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RESEARCH ARTICLE

iPSC-Derived Mesenchymal Stem Cells: Navigating the Transition to Xeno-Free Culture for Next Generation Regenerative Therapies

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Abstract

Mesenchymal stem cells (MSCs) are multipotent cells with the capacity to differentiate into mesodermal lineages and exhibit immunomodulatory and regenerative effects. Traditionally, MSCs can be isolated from bone marrow, adipose tissue, and umbilical cord. MSCs have been investigated for their therapeutic potential in regenerative medicine and immunomodulatory applications. However, their clinical applications remain constrained by several factors, including donor-to-donor variability and senescence. Therefore, induced pluripotent stem cells (iPSCs) have been explored as an alternative source for generating induced pluripotent stem cell-derived mesenchymal stem cells (iMSCs) that retain the key characteristics of MSCs. Nevertheless, iMSCs' properties and performance vary significantly across iPSC lines, differentiation protocols, and cellular maturation state. Furthermore, the development of xenofree and chemically defined media has improved consistency and reduced medium-related risks by reducing the use of animal components. This review aims to summarize the biological characteristics of MSCs, highlight the use of xenofree and chemically defined medium, and outline their impacts on future clinical applications.

Keywords: Induced pluripotent stem cell (iPSC), Mesenchymal stem cell (MSC), Regenerative medicine, Stem cell, Xeno-free medium

1. Introduction

In recent years, significant advancements in biomedical research have established stem cells as one of the most promising and groundbreaking technologies worldwide. Stem cells possess a unique ability that has the capacity to differentiate into specialized cell types under controlled conditions and hold a capability for regenerative medicine and therapeutic applications [1]. Over the past decade, mesenchymal stem cells (MSCs) have emerged as central players in the discourse of regenerative and immunomodulatory therapies [2]. Among the different types of stem cells, MSCs have attracted significant attention due to their capacity to differentiate into mesodermal lineage cells, such as osteoblasts, adipocytes, and chondrocytes, as well as into several other cell types in different lineages [3], [4], [5], [6]. MSCs are multipotent cells that can be harvested from bone marrow, adipose tissue, and umbilical cord blood [7], [8].

The biological advantages of MSCs, including their immunomodulatory capacity and multipotent differentiation potential, have made them prime candidates for the development of cell-based therapies to address various degenerative and chronic inflammatory conditions [9], [10], [11]. MSCs can modulate the immune system through various mechanisms, including interactions with other immune cells [12], [13]. MSCs are generally considered to have low immunogenicity under homeostatic conditions, making them attractive candidates for allogeneic applications. However, their immunogenic profile is not absolute but rather conditional, particularly in inflammatory microenvironments where upregulation of major histocompatibility complex (MHC) class II molecules, including HLA-DR, can occur in response to pro-inflammatory cytokines such as interferon-gamma (IFN-γ), potentially triggering immune recognition and allogeneic rejection [14], [15], [16], [17]. However, the inherent limitations of adult-derived MSCs, including donor heterogeneity, limited cell yields, and reduced biological potency due to in vitro expansion, have highlighted the urgent need for more sustainable sources of MSCs. These challenges not only limit their scalability for large-scale clinical use but also compromise the reproducibility of therapeutic outcomes. Moreover, the selection of a suitable source is highly specific, particularly to minimize the risk of immune rejection in clinical applications [18]. Therefore, induced pluripotent stem cells (iPSCs) have been introduced as an alternative source for generating MSCs and to overcome the limitation of donor variability [19].

iPSCs are generated by reprogramming adult somatic cells, such as human fibroblasts or blood cells, back into their pluripotent state. Unlike embryonic stem cells (ESCs), which raised ethical concerns regarding their derivation from human embryos and may face immunological barriers in allogeneic settings due to MHC mismatch, iPSCs can be derived from autologous sources, offering a potentially personalized approach that minimizes immunological complications while avoiding ethical constraints [20], [21], [22]. These cells then regain their ability to differentiate into almost any type of cell in the body and are subsequently directed towards a mesenchymal lineage to produce iPSC-derived MSCs (iMSCs) [23], [24], [25], [26]. This approach enables it to produce an unlimited supply of stem cells, making iPSCs a great alternative for regenerative medicine and disease modelling [27]. These iMSCs not only replicate most of the characteristics of conventional MSCs but also present advantages in terms

of genetic control, batch-to-batch consistency, and the capacity for expansion without loss of biological potential. In the clinical context, iMSCs are regarded as the next generation of cell therapies, promising higher predictability and scalability [28].

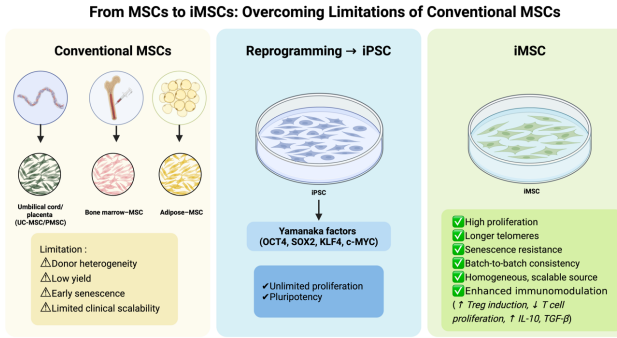

Figure 1. Schematic illustration of the transition from MSCs to iMSCs as a strategy to address the limitation of conventional MSCs

Despite the enormous potential of iMSCs, their clinical translation remains strongly dependent on the culture conditions used for their derivation and expansion. A variety of culture media have been utilized in the derivation and expansion of iMSCs, including serum-based and xeno-free chemically defined formulations [29], [30]. Traditionally, MSCs have been expanded in media supplemented with fetal bovine serum (FBS), which provides a rich source of growth factors and nutrients. However, the use of FBS raises significant concerns due to risks of xeno-immunogenic responses, batch variability, and potential transmission of animal-derived pathogens, thereby limiting their safety and reproducibility in clinical applications. To address these challenges, xenofree and chemically defined culture systems have been developed as safer and more standardized alternatives [31]. Xenofree culture media, formulated without animal-derived components, aim to maintain MSC and iMSC characteristics while enhancing consistency, safety, and regulatory compliance [32].

