematopoietic growth factors or other stimuli. StemSpan expansion supplements are pre-mixed cocktails of recombinant human cytokines and other additives. Thus, it believed that this media able to encourage the expansion with the designed technologies. Besides that, three studies conduct the culture trial by using DMEM as their media. DMEM was originally formulated with low glucose (1 g/L) and sodium pyruvate, but is often used with higher glucose levels, with or without sodium pyruvate. It contains no proteins, lipids, or growth factors. Therefore, it requires supplementation, commonly with 10% Fetal Bovine Serum (FBS). Thus, DMEM plays an important role by providing nutrients to the HSCs. Apart from that, three studies prefer to use IMDM for their culture media. IMDM is a modification of DMEM that introduces selenium and other amino acids and vitamins. IMDM offers rapid proliferation and is appropriate for high-density cell cultures to support expansion of HSCs.

Rate of Expansion

Throughout extraction of data from all papers included in this study, the expansion method by Bai et al., (2019) shows the highest outcome compared to others. The authors used combination of polymers and hydrogel to mimic the natural microenvironment. Therefore, the HSCs may recognize the in vitro conditions same as in vivo niche. Interestingly, in this three-dimensional (3D) zwitterionic hydrogels, an increase in long-term (LT)-HSC growth of 73-folds was recorded after 24 days. The corresponding in vivo outcomes showed that the enlarged HSCs could restore the haematopoiesis for a minimum of twenty-four weeks in immunocompromised mice. Other than that, the rate of expansion after 7 days depicts a satisfy outcomes where the folds changed from initial number. This indicates that the designed scaffold has potential to supplies reliable condition for HSCs to expand. The rate of expansion after 7 days can reach 6.2-folds according to Li et al., (2023). Meanwhile, the studies show a higher rate of expansion after 14 days for instance 13.9-folds, 8.0-folds and 16.66-folds. This indicates that the when the culture period increases, the rate of expansion increases.

Days of Culture

Five out of fifteen studies indicate the shortest period of culture which is 7 days to obtain an increased number of HSCs. This indicate that the approach used very efficiently as combination of selected polymeric biomaterials comply in vivo conditions. This suggests that the expansion of HSCs is not impossible to achieve within 1 week even in vitro settings. However, there were studies require 14 days to complete the culture. After that, it shows that a satisfactory result as the rate of expansion achieve 13.9-folds (Miyoshi et al., 2021), 8.0-folds (Miyoshi et al., 2020) and 16.66-folds (Zhou et al., 2020). Interestingly, Bai et al., (2019) require 24 days for their culture and obtain very satisfying result which is 73-folds of HSCs expansion. It is quite outstanding approach as the culture does not involve other cells to support expansion of HSPCs. Finally, two studies require 28 days representing the longest culture period for expanding HSCs. It cannot be denied that the expansion still possible to sustain as the outcome indicate a positive response after long period (Igarashi et al., 2023; Severn et al., 2019).

Optimizing Conditions for HSCs Expansion

This review highlights that most trial focus on to mimic and resemble the structural and mechanical properties of BM niche. This due to provide a conducive environment towards HSCs to undergoes expansion. This mechanism can be achieved by building of polymers that align with the condition of BM niche thus it will lead to natural scaffolding that help to keep HSCs in primitive. In contrast with Igarashi et al., (2023), they aim to optimise O2 concentrations as the conditions should be in hypoxic. This mechanism restricts HSCs to become mature cells rapidly as it should be expanded at the first place. Other than that, several trials have done by enhancing cell-cell interactions in cultured scaffold. This mechanism guarantees HSCs to expand in presence of MSCs or MNCs

for activation of molecular signalling pathways. Hence, a stable performance can be achieved as well as support HSCs in vitro effectively.

Summary of Findings

The studies here demonstrated creation and sustainment of the 3D bone marrow is the most important and encouraging factor for the subsequent HSCs expansion. The combination of various parameters will support and provide the essential nutrients for the HSCs development and maintenance. These are promising results to be subsequently applied on future approach in vitro expansion of HSCs. The suitable polymeric biomaterials could resemble the architecture of BM niche and enhance cell to cell interaction. The HSCs should be bonded to reliable feeder cells such as MNCs and MSCs to facilitate a faithful cellular microenvironment. Most importantly, the consistency of renewing or changing culture media for in vitro expansion of HSCs will promise positive formation of cell in certain period. Hence, the HSCs expansion in 3D technique holds promise for researchers to achieve continuous solution in treating various blood disorders.

CONCLUSION

In conclusion, this scoping review study showed that polymeric biomaterials can improve the expansion of HSCs by ensuring right culture technique. The development of sophisticated cell treatments for bone marrow transplantation and various blood diseases has made the expansion of HSCs a crucial objective. The comparison of various research in five years range proved that there was a potential to stabilise and expanding HSCs in laboratory settings. Thus, the objectives of this study have been achieved as it was able to identify type of polymeric biomaterials that support in vitro expansion of HSCs. Other than that, this study also manages to determine the contributing parameters that assist stabilisation of polymeric biomaterials towards expansion of HSCs. Improvement has been made possible by using effective polymers, useful feeder cells and right culture technique. 3D structures have frequently taken the role of 2D cultures as study models because they appear to be particularly important for maintaining as much of the original system as possible, including avoiding polarization or phenotypic changes as well as gene expression adjustments. Therefore, comprehension of HSCs behaviour in culture and their reaction to artificial niche signals may aid in the success of their in vitro expansion in 3D scaffolds. Not only that but this study could become advances solution in resolving blood shortage. The mobile donation can be reduced by providing a flexible human HSCs expansion strategy with considerable application potential. To fully understand the efficacy and safety of this mechanism, more research is necessary, and they should be taken with a various potential strategy. It will be fascinating to see if these various strategies work well together and enhance HSCs proliferation and stability in vitro.

ACKNOWLEDGEMENT

This research was not funded by any grant. We would like to thank and acknowledge the Department of Biomedical Science, Kulliyyah of Allied Health Sciences, IIUM for their support and motivation.

REFERENCES

Ananth, K. P., & Jayram, N. D. (2023). A comprehensive review of 3D printing techniques for biomaterial-based scaffold fabrication in bone tissue engineering. Annals of 3D Printed Medicine, 100141. https://doi.org/10.1016/j.stlm.2023.100141

Arabkari, V., Amirizadeh, N., Nikougoftar, M., & Soleimani, M. (2019). MicroRNA expression profiles in two- and three-dimensional culture conditions of human-umbilical-cord blood-derived CD34+ cells. Journal of Cellular Physiology, 234(11), 20072–20084. https://doi.org/10.1002/jcp.28606

Askari, M. H., Shahabi, M., Kojabad, A. A., & Zarif, M. N. (2023). Reconstruction of bone marrow microenvironment for expansion of hematopoietic stem cells by a histone deacetylase inhibitor. Cytotechnology, 75(3), 195–206. https://doi.org/10.1007/s10616-022-00564-w

Bai, T., Li, J., Sinclair, A., Imren, S., Merriam, F., Sun, F., O'Kelly, M. B., Nourigat, C., Jain, P., Delrow, J. J., Basom, R. S., Hung, H.-C., Zhang, P., Li, B., Heimfeld, S., Jiang, S., & Delaney, C. (2019). Expansion of primitive human hematopoietic stem cells by culture in a zwitterionic hydrogel. Nature Medicine, 25(10), 1566–1575. https://doi.org/10.1038/s41591-019-0601-5

Bastani, S., Staal, F. J., & Canté-Barrett, K. (2023). The quest for the holy grail: Overcoming challenges in expanding human hematopoietic stem cells for clinical use. Stem Cell Investigation, 10, 15–15. https://doi.org/10.21037/sci-2023-016

Bozhilov, Y. K., Hsu, I., Brown, E. J., & Wilkinson, A. C. (2023). In vitro human haematopoietic stem cell expansion and differentiation. Cells, 12(6), 896. https://doi.org/10.3390/cells12060896

Bruschi, M., Vanzolini, T., Sahu, N., Balduini, A., Magnani, M., & Fraternale, A. (2022). Functionalized 3D scaffolds for engineering the hematopoietic niche. Frontiers in Bioengineering and Biotechnology, 10. https://doi.org/10.3389/fbioe.2022.968086

Chatterjee, C., Schertl, P., Frommer, M., Ludwig-Husemann, A., Mohra, A., Dilger, N., Naolou, T., Meermeyer, S., Bergmann, T. C., Alonso Calleja, A., & Lee-Thedieck, C. (2021). Rebuilding the hematopoietic stem cell niche: Recent developments and future prospects. Acta Biomaterialia, 132, 129–148. https://doi.org/10.1016/j.actbio.2021.03.061