Given these considerations, the optimization of xenofree systems represents a critical step toward the clinical readiness of iMSCs. A systematic evaluation of how xenofree and chemically defined conditions influence iMSC biology, including proliferation, differentiation potential, immunomodulatory activity, and genomic stability, is essential to fully unlock their therapeutic promise. Indeed, while iMSCs overcome many of the intrinsic limitations of adult-derived MSCs, their clinical potential cannot be realized without safe, standardized, and xenofree culture conditions that ensure reproducibility and compliance with regulatory standards. Despite considerable progress in iMSC biology, there is still no consensus on the optimal xenofree and chemically defined culture conditions to guarantee their safety, genomic stability, and therapeutic efficacy. This represents a critical knowledge gap that must be addressed before iMSCs can be widely adopted in clinical practice. Therefore, this review aims to provide a comprehensive overview of the current progress in iMSCs research, with a particular focus on xenofree and chemically defined culture strategies, highlighting

their implications for regenerative medicine, disease modeling, and future clinical translation.

2. Mesenchymal Stem Cells (MSCs): Properties and Limitations

Mesenchymal stem cells (MSCs) were first identified by Alexander Friedenstein in the late 1960s to early 1970s, who isolated them from bone marrow and described their ability to form fibroblastic colony-forming units (CFU-Fs) and differentiate into bone-forming cells [33]. Since their discovery, MSCs have demonstrated significant therapeutic potential across a wide range of disease models and have been extensively investigated in preclinical studies [34], [35]. MSCs are currently characterized as multipotent adult stem cells with a finite proliferative lifespan and susceptibility to replicative senescence. These cells possess the ability to differentiate into various cell types in response to paracrine and autocrine signaling under controlled in vitro conditions [36], [37].

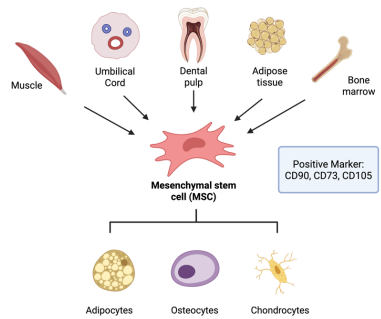

Figure 2. The Source of MSCs

MSCs can be sourced from a variety of tissues in the human body (Figure 1). However, it is important to recognize that MSCs derived from different tissue sources exhibit distinct biological characteristics, including proliferation kinetics, differentiation capacity, immunomodulatory potency, and therapeutic efficacy, which significantly impact their clinical and manufacturing outcomes [38], [39], [40]. Historically, bone marrow was the initial source identified for the isolation of MSCs. In the middle of the 19th century, Cohnheim observed that nonhematopoietic stem cells that could give rise to fibroblasts involved in the wound healing process were present in the bone marrow [33]. This raised the possibility that bone marrow may be the source of fibroblasts that deposit collagen fibers as part of the normal process of wound repair [41]. And then in 1970, Friedenstein and his colleagues revealed that these cells from bone marrow with osteogenic potential differed from hematopoietic cells during in vitro culture. They were fibroblastoid shape and adhered to culture vessels, forming clonogenic colonies termed colony-forming unit-fibroblast (CFU-F). These cells can differentiate into adipocytes, osteoblasts, chondrocytes, and myocytes. Nevertheless, obtaining autologous bone marrow presents challenges, as the procedure is often

invasive, painful, requires anesthesia, and typically produces only a small number of MSCs [42], [43], [44].

In 2001, Patricia Zuk and colleagues described the isolation of a new population of adult stem cells from liposuctioned adipose tissue called Processed Lipoaspirate Cells or PLA cells [45]. They isolate stromal vascular fraction (SVF), which contains a variety of cells, including MSCs. Zuk et al found that when the SVF is cultured over time, it gradually eliminates many of these cell types, resulting in an adherent population known as PLA. These cells can differentiate into adipocytes, osteoblasts, and chondrocytes. This suggests that adipose tissue can serve as a rich and viable source of MSCs. These cells also exhibited stable growth rates over extended cultures (up to 175 days), with minimal senescence observed, indicating their potential for long-term use in regenerative medicine [44], [45]. Notably, adipose-derived MSCs (AD-MSCs) typically demonstrate higher cell yields and proliferation rates compared to bone marrow-derived MSCs (BM-MSCs), though BM-MSCs often exhibit superior osteogenic differentiation potential, highlighting the tissue-specific functional heterogeneity that influences source selection for particular clinical applications [39], [40], [46], [47].

Numerous researchers are exploring alternatives to traditional stem cells for clinical use. Placental tissue is a highly valuable source for regenerative medicine, as human placenta-derived mesenchymal stem cells (hPMSCs) are easy to isolate and can be expanded in culture with the right medium. These cells possess significant phenotypic flexibility, and due to the placenta's role in maintaining fetal tolerance during pregnancy, they also exhibit immunomodulatory properties, with lower immunogenicity due to reduced expression of human leukocyte antigens, making them particularly beneficial for cell-based therapies in clinical settings [42]. Placenta-derived mesenchymal stem cells (PMSCs) were first characterized in 2004 and subsequently attracted significant attention as a potentially superior alternative to MSCs for therapeutic applications across a wide range of disease conditions [43], [48], [49]. Additionally, PMSCs can be banked for future autologous or allogeneic applications, making them highly suitable for clinical use due to their enhanced expansion capabilities, plasticity, and immunological advantages [48].

Another source of MSCs from extra-embryonic tissue, which shares similar fundamental characteristics with BM-MSCs, including the expression of specific markers, differentiation capacity, and adherence to plastic as defined by the International Society for Cell & Gene Therapy (ISCT), is Umbilical Cord-Mesenchymal Stem Cells (UC-MSCs) [48]. UC-MSCs were first reported in 1991 when McElreavey and colleagues isolated fibroblast-like cells from Wharton's jelly, the connective tissue of the human umbilical cord [50]. The umbilical cord became recognized as a rich, non-invasive source of MSCs, with the first research on cord blood stem cells dating back to the late 1980s, particularly with the first cord blood transplantation performed in 1988 [51]. In comparison with BM-MSCs, UC-MSCs display a more primitive stromal gene expression profile and exhibit a higher self-renewal capacity [52]. UC-MSCs present several advantages over BM-MSCs, including higher stem cell yield per unit volume, great tolerance to Human Leukocyte Antigen (HLA) mismatches that reduces the risk of graft-versus-host disease, and a simpler, painless, and risk-free

collection process for both mother and infant. Moreover, like PMSCs, UC-MSCs can be cryopreserved for 'off the shelf' use, unlike bone marrow stem cells, and they exhibit a lower risk of transmitting infectious agents such as Epstein-Barr virus and cytomegalovirus, further supporting their therapeutic potential [36], [41], [50], [52]. However, comparative studies have demonstrated that UC-MSCs show enhanced immunosuppressive capacity and anti-inflammatory effects compared to BM-MSCs and AD-MSCs, while BM-MSCs may be more suitable for bone regeneration applications due to their stronger osteogenic potential, underscoring the importance of matching MSC source to the intended therapeutic target [53], [54].

Dental tissue stem cells (DT-MCs) also constitute a notable source of MSCs, from which several types can be obtained, including dental pulp, dentin, and the periodontal ligament [55]. DT-MSCs encompass the various MSC populations that can be isolated from distinct sites within the oral cavity. Eight major populations have been identified, including dental pulp stem cells (DP-MSCs), stem cells from human exfoliated deciduous teeth (SHEDs), periodontal ligament stem cells (PL-MSCs), dental follicle progenitor cells (DFP-MSCs), alveolar bone-derived MSCs (AB-MSCs), stem cells from the apical papilla (AP-MSCs), tooth germ progenitor (TP-MSCs), and gingival mesenchymal stem cells (G-MSCs) [56]. Dental pulp was recognized as a source of MSCs in the early 2000s; Gronthos et al reported the first isolation and characterization of Dental Pulp Stem Cells (DPSCs). They isolated these cells from extracted third molars (wisdom teeth) and showed that DPSCs possess high clonogenicity, proliferation, and the ability to form densely calcified colonies [57]. DPSCs were confirmed as MSCs by their capacity to differentiate into various cell types, including odontoblasts, osteoblasts, chondrocytes, adipocytes, and neural cells, demonstrating their multilineage potential [55], [58]. These cells reside within the dental pulp, a connective tissue inside the tooth, which is a niche containing various cell types, including pulpoblasts, neural, vascular, and immune cells [55], [56].

In the 21st century, several new sources of MSCs beyond the traditional bone marrow and adipose tissue have been identified and extensively studied for regenerative medicine. These include synovial membrane, breast milk, menstrual blood, and cervix [59]. De Bari et al in 2001 isolated synovium (SM) of human knee joints for the first time. They found that these cells possess stem cell properties with multidirectional differentiation capacity in vitro [60]. They are of particular interest due to their accessibility, high proliferative potential, low immunogenicity, and superior chondrogenic differentiation compared to MSCs from other sources [60], [61].

Breast milk, on the other hand, is recognized as a valuable and non-invasive source of MSCs with promising regenerative potential. Research by Patki et al demonstrated multilineage differentiation potential (adipogenic, chondrogenic, and osteogenic lineages) of human breast milk. They also showed epithelial-to-mesenchymal transition characteristics and expressed MSC surface markers [62]. Sani et al found that fresh human breast milk contains a heterogeneous cell population including MSC-like cells, expressing CD90, CD44, CD271, CD146, selected embryonic stem cell-associated markers, and hematopoietic or endothelial markers. These breast milk-derived cells differentiated into adipocytes and osteoblasts in vitro [62], [63].

Menstrual blood has emerged as an exciting and accessible source of MSCs with

unique features and therapeutic potential. The first recognition and isolation of MSCs from menstrual blood were reported in 2007 by Meng et al [64]. From menstrual blood, they isolated a unique adherent cell population termed endometrial regenerative cells (ERCs). These cells were negative for hematopoietic markers but expressed MSC markers, confirming their mesenchymal identity. Notably, ERCs exhibit a faster doubling rate compared to UC-MSCs, can be obtained through a noninvasive collection process, avoiding the ethical issues, and do not form teratomas, making them attractive for potential clinical application [64], [65].

Recent studies described a new type of MSC, called human Uterine Cervical Stem Cells (hUCESC), which are obtained from the transitional zone of the cervix of healthy women [59], [66]. Eiro et al first successfully isolated and characterized these cells using minimally invasive approaches such as a pap cervical smear or hysterectomy. hUCESC displays typical MSC properties and anti-tumor activity. hUCESC-CM has been shown to suppress proliferation, invasion, and induce apoptosis of cancer-associated fibroblasts, and inhibit or reverse monocyte to macrophage differentiation. Furthermore, hUCESC can be obtained in relatively high yields and exhibit a strong proliferative capacity, enabling the rapid expansion of large numbers of stem cells suitable for both research and potential clinical applications [66], [67].

Beyond their diverse sources, MSCs are particularly valued for their biological advantages that contribute to their prominence in regenerative medicine and therapeutic research. MSCs are multipotent stromal cells capable of differentiating into a variety of cell types, including osteoblasts (bone cells), chondrocytes (cartilage cells), adipocytes (fat cells), myocytes (muscle cells), and potentially neural cells [68]. This broad differentiation potential enables MSCs to contribute to tissue repair and regeneration across different tissues. However, the extent and efficiency of differentiation vary significantly based on tissue origin; for instance, synovium-derived MSCs demonstrate exceptional chondrogenic capacity relevant for cartilage repair, while BM-MSCs show greater osteogenic commitment for bone tissue engineering [38], [69], [70]. They also exhibit self-renewal and plastic adherence, with a specific marker profile (CD73, CD90, CD105 positive; hematopoietic/endothelial markers negative) [71]. Several molecular regulators, including cyclin L2 (CCNL2), ubiquitin carboxyl-terminal hydrolase 1 (USP1), podocalyxin-like protein (PODXL), and stromal cell-derived factor 1 (CXCL12), have been identified as key genes involved in maintaining the multipotency, genomic stability, and functional properties of MSCs [71]. Otherwise, MSCs tend to lose multipotency during prolonged culture, which can trigger spontaneous differentiation and senescence. Therefore, optimized culture conditions and regulatory understanding are essential to preserve their stemness for therapeutic use [72].

Besides their multipotency, their immunomodulatory capacity further enhances the therapeutic value of MSCs. Through the secretion of bioactive molecules such as cytokines, chemokines, and growth factors, MSCs create an anti-inflammatory environment by downregulating pro-inflammatory mediators while promoting tissue repair [73], [74]. They apply immunoregulatory effects by interacting with diverse immune cell populations, including T cells, B cells, natural killer cells, dendritic cells, and macrophages, thereby modulating their proliferation, differentiation, and

effector functions. Importantly, the immunomodulatory potency also varies by tissue source; UC-MSCs and PMSCs generally exhibit more robust immunosuppressive properties compared to BM-MSCs and AD-MSCs, which have direct implications for their selection in treating inflammatory and autoimmune conditions.[75] This unique ability to fine-tune immune response underlies the clinical application of MSCs in autoimmune disorders, graft-versus-host disease, and other inflammation-driven pathologies.