Comazzetto, S., Shen, B., & Morrison, S. J. (2021). Niches that regulate stem cells and hematopoiesis in adult bone marrow. Developmental Cell, 56(13), 1848–1860. https://doi.org/10.1016/j.devcel.2021.05.018

Congrains, A., Bianco, J., Rosa, R. G., Mancuso, R. I., & Saad, S. T. O. (2021). 3D Scaffolds to Model the Hematopoietic Stem Cell Niche: Applications and Perspectives. Materials (Basel, Switzerland), 14(3), 569. https://doi.org/10.3390/ma14030569

Darvish, M., Payandeh, Z., Soleimanifar, F., Taheri, B., Soleimani, M., & Islami, M. (2019). Umbilical cord blood mesenchymal stem cells application in hematopoietic stem cells expansion on nanofiber three-dimensional scaffold. Journal of Cellular Biochemistry, 120(7), 12018–12026. https://doi.org/10.1002/jcb.28487

Derakhshani, M., Abbaszadeh, H., Movassaghpour, A. A., Mehdizadeh, A., Ebrahimi-Warkiani, M., & Yousefi, M. (2019). Strategies for elevating hematopoietic stem cells expansion and engraftment capacity. Life Sciences, 232, 116598. https://doi.org/10.1016/j.lfs.2019.116598

Fröbel, J., Landspersky, T., Percin, G., Schreck, C., Rahmig, S., Ori, A., Nowak, D., Essers, M., Waskow, C., & Oostendorp, R. A. (2021). The hematopoietic bone marrow niche ecosystem. Frontiers in Cell and Developmental Biology, 9. https://doi.org/10.3389/fcell.2021.705410

Geevarghese, R., Sajjadi, S. S., Hudecki, A., Sajjadi, S., Jalal, N. R., Madrakian, T., Ahmadi, M., Włodarczyk-Biegun, M. K., Ghavami, S., Likus, W., Siemianowicz, K., & Łos, M. J. (2022). Biodegradable and non-biodegradable biomaterials and their effect on cell differentiation. International Journal of Molecular Sciences, 23(24), 16185. https://doi.org/10.3390/ijms232416185

Gilchrist, A. E., & Harley, B. A. (2022). Engineered tissue models to replicate dynamic interactions within the hematopoietic stem cell niche. Advanced Healthcare Materials, 11(7). https://doi.org/10.1002/adhm.202102130

Gilchrist, A. E., Serrano, J. F., Ngo, M. T., Hrnjak, Z., Kim, S., & Harley, B. A. C. (2021). Encapsulation of murine hematopoietic stem and progenitor cells in a thiol-crosslinked maleimide-functionalized gelatin hydrogel. Acta Biomaterialia, 131, 138–148. https://doi.org/10.1016/j.actbio.2021.06.028

Gutiérrez-García, A. K., Flores-Kelly, J. M., Ortiz-Rodríguez, T., Kalixto-Sánchez, M. A., & De León-Rodríguez, A. (2019). Phthalates affect the in vitro expansion of human hematopoietic stem cell. Cytotechnology, 71(2), 553–561. https://doi.org/10.1007/s10616-019-00300-x

Hashemi Bahramani, M., Gharib, A., Soeimani, M., & Rabiei, M. (2023). Do cord blood CD34 cells stay the same or change after expansion: A comprehensive analysis of gene expression results before and after seven days of cell culture. Transfusion and Apheresis Science, 62(5), 103748. https://doi.org/10.1016/j.transci.2023.103748

Ho, T.-C., Chang, C.-C., Chan, H.-P., Chung, T.-W., Shu, C.-W., Chuang, K.-P., Duh, T.-H., Yang, M.-H., & Tyan, Y.-C. (2022). Hydrogels: Properties and applications in Biomedicine. Molecules, 27(9), 2902. https://doi.org/10.3390/molecules27092902

Hong, J., Zheng, W., Wang, X., Hao, Y., & Cheng, G. (2022). Biomedical polymer scaffolds mimicking bone marrow niches to advance in vitro expansion of hematopoietic stem cells. Journal of Materials Chemistry B, 10(47), 9755–9769. https://doi.org/10.1039/d2tb01211a

Huang, X., Wang, Y., Wang, T., Wen, F., Liu, S., & Oudeng, G. (2022). Recent advances in engineering hydrogels for niche biomimicking and hematopoietic stem cell culturing. Frontiers in Bioengineering and Biotechnology, 10. https://doi.org/10.3389/fbioe.2022.1049965

Igarashi, K. J., Kucinski, I., Chan, Y. Y., Tan, T.-K., Khoo, H. M., Kealy, D., Bhadury, J., Hsu, I., Ho, P. Y., Niizuma, K., Hickey, J. W., Nolan, G. P., Bridge, K. S., Czechowicz, A., Gottgens, B., Nakauchi, H., & Wilkinson, A. C. (2023). Physioxia improves the selectivity of hematopoietic stem cell expansion cultures. Blood Advances, 7(14),

3366–3377. https://doi.org/10.1182/bloodadvances.2023009668

Ingavle, G., Vaidya, A., & Kale, V. (2019). Constructing three-dimensional microenvironments using engineered biomaterials for hematopoietic stem cell expansion. Tissue Engineering Part B: Reviews, 25(4), 312–329. https://doi.org/10.1089/ten.teb.2018.0286

Islami, M., Payandeh, Z., Dalir Abdolahinia, E., Saburi, E., Soleimanifar, F., Kehtari, M., Mortazavi, Y., Nadri, S., & Darvish, M. (2019). Fucosylated umbilical cord blood hematopoietic stem cell expansion on selectin-coated scaffolds. Journal of Cellular Physiology, 234(12), 22593–22603. https://doi.org/10.1002/jcp.28825

Jansen, L. E., Kim, H., Hall, C. L., McCarthy, T. P., Lee, M. J., & Peyton, S. R. (2022). A poly(ethylene glycol) three-dimensional bone marrow hydrogel. Biomaterials, 280, 121270. https://doi.org/10.1016/j.biomaterials.2021.121270

Katagiri, T., Uemura, S., Ushiki, T., Nakajima-Takagi, Y., Oshima, M., Mikami, T., Kawasaki, A., Ishiguro, H., Tanaka, T., Sone, H., Kitagawa, H., Igarashi, M., Iwama, A., & Masuko, M. (2021). Distinct effects of chondroitin sulfate on hematopoietic cells and the stromal microenvironment in bone marrow hematopoiesis. Experimental Hematology, 96. https://doi.org/10.1016/j.exphem.2021.02.003

Kefallinou, D., Grigoriou, M., Boumpas, D. T., Gogolides, E., & Tserepi, A. (2020). Fabrication of a 3D microfluidic cell culture device for bone marrow-on-a-chip. Micro and Nano Engineering, 9, 100075. https://doi.org/10.1016/j.mne.2020.100075

Kemppi, H., Finnilä, M. A., Lorite, G. S., Nelo, M., Juuti, J., Kokki, M., Kokki, H., Räsänen, J., Mobasheri, A., & Saarakkala, S. (2021). Design and development of Poly-L/D-lactide copolymer and barium titanate nanoparticle 3D composite scaffolds using breath figure method for tissue engineering applications. Colloids and Surfaces B: Biointerfaces, 199, 111530. https://doi.org/10.1016/j.colsurfb.2020.111530

Khan, M. U., Aslam, M. A., Bin Abdullah, M. F., Hasan, A., Shah, S. A., & Stojanović, G. M. (2023). Recent perspective of polymeric biomaterial in tissue engineering– A Review. Materials Today Chemistry, 34, 101818. https://doi.org/10.1016/j.mtchem.2023.101818

Lee, J. W., Kim, H. S., Yon, S.-J., Matsumoto, T., Lee, S.-K., & Lee, K. Y. (2022). In vitro culture of hematopoietic stem cell niche using angiopoietin-1-coupled alginate hydrogel. International Journal of Biological Macromolecules, 209, 1893–1899. https://doi.org/10.1016/j.ijbiomac.2022.04.163

Li, J., Zhang, L., Yin, L., Ma, N., Wang, T., Wu, Y., Wang, M., Yang, X., Xu, H., Hao, C., Li, W., Wei, W., Xu, Y., Zhang, F., Breslin, P., Zhang, J., & Zhang, J. (2019). In vitro expansion of hematopoietic stem cells by inhibition of both GSK3 and p38 signaling. Stem Cells and Development, 28(22), 1486–1497. https://doi.org/10.1089/scd.2019.0119