MSCs naturally express low levels of major histocompatibility complex (MHC) class II molecules and co-stimulatory molecules, which reduces their recognition and rejection by the host immune system [76]. This property enables allogeneic (donor-derived) MSC transplantation without the need for extensive immunosuppression [68], [71]. In addition, MSCs lack key co-stimulatory molecules such as CD80, CD86, and CD40, preventing full T-cell activation and further minimizing immune recognition [77]. They are also capable of modulating their phenotype in response to inflammatory cues via Toll-like receptor signaling, thereby enhancing their immune evasion capacity [76]. Furthermore, MSCs secrete a variety of immunoregulatory factors, including prostaglandin E2 (PGE2), interleukin-10 (IL-10), and transforming growth factor-β (TGF-β), which further contribute to the suppression of pro-inflammatory immune responses[76]. The combination of immune evasion and active immunomodulation makes MSCs suitable for various clinical applications, including allogeneic cellular therapies [37], [68], [76], [77]. Nevertheless, manufacturing scalability, standardization challenges, and cost-effectiveness differ substantially across tissue sources, with UC-MSCs and AD-MSCs offering advantages in large-scale production due to their higher yields and easier accessibility, whereas BM-MSCs may require more invasive collection procedures and yield fewer cells, factors that critically influence translational feasibility and clinical implementation strategies [78].

3. Induced Pluripotent Stem Cells (iPSCs) as an Alternative Source

iPSCs are pluripotent stem cells generated by reprogramming somatic cells to an embryonic-like state. This concept was pioneered in 2006 when Takahashi and Yamanaka introduced a set of transcription factors consisting of Oct4, Sox2, Klf4, and c-Myc into mouse fibroblasts, successfully generating cells with properties similar to embryonic stem cells [79]. The following year, the same team achieved reprogramming in human fibroblasts using the same factors [80], while Yu and colleagues demonstrated that a different combination of transcription factors, namely Oct4, Sox2, Nanog, and Lin28, could also induce pluripotency in human somatic cells [81]. These discoveries established the so-called "Yamanaka factors" as the foundation of iPSC technology. Early reprogramming relied on integrating retroviral or lentiviral vectors, which were efficient but raised safety concerns due to risks of insertional mutagenesis. Advances in the field have since shifted toward non-integrating methods such as Sendai virus, episomal plasmids, synthetic mRNA, and small-molecule cocktails, which improve efficiency while reducing the likelihood of permanent genomic alterations. Regardless of the method, the process requires extensive epigenetic remodeling and a mesenchymal-to-epithelial transition that restores a self-renewing, pluripotent state [82].

A central advantage of iPSCs is their virtually unlimited expansion capacity, coupled with the ability to differentiate into all cell types of the three germ layers. Unlike adult stem cells, which face limitations in both proliferation and lineage potential, iPSCs can be propagated indefinitely while maintaining pluripotency, thereby providing an inexhaustible cell source for research and therapeutic applications [82], [83]. Another significant benefit is their patient-specific origin. iPSCs generated from an individual's own somatic cells yield genetically matched, more immunologically compatible derivatives that reduce the risk of graft rejection and bypass the ethical controversies associated with embryonic stem cells. However, it is important to note that autologous iPSC-derived cells are not fully immunologically inert; studies have documented unexpected immunogenicity even in syngeneic settings, attributed to factors such as abnormal gene expression, epigenetic alterations, and neoantigen formation during reprogramming and differentiation processes [84], [85]. Moreover, iPSCs are highly amenable to precise genetic manipulation, enabling the creation of isogenic cell lines or the correction of pathogenic mutations before therapeutic use. This genetic control makes iPSCs particularly valuable for disease modeling and the development of personalized regenerative medicine. In contrast to adult-derived stem cells, which often suffer from donor heterogeneity and age-related decline, iPSCs can be clonally derived, thoroughly screened for genomic and epigenetic stability, and expanded under standardized conditions. These features ensure consistent quality and rejuvenated characteristics even after extensive culture [86], [87].

The exceptional qualities of iPSCs have been translated into broad applications in regenerative medicine and disease modeling. One of the most transformative applications has been the generation of three-dimensional organoids. By self-organizing into structures that mimic organ development, iPSCs have enabled the creation of cerebral, intestinal, and hepatic organoids. Notably, iPSC-derived cerebral organoids have successfully recapitulated human brain development and been used to model neurodevelopmental disorders such as microcephaly, providing insights into pathologies that are difficult to study in animal systems [83]. Patient-specific disease modeling is another area where iPSCs have proven invaluable. Cells obtained from patients with genetic mutations can be reprogrammed into iPSCs and differentiated into disease-relevant cell types, such as neurons or cardiomyocytes, allowing researchers to study disease phenotypes directly in vitro. In addition, iPSCs provide robust platforms for drug discovery and toxicity testing. Their ability to generate reproducible batches of human cells at scale has facilitated the development of high-throughput assays for candidate drugs. Finally, iPSC-derived cells are already moving toward clinical applications, with translational studies investigating their use in cell replacement therapies, including transplantation of retinal pigment epithelium for macular degeneration and cardiomyocytes for heart failure. These efforts underscore the potential of iPSCs to provide autologous or HLA-matched therapeutic cells with reduced risks of immune rejection [82], [87].

Another important development is the differentiation of iPSCs into MSCs, producing iPSC-derived mesenchymal stem/stromal cells (iMSCs). These cells display the core characteristics of conventional MSCs, including plastic adherence, expression of markers such as CD73, CD90, and CD105, absence of hematopoietic markers

like CD34 and CD45, and the ability to differentiate into osteogenic, chondrogenic, and adipogenic lineages [86], [87]. Protocols for generating iMSCs vary considerably, ranging from simple serum-based cultures with fetal bovine serum and bFGF supplementation to more structured stepwise induction strategies employing early mesodermal inducers such as Activin A, Wnt agonists, and BMP4, followed by maturation factors. However, there is currently no standardized protocol consensus, and these diverse approaches can yield variable outcomes in terms of iMSC phenotype, functional properties, and therapeutic potency, highlighting the need for further optimization and standardization efforts [87]. Importantly, iMSCs exhibit enhanced proliferative potential compared to primary MSCs, with some lines maintaining stable karyotypes and consistent phenotypes even after more than 40 passages. Gene expression profiling reveals notable differences, as iMSCs often display higher expression of mesoderm-associated genes like KDR and MSX2 and a stronger adipogenic potential, whereas bone marrow-derived MSCs are enriched in extracellular matrix components and PDGFRα expression. Immunomodulatory profiles also diverge; while bone marrow MSCs typically suppress T-cell proliferation more effectively, iMSCs have been reported to secrete higher levels of anti-inflammatory mediators such as FOXP3 and TGF-β with reduced production of IL-6 [87].

iMSCs combine the rejuvenated, scalable nature of iPSCs with the therapeutic versatility of MSCs, thereby addressing some of the limitations of donor-derived MSCs, such as variability and replicative senescence. This unique profile positions iMSCs as a promising next-generation cell source for regenerative medicine and a potential "off-the-shelf" alternative to conventional MSCs [87].

4. iPSC-derived MSCs (iMSCs): Advantages and Therapeutic Potential

Research identifying differences between iPSC-derived MSCs (iMSCs) and bone marrow-derived MSCs (MSCs) from the same donor exhibited similar heterogeneity. However, iMSCs tended to form fewer colonies. Furthermore, findings regarding the differentiation potential of iMSCs show considerable variability across studies. While some studies report decreased adipogenic and osteogenic potential in iMSCs compared to MSCs, others have demonstrated comparable or even enhanced differentiation capacity depending on the differentiation protocol, culture conditions, and iPSC source used, indicating that these functional properties are highly context-dependent rather than representing a consistent characteristic of all iMSCs [88], [89], [90], [91].

Furthermore, both MSCs and iMSCs experienced senescence. This was evidenced by the similarity in senescence-related gene expression. Furthermore, 67 metabolites decreased, and 9 metabolites increased during senescence. Both cell types also exhibited a metabolic shift toward glycolysis, characterized by an increase in the Extracellular Acidification Rate (ECAR) and a decrease in the Oxygen Consumption Rate (OCR) [92]. Although iMSCs exhibit spindle-like morphology and express MSC markers such as CD44, CD90, and CD105, they exhibit higher proliferation and longer telomeres than MSCs [88], [93], [94]. This is further evidenced by iMSCs expressing OCT4 at higher levels than MSCs, which reflects residual stemness-related transcriptional activity rather than true pluripotency and represents a potential safety concern, as the persistence of OCT4 expression has been associated with an increased

risk of tumorigenicity, necessitating rigorous quality control prior to clinical application [88], [95]. iMSCs also express higher levels of stemness-related genes and the protein NESTIN [88]. This suggests that iMSCs are more resistant to senescence and can therefore be expanded in vitro in large numbers for therapy [93].

OCR is also related to mitochondrial function. A lower OCR in iMSCs indicates a weaker mitochondrial respiratory capacity and ATP production, making iMSCs more susceptible to oxidative stress than MSCs. Mutations in mitochondrial DNA also impact mitochondrial function in iMSCs. iPSCs, the cells from which iMSCs originate, are known to carry more mtDNA mutations than MSCs, and most of these mutations are inherited by iMSCs [94].

Gene expression analysis shows that iMSCs express a number of significantly different genes due to the reprogramming process. Specifically, iMSCs express higher levels of epithelial-to-mesenchymal transition (EMT) genes. However, elevated EMT signatures should be interpreted as indicators of cellular instability or an incomplete differentiation state rather than confirmation of fully functional mesenchymal identity, as these markers do not necessarily equate to stable MSC characteristics and may reflect transitional cellular states that require further maturation [88], [96].

Proteomic studies have shown that MSCs and iMSCs share many similarities in their secretomes (86%), but each also produces unique proteins that potentially explain their differences in biological function. Furthermore, immunological assays have yielded mixed results regarding the immunomodulatory capabilities of iMSCs compared to MSCs. While some studies report that iMSCs possess stronger immunosuppressive effects, particularly in inhibiting T cell proliferation, other investigations have found comparable or context-dependent immunomodulatory potency that varies based on assay conditions, passage number, differentiation protocol, and inflammatory priming. This variability underscores the need for standardized functional assessment and mechanistic understanding before definitive conclusions can be drawn [88], [93], [97], [98], [99]. iMSCs are more effective in suppressing the proliferation of activated T cells and are more potent in inducing and activating Tregs (CD4+CD25+Foxp3+), which are capable of suppressing effector immune responses. Furthermore, iMSCs modulate cytokines more evenly by increasing IL-10 and IFN-γ and decreasing Th2 cytokines (IL-4, IL-5, IL-13), thereby shifting the immune response toward a more stable regulatory pathway [93].

iMSCs differentiated into osteogenic cells using the AMOR (Antibody-Mediated Osteogenic Regeneration) concept produce new bone that is more similar to native bone, more mature, and more vascularized. This finding offers a new, safer, and more efficient iMSC-based regenerative therapy that avoids the drawbacks of conventional therapy with exogenous BMP2 [100].

Research using iMSCs derived from HLA-homozygous hiPSCs showed that after transplantation into mouse eyes (a xenograft model), the iMSCs survived for several days, migrated to the optic nerve, and did not cause damage to retinal structures or the risk of tumorigenesis. These findings indicate that iMSCs have great potential as clinical therapy candidates, including for retinal transplantation. Furthermore, iMSCs can be produced in large quantities with more consistent quality, making them highly promising for meeting broad clinical needs [101].

Other research has shown that iMSC-conditioned medium (iMSC-CdM) is effective in accelerating wound healing. Evidence of this includes increased angiogenesis (indicated by higher expression of CD31 and angiogenic factors), endothelial cell protection against oxidative stress by suppressing Reactive Oxygen Species (ROS) production, and improved mitochondrial function through regulation of mitochondrial fusion and fission dynamics [102]. Skin wound healing can also be achieved using exosomes derived from iMSCs (iMSC-exo). These iMSC-exo have been shown to increase the proliferation, migration, and survival of skin cells (keratinocytes and dermal fibroblasts), activate the ERK1/2 signaling pathway, which is essential for cell growth and regeneration, and trigger increased expression of genes involved in wound healing [103].

iMSCs can also be further differentiated into extracellular vesicles (iMSC-EVs) that inherit the immunomodulatory effects of their parent cells. These iMSC-EVs can suppress lymphocyte proliferation, modulate T cell subsets, and promote M2 macrophage polarization. EVs also possess regenerative potential, such as accelerating skin fibroblast migration, supporting wound healing, angiogenesis, and tissue regeneration. These findings reinforce the role of iMSC-EVs in tissue repair in various disease models, including chronic wounds, cardiovascular disease, musculoskeletal disorders, and organ damage such as liver, kidney, lung, and heart [104].