Li, W., Liang, H., Ao, Y., Tang, B., Li, J., Li, N., Wang, J., & Du, Y. (2023). Biophysical cues of bone marrow-inspired scaffolds regulate hematopoiesis of hematopoietic stem and progenitor cells. Biomaterials, 298, 122111. https://doi.org/10.1016/j.biomaterials.2023.122111

Li, Y., He, M., Zhang, W., Liu, W., Xu, H., Yang, M., Zhang, H., Liang, H., Li, W., Wu, Z., Fu, W., Xu, S., Liu, X., Fan, S., Zhou, L., Wang, C., Zhang, L., Li, Y., Gu, J., … Gao, Y. (2023). Expansion of human megakaryocyte-biased hematopoietic stem cells by biomimetic Microniche. Nature Communications, 14(1). https://doi.org/10.1038/s41467-023-37954-3

Liang, G., & Liu, F. (2023, April 19). Long-term expansion of human hematopoietic stem cells - cell regeneration. SpringerOpen. https://doi.org/10.1186/s13619-023-00163-w

Liang, H., Ao, Y., Li, W., Liang, K., Tang, B., Li, J., Wang, J., Zhu, X., & Du, Y. (2023). Injectable bone marrow microniches by co-culture of hspcs with mscs in 3D microscaffolds promote hematopoietic reconstitution from acute lethal radiation. Bioactive Materials, 22, 453–465. https://doi.org/10.1016/j.bioactmat.2022.10.015

Lin, H. D., Fong, C.-Y., Biswas, A., & Bongso, A. (2020). Allogeneic human umbilical cord Wharton's jelly stem cells increase several-fold the expansion of human cord blood CD34+ cells both in vitro and in vivo. Stem Cell Research & Therapy, 11(1). https://doi.org/10.1186/s13287-020-02048-0

Liu, B., Jin, M., & Wang, D.-A. (2023). In vitro expansion of hematopoietic stem cells in a porous hydrogel-based 3D Culture system. Acta Biomaterialia, 161, 67–79. https://doi.org/10.1016/j.actbio.2023.01.057

Liu, B., Tao, C., Wu, Z., Yao, H., & Wang, D.-A. (2022). Engineering strategies to achieve efficient in vitro expansion of haematopoietic stem cells: Development

and improvement. Journal of Materials Chemistry B, 10(11), 1734–1753. https://doi.org/10.1039/d1tb02706a

Lucas, D. (2017). The bone marrow microenvironment for hematopoietic stem cells. Advances in Experimental Medicine and Biology, 5–18. https://doi.org/10.1007/978-3-319-69194-7_2

Mansoorabadi, Z., & Kheirandish, M. (2022). The upregulation of GATA transcription factors family and fog-1 in expanded and differentiated cord blood-derived CD34+ hematopoietic stem cells to megakaryocyte lineage during co-culture with cord blood mesenchymal stem cells. Transfusion and Apheresis Science, 61(6), 103481. https://doi.org/10.1016/j.transci.2022.103481

Manzo, P., Scala, P., Giudice, V., Gorrese, M., Bertolini, A., Morini, D., D'Alto, F., Pepe, R., Pedicini, A., Izzo, B., Verdesca, F., Langella, M., Serio, B., Della Porta, G., & Selleri, C. (2022). C-kit M541L variant is related to ineffective hemopoiesis predisposing to clonal evolution in 3D in vitro biomimetic co-culture model of bone marrow niche. Heliyon, 8(12). https://doi.org/10.1016/j.heliyon.2022.e11998

Marx-Blümel, L., Marx, C., Sonnemann, J. et al. Molecular characterization of hematopoietic stem cells after in vitro amplification on biomimetic 3D PDMS cell culture scaffolds. Sci Rep 11, 21163 (2021). https://doi.org/10.1038/s41598-021-00619-6

Marx-Blümel, L., Marx, C., Weise, F., Frey, J., Perner, B., Schlingloff, G., Lindig, N., Hampl, J., Sonnemann, J., Brauer, D., Voigt, A., Singh, S., Beck, B., Jäger, U.-M., Wang, Z. Q., Beck, J. F., & Schober, A. (2020). Biomimetic reconstruction of the hematopoietic stem cell niche for in vitro amplification of human hematopoietic stem cells. PLOS ONE, 15(6). https://doi.org/10.1371/journal.pone.0234638