Natural MSCs possess immunomodulatory capabilities (suppressing the activation of T cells, NK cells, etc.), making them widely used for autoimmune, inflammatory, and cancer therapies. However, MSCs have limitations such as being difficult to propagate, heterogeneous, and difficult to obtain from donors in sufficient quantities, which hinders clinical application. iMSCs have immunomodulatory effects comparable to MSCs [104], [105], [106]. MSCs are able to suppress the proliferation of activated CD4+ and CD8+ T cells, comparable to MSCs [104], [107]. Under inflammatory conditions, iMSCs can convert CD14+ monocytes into M2-like macrophages [104]. In studies using urine-derived epithelial (UE) cells, iMSCs remained stable until late passage without losing MSC markers (CD73, CD90, CD105), in contrast to MSCs that began to lose MSC properties and express hematopoietic markers at high passage. In terms of safety, iMSCs derived from autologous sources are non-immunogenic because they do not express MHC class II or costimulatory molecules, thus minimizing the risk of immune rejection that is often a problem in allogeneic therapy with MSCs. In addition, iMSCs expressed higher levels of immunomodulatory factors such as TSG-6, IL-11, and TGF-β1 even at late passage, while maintaining low expression of pro-inflammatory IL-6, indicating a stronger anti-inflammatory capacity [106]. In fact, iMSCs showed greater support for the expansion of primitive hematopoietic progenitors (CD34+CD90+), which are important in maintaining immune system balance [107]. In in vivo models, iMSCs have been shown to inhibit lymphocyte proliferation, suppress Th2 cytokines (IL-4, IL-5, IL-13), and reduce local inflammation in contact hypersensitivity (CHS) and allergic airway inflammation models in mice [108].

Research into iMSCs derived from urine-derived iPSCs excels due to their easy cell source availability, higher proliferation rates, homogeneity, lower immunogenicity, safety from the immune system, and retained homing ability, as well as their potential

for clinical therapy. Furthermore, these iMSCs are readily available from a source (urine cells), are non-invasive, and can produce large numbers of cells. With their low immunogenicity, these iMSCs are suitable for allogeneic therapy, tissue regeneration, and drug delivery to tumors. However, these iMSCs have a weaker immunosuppressive capacity, making them unsuitable for autoimmune or inflammatory diseases [105].

iMSCs derived from Jaw Periosteal Cells (JPCs) also demonstrate similar results. These iMSCs demonstrate insensitivity to IFN-γ stimulation, specifically, the absence of an increase in HLA-DR expression as seen in JPCs. This means that iMSCs are more resistant to increased immunogenicity in an inflammatory environment [109].

5. Culture Systems for MSCs and iMSCs: From FBS to Xenofree Medium

Culture systems for MSCs and iMSCs have come a long way, from the first conventional use of serum to the work of using xeno-free medium, ensuring safety for future clinical usage. Historically, fetal bovine serum (FBS) is necessary for the development and multiplication of human and animal cells, tissues, and organs in vitro. Micro- and macronutrients, growth factors, hormones, attachment and spreading factors, and transport proteins are all abundant in it [110]. Nonetheless, its inconsistency, ethical issues, and steep price have propelled the quest for feasible substitutes. Encouraging alternatives consist of human platelet lysate, sericin protein, and media devoid of animal components, presenting possible remedies to the issues created by FBS [110], [111]. The culture system by using Fetal Bovine Serum (FBS) is not inherently bad. It has pros and cons for further consideration.

From a beneficial perspective, FBS has a lot to offer, starting with its properties that contain a variety of growth factors that could facilitate cell attachment to plastic surfaces, proliferation, and differentiation [110]. Not only that, MSCs or iMSCs cultured using FBS have been proven to develop into different lineages, including osteogenic, adipogenic, and chondrogenic cells [112]. In that case, the application of FBS is extensively recorded and broadly recognized in studies, offering a consistent method for MSC cultivation [113].

On the other hand, FBS has an increased risk of contamination, FBS can carry pathogens, including viruses and prions, which pose a risk of transmitting diseases since it was taken from bovine fetuses as a byproduct of the meatpacking industry, while there are steps to guarantee safety and quality, that FBS must only be collected in licensed establishments and in aseptic environments that comply with federal guidelines, this risk is still a problem on the first place leading to research on other alternatives [114], that being said, components of FBS can trigger some xenogenic immune responses that leads to immunological rejection in human patients [114], [115] and talking about ethical concern, the use of products sourced from animals brings forth ethical concerns, especially in regenerative medicine [116].

In response to these limitations, researchers have increasingly explored human-derived and chemically defined supplements to provide safer and more consistent culture systems. Among the first human-derived alternatives explored was human platelet lysate (hPL) [117], [118] .hPL has emerged as one of the most widely studied human-derived supplements, generated through the controlled lysis of platelet concentrates to release a rich pool of growth factors, cytokines, and chemokines [119],

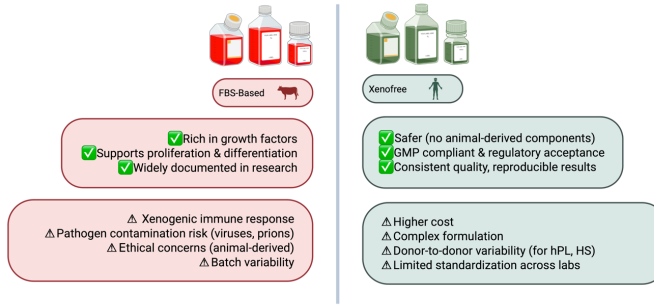

Figure 3. Comparison between serum-based and xeno-free culture medium for MSCs expansion

[120], [121]. Compared with fetal bovine serum (FBS), hPL consistently supports superior proliferation, preserves canonical MSC morphology and marker expression, and enhances immunomodulatory properties, thereby offering a compelling xenofree alternative for clinical-scale MSC expansion [120], [122]. Importantly, hPL minimizes the risk of zoonotic contamination and immune incompatibility, making it more suitable for translational use [120], [123]. Nevertheless, limitations remain, including donor-to-donor variability, dependence on anticoagulants such as heparin, and reports of altered surface molecule expression that may influence MSC immunological functions and differentiation efficiency [124], [125], [126]. These challenges underscore the need for standardized preparation methods to ensure reproducible outcomes across laboratories.