Miyoshi, H., Abo, K., Hosoya, D., Matsuo, K., & Utsumi, Y. (2021). Effects of mouse fetal liver cell culture density on hematopoietic cell expansion in three-dimensional cocultures with stromal cells. The International Journal of Artificial Organs, 45(1), 103–112. https://doi.org/10.1177/0391398821996377

Miyoshi, H., Shimizu, Y., Yasui, Y., & Sugiyama, S. (2020a). Expansion of mouse primitive hematopoietic cells in three-dimensional cultures on chemically fixed stromal cell layers. Cytotechnology, 72(5), 741–750. https://doi.org/10.1007/s10616-020-00417-4

Moghadasi, M. H., Hajifathali, A., Azad, M., Rahmani, M., & Soleimani, M. (2022). Expansion of cord blood stem cells in fibronectin-coated microfluidic bioreactor. Hematology, Transfusion and Cell Therapy, 44(4), 504–511. https://doi.org/10.1016/j.htct.2021.06.011

Nurhayati, R. W., Cahyo, R. D., Pratama, G., Anggraini, D., Mubarok, W., Kobayashi, M., & Antarianto, R. D. (2021). Alginate-chitosan microencapsulated cells for improving CD34+ progenitor maintenance and expansion. Applied Sciences, 11(17), 7887. https://doi.org/10.3390/app11177887

Oleksy, M., Dynarowicz, K., & Aebisher, D. (2023). Advances in biodegradable polymers and biomaterials for medical applications—a review. Molecules, 28(17), 6213. https://doi.org/10.3390/molecules28176213

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The Prisma 2020 statement: An updated guideline for reporting systematic reviews. BMJ. https://doi.org/10.1136/bmj.n71

Park, W., Jang, S., Kim, T. W., Bae, J., Oh, T. I., & Lee, E. (2019). Microfluidic-printed Microcarrier for in vitro expansion of adherent stem cells in 3D culture platform. Macromolecular Bioscience, 19(8). https://doi.org/10.1002/mabi.201900136

Petaroudi, M., Rodrigo-Navarro, A., Dobre, O., Dalby, M. J., & Salmeron-Sanchez, M. (2022). Living biomaterials to engineer hematopoietic stem cell niches. Advanced Healthcare Materials, 11(20). https://doi.org/10.1002/adhm.202200964

Radu, P., Zurzu, M., Paic, V., Bratucu, M., Garofil, D., Tigora, A., Georgescu, V., Prunoiu, V., Pasnicu, C., Popa, F., Surlin, P., Surlin, V., & Strambu, V. (2023a). CD34—structure, functions and relationship with Cancer Stem Cells. Medicina, 59(5), 938. https://doi.org/10.3390/medicina59050938

Ren, Y., Cui, Y., Tan, Y., Xu, Z., & Wang, H. (2023). Expansion strategies for umbilical cord blood haematopoietic stem cells in vitro. Vox Sanguinis, 118(11), 913–920. https://doi.org/10.1111/vox.13505

Rubio-Lara, J. A., Igarashi, K. J., Sood, S., Johansson, A., Sommerkamp, P., Yamashita, M., & Lin, D. S. (2023). Expanding hematopoietic stem cell ex vivo: Recent advances and technical considerations. Experimental

Hematology, 125–126, 6–15. https://doi.org/10.1016/j.exphem.2023.07.006

Sakurai, M. (2023). Recent advances in ex vivo expansion of human hematopoietic stem cells. (2023). BLOOD CELL THERAPY / The Official Journal of APBMT, 6(4), 151-157. https://doi.org/10.31547/bct-2023-026

Sakurai, M., Ishitsuka, K., Ito, R., Wilkinson, A. C., Kimura, T., Mizutani, E., Nishikii, H., Sudo, K., Becker, H. J., Takemoto, H., Sano, T., Kataoka, K., Takahashi, S., Nakamura, Y., Kent, D. G., Iwama, A., Chiba, S., Okamoto, S., Nakauchi, H., & Yamazaki, S. (2023). Chemically defined cytokine-free expansion of human haematopoietic stem cells. Nature, 615(7950), 127–133. https://doi.org/10.1038/s41586-023-05739-9

Sánchez-Lanzas, R., Kalampalika, F., & Ganuza, M. (2022). Diversity in the bone marrow niche: Classic and novel strategies to uncover niche composition. British Journal of Haematology, 199(5), 647–664. https://doi.org/10.1111/bjh.18355

Severn, C. E., Eissa, A. M., Langford, C. R., Parker, A., Walker, M., Dobbe, J. G. G., Streekstra, G. J., Cameron, N. R., & Toye, A. M. (2019). Ex vivo culture of adult CD34+ stem cells using functional highly porous polymer scaffolds to establish biomimicry of the bone marrow niche. Biomaterials, 225, 119533. https://doi.org/10.1016/j.biomaterials.2019.119533

Sola, A., Bertacchini, J., D'Avella, D., Anselmi, L., Maraldi, T., Marmiroli, S., & Messori, M. (2019). Development of solvent-casting particulate leaching (SCPL) polymer scaffolds as improved three-dimensional supports to mimic the bone marrow niche. Materials Science and Engineering: C, 96, 153–165. https://doi.org/10.1016/j.msec.2018.10.086

Soleimani, M., & Naghani, A. S. (2023). The differentiation of human induced pluripotent stem cells into hematopoietic stem cells on 3D bone scaffold in a dynamic culture system. Tissue and Cell, 82, 102044. https://doi.org/10.1016/j.tice.2023.102044

Sudo, K., Yamazaki, S., Wilkinson, A. C., Nakauchi, H., & Nakamura, Y. (2021). Polyvinyl alcohol hydrolysis rate and molecular weight influence human and murine HSC activity ex vivo. Stem Cell Research, 56, 102531. https://doi.org/10.1016/j.scr.2021.102531

Tellechea, M. F., Chagraoui, J., Cohen, S., & Sauvageau, G. (2023). Towards clinically meaningful expansion of human hscs. Cell Research, 33(9), 659–660. https://doi.org/10.1038/s41422-023-00817-z

Trifanova, E. M., Khvorostina, M. A., Mariyanats, A. O., Sochilina, A. V., Nikolaeva, M. E., Khaydukov, E. V., Akasov, R. A., & Popov, V. K. (2022). Natural and synthetic polymer scaffolds comprising upconversion nanoparticles as a bioimaging platform for tissue engineering. Molecules, 27(19), 6547. https://doi.org/10.3390/molecules27196547

Uslu, M., & Kocabaş, F. (2021). Development of a novel and synthetic HematoMiR technology that broadly modulates quiescence of stem cells and enhances HSC Expansion. Cellular and Molecular Life Sciences, 79(1). https://doi.org/10.1007/s00018-021-04031-1

Wang, Y., & Sugimura, R. (2023). Ex vivo expansion of hematopoietic stem cells. Experimental Cell Research, 427(1), 113599. https://doi.org/10.1016/j.yexcr.2023.113599

Wasyłeczko, M., Remiszewska, E., Sikorska, W., Dulnik, J., & Chwojnowski, A. (2023). Scaffolds for cartilage tissue engineering from a blend of Polyethersulfone and polyurethane polymers. Molecules, 28(7), 3195. https://doi.org/10.3390/molecules28073195

World Health Organization. (n.d.). Anaemia. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/anaemia

Wilkinson, A. C., & Nakauchi, H. (2020a). Stabilizing hematopoietic stem cells in vitro. Current Opinion in Genetics & Development, 64, 1–5. https://doi.org/10.1016/j.gde.2020.05.035

Xiao, X., Lai, W., Xie, H. et al. Targeting JNK pathway promotes human hematopoietic stem cell expansion. Cell Discov 5, 2 (2019). https://doi.org/10.1038/s41421-018-0072-8

Yin, S., & Cao, Y. (2021). Hydrogels for large-scale expansion of Stem Cells. Acta Biomaterialia, 128, 1–20. https://doi.org/10.1016/j.actbio.2021.03.026

Zhou, D., Chen, L., Ding, J., Zhang, X., Nie, Z., Li, X., Yang, B., & Xu, T. (2020). A 3D engineered scaffold for hematopoietic progenitor/stem cell co-culture in vitro. Scientific Reports, 10(1). https://doi.org/10.1038/s41598-020-68250-5

Zhu, M., Wang, Q., Gu, T., Han, Y., Zeng, X., Li, J., Dong, J., Huang, H., & Qian, P. (2023). Hydrogel-based microenvironment engineering of Haematopoietic Stem Cells. Cellular and Molecular Life Sciences, 80(2). https://doi.org/10.1007/s00018-023-04696-w