In parallel, other human-derived supplements have been explored as an alternatives to FBS. Human serum (HS), particularly from autologous donors, has been shown to effectively support MSC proliferation and differentiation. In 2008, Tateishi et al. compared the effect of HS and FBS on MSCs and demonstrated that human bone marrow–derived stromal cells cultured in HS proliferated and differentiated as effectively as in FBS [127]. Other studies also showed that HS could serve as a substitute for FBS in promoting MSC proliferation without compromising their differentiation into osteoblasts and chondrocytes, while additional experiments reported that cells grown in HS exhibited motility and a spindle-shaped morphology [128], [129]. Autologous HS provides superior immunological compatibility, making it advantageous for personalized applications. However, its broader use is constrained by limited scalability and the batch-to-batch variability of allogeneic HS, which often fails to sustain MSC proliferation beyond the early passages [128], [130]. Platelet-rich plasma (PRP) and platelet-rich growth factors (PRGF) similarly provide mitogenic support but suffer from inconsistencies in composition and preparation protocols [131], [132]. Additional derivatives, such as platelet-poor plasma (PPP), have been shown to mitigate the use of heparin, but their proliferative potential and immunosuppressive capabilities are reduced [133]. Collectively, these human-based supplements highlight both the promise and the inherent variability of biologically sourced media, necessitating harmonized protocols and rigorous quality control frameworks to enable clinical adoption.

To address the unpredictability associated with human-derived products, re-

searchers have increasingly turned toward serum-free and chemically defined media (CDM). By eliminating animal- and human-derived components, these formulations offer enhanced reproducibility and reduced contamination risk [134], [135]. CDM provides high consistency and purity in composition, reducing batch-to-batch variability and ensuring safer conditions for clinical applications [134], [135]. Experimental studies have shown that MSCs cultured in certain CDM formulations, such as STK2, may exhibit improved surface marker expression, enhanced tri-lineage differentiation potential, reduced senescence, and greater genetic stability compared with traditional DMEM/FBS media [134]. Other formulations, like NBVbe medium, further demonstrate the ability of CDM to support the isolation and expansion of MSCs from diverse sources, including umbilical cords, while synthetic substrates such as Corning® Synthemax® surfaces have been applied in combination with defined media for scalable MSC production [135], [136]. Despite these advantages, several challenges remain. The complexity of CDM formulation requires careful optimization of components such as vitamins, amino acids, and growth factors, while the high production costs continue to limit widespread adoption [137]. Ongoing efforts are therefore focused on optimization, standardization, and the application of advanced analytical techniques to improve stability and quality control [137], [138]. Collectively, serum-free and xeno-free media represent a critical step toward establishing robust, reproducible, and clinically compliant MSC production platforms.

Beyond media optimization, clinical translation of MSC therapies requires robust scale-up strategies that maintain cell quality while meeting manufacturing demands. Traditional two-dimensional (2D) flask-based culture systems face significant limitations in terms of labor intensity, spatial requirements, and scalability for producing clinically relevant cell numbers []. To overcome these constraints, three-dimensional (3D) culture technologies using microcarriers in bioreactors have emerged as a promising approach, enabling high-density cell growth while preserving MSC characteristics [139]. Stirred-tank bioreactors provide controlled environments with precise regulation of pH, dissolved oxygen, temperature, and nutrient delivery, facilitating reproducible large-scale expansion under good manufacturing practice (GMP) conditions [140], [141]. Hollow fiber bioreactors offer an alternative platform with continuous perfusion systems that support high cell densities and prolonged culture periods [142]. The integration of process analytical technology (PAT) enables real-time monitoring of critical process parameters, including cell density, viability, glucose consumption, and lactate production, thereby ensuring consistent product quality and facilitating process optimization [143], [144]. Comprehensive release testing protocols—encompassing identity verification through surface marker analysis, purity assessment, potency evaluation via differentiation and immunomodulatory assays, and safety testing for adventitious agents—are essential for regulatory compliance and clinical application. Collectively, the integration of optimized serum-free and xeno-free media with advanced bioprocessing technologies and rigorous quality control frameworks establishes a comprehensive platform for clinically compliant, large-scale MSC production.

6. Applications and Clinical Relevance

The clinical translation of iMSCs represents an important early-stage development in the evolution of regenerative medicine as an alternative source of MSCs [145], [146]. As the demand for cell-based therapies continues to rise, particularly in the treatment of degenerative, inflammatory, and immune-mediated conditions, the development of clinical-grade MSCs has become a paramount concern [147], [148]. Traditional tissue-derived MSCs, while widely used, are hindered by issues such as donor variability, finite proliferation capacity, and declining potency with donor age or repeated passaging [149], [146]. In contrast, iMSCs offer a scalable, rejuvenated, and customizable alternative with the potential to overcome many of these limitations [146], [148]. However, the therapeutic utility of iMSCs is inextricably linked to their quality, safety, and compliance with stringent regulatory standards, factors heavily influenced by the culture conditions under which they are generated [149], [148].

In recent years, an increasing number of preclinical studies have suggested the future therapeutic potential of iMSCs across a broad spectrum of disease models. These include applications in osteoarthritis, myocardial infarction, spinal cord injury, liver fibrosis, and graft-versus-host disease, among others [149], [146]. In such contexts, iMSCs have been shown to exert immunomodulatory effects, secrete trophic factors, and support tissue regeneration through paracrine signaling and matrix remodeling [146], [148]. Importantly, these preclinical successes have translated into early-phase clinical trials. For instance, several ongoing investigations are evaluating the safety and efficacy of iMSCs in treating conditions such as ischemic stroke, Crohn's disease, and COVID-19-associated acute respiratory distress syndrome (ARDS) [149], [148]. These studies underscore the growing recognition of iMSCs as a viable therapeutic platform, particularly due to their consistent phenotypic and functional characteristics when produced under tightly controlled conditions [146], [148]. A summary of representative preclinical and clinical studies utilizing iMSCs in various disease models is provided in Table 1, highlighting the breadth of their therapeutic potential and translational progress.

7. Future Perspectives and Challenges

Despite the significant progress that has been achieved in the development of iMSCs and their applications, several challenges still restrict their full potential for clinical realization [96], [97], [98]. Biological complexity appeared as a challenge in recapitulating mesenchymal differentiation from a pluripotent state [158]. Although the protocols have evolved to become more specific and efficient, the conversion of iPSCs into MSCs remains a multi-step process that represents mesodermal specification. These difficulties were worsened by a lack of specific standardized differentiation protocols, which affects lineage fidelity, phenotypic stability, immunomodulatory function, and differentiation potential [146], [148], [159]. Moreover, overcoming the challenges of differentiation reproducibility and cellular consistency is essential to developing safe and effective iMSCs for clinical use.

Table 1. Summary of Preclinical and Clinical Studies Utilizing iPSC-Derived MSCs (iMSCs) in Disease Models

Disease Model	Study Type	iMSC Source / Protocol	Therapeutic Mechanism	Key Outcomes	Ref.
Osteoarthritis	Preclinical (miniature pig model)	Autologous iPSCs generated from minipig fibroblasts, reprogrammed using episomal plasmids; iMSCs derived via mesodermal induction using feeder-free serum-based medium	Hyaline cartilage regeneration, chondrogenic support from iMSC-derived implants	Enhanced joint repair; higher COL2A1 expression, minimal COL1A1 and COL10A1; superior hyaline cartilage formation	[150]
Limb Transplantation	Preclinical (mice model)	Human iPSCs cultured on Matrigel with mTESR1; iMSCs derived via spontaneous differentiation using serum-based medium (low-glucose DMEM + 10 % FBS) and serial passaging	Paracrine signaling via exosomes promoting angiogenesis; stimulation of endothelial cell migration, proliferation, tube formation; upregulation of angiogenesis-related genes and proteins (e.g., VEGF, TGFB1, HIF-1α)	Improved blood perfusion, enhanced microvessel density, reduced tissue necrosis, and functional recovery in hind-limb ischemia model	[151]
Chronic obstructive pulmonary disease (COPD)	Preclinical (rat model)	Three human iPSC lines : iPSC(iMR90)-5 (lentiviral Oct4, Sox2, Nanog, Lin28), iPSC(iMR90)-4, and iPSC(foreskin)-1 differentiated via serum-based, growth factor-enriched medium (bFGF, PDGF-AB, EGF), followed by CD24-CD105+ FACS sorting and clonal expansion	Mitochondrial transfer via TNTs; bioenergetic rescue of lung epithelium; anti-inflammatory and regenerative support	IEnhanced lung repair; restored ATP levels; reduced epithelial damage and apoptosis; improved retention and mitochondrial transfer efficiency in CS-induced lung injury	[152], [153]
Inflammatory Bowel Disease	Preclinical (mice model)	iPSC-derived MSCs (from iPSC-iMR90-5, WiCell) were cultured with serum replacement and bFGF, validated by typical MSC markers.	iPSC-MSCs promote mucosal healing via TSG-6, which acts through CD44 and activates Akt signaling to boost epithelial cell proliferation.	Improved healing in colitic mice and organoids, increased epithelial growth, and required TSG-6 and CD44 for their effect. Recombinant TSG-6 showed similar benefits	[154]
Acute Kidney Injury	Preclinical (mice model)	iMSCs were provided by Brexogen, Inc. and cultured in high-glucose DMEM with 15% FBS and antibiotics. Cells at passages 6-7 were used.	Enhanced renal repair via PPAR-primed iMSC-EVs through reduced inflammation, apoptosis, and increased capillary density.	Stronger renoprotective effects than unprimed EVs in cisplatin-induced AKI. Better HK-2 cell survival, greater reduction of inflammatory cytokines, less tissue damage, and improved kidney function.	[155]
Bone Fracture	Preclinical (miniature pig model)	iPSCs derived from human fetal foreskin fibroblasts and reprogrammed via Sendai virus.	Differentiating into osteoblasts and secreting factors that stimulate host stem cells and immune modulation. BMP and NF-κB pathways through secretome, enhancing regeneration.	Improved bone healing, matching autologous BMC + CPG and outperforming CPG alone. No immune rejection or tumor formation was observed, showing strong clinical potential.	[156]
Graft-versus-Host Disease	Clinical Phase I	Patient-derived iPSC-MSCs	Immunomodulation and tissue repair via iPSC-derived MSCs, differentiating from mesodermal progenitors. Acts through anti-inflammatory secretome and paracrine signaling in xenogen-/serum-free conditions, minimizing variability and risk.	Alleviation of steroid-refractory aGvHD symptoms, improved survival, and consistent response with minimal variability across doses	[157]

In addition, technical and operational issues also play a significant role as barriers. Long-term risks, such as residual pluripotent cells, chromosomal abnormalities, and neoplastic transformation, must be carefully evaluated [160], [161], [162]. Although short-term safety has shown promising results, further studies are still urgently required to confirm the long-term stability, functionality, and clinically safe applications.

Another determinant of successful iMSCs production resides in the optimized culture conditions. Meticulous design, composition, and standardized culture media play a significant role throughout both the differentiation and expansion processes. Serum-containing media are proven to support cell proliferation, but their variability raises biosafety concerns, such as xenogenic contamination and immunogenicity [163], [164]. Consequently, xeno-free and chemically defined media have gained traction for their reproducibility and clinical compatibility, offering the potential to reduce medium-specific risks such as xenogenic contamination and batch-to-batch variability. However, the comprehensive safety of iMSCs depends on multiple factors, including genomic stability, complete elimination of residual pluripotent cells, and rigorous quality control measures throughout the production process, not solely on media composition. At the same time, the integration of biomaterials such as hydrogel, microcarriers, and biofunctional scaffolds has emerged as a transformative strategy and considerable promise in enhancing the cellular microenvironment [163].

Therefore, the continued advancement of iMSCs technologies is essential. By addressing these challenges through protocol optimization, technological integration, and improved differentiation efficiency, iMSCs can be positioned as a promising and innovative solution for a broad application and pave the way for a new era in biomedical research.

8. Conclusion

Mesenchymal stem cells (MSCs) showed up as a potential candidate for regenerative medicine due to their capacity for differentiation and immunomodulatory functions. Nevertheless, their clinical application remains constrained by donor variability, limited proliferative potential, and senescence. Thus, iMSCs appeared to overcome these challenges by providing a scalable and standardized cell source along with several therapeutic prospects. Ongoing advances in xenofree and chemically defined culture systems constantly maximize their translational potential by minimizing risks associated with animal-derived supplements and maintaining clinical-grade safety. However, several challenges remain, including the need for standardized differentiation protocols, a greater understanding of long-term genomic and epigenetic stability, and large-scale manufacturing strategies. Therefore, integrating iMSCs with optimized culture systems will be necessary to further advance their safe and effective application in tissue engineering, immunotherapy, and regenerative medicine.

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