Journal of Medical Bacteriology

Beyond Regeneration: Mesenchymal Stem Cells as Antimicrobial Agents in Burn Wound Healing

Behnam Poureslamfar [1#], Sahar Yadegari [2#], Kanzur Rahman Mufazzil [3], Mahmood Karimi [4], Behnaz Misaii [5], Faezeh Tehrani Niya [6], Reza Yekani [7], Forouzan Esmaeili Dahaj [8], Ali Abesi [9*], Mona Mohammadzadeh [10*]*

1 Department of Biology, Faculty of Science, Yasouj University, Yasouj, Iran.

2 Clinical Diagnostic Laboratories, Erfan Hospital.

3 Department of Medicine, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

4 Student Research Committee, Shahrekord University of Medical Sciences, Shahrekord, Iran.

5 Department of Cell and Molecular Biology, Faculty of Chemistry, University of Kashan, Kashan, Iran.

6 Department of Biotechnology, Azad University of Urmia, Urmia, Iran.

7 Department of Biochemistry and Biophysics, Faculty of Advanced Science and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.

8 Stem Cell Biology Research Center, Yazd Reproductive Science Institute ,Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

9 Student Research Committee, School of Medicine,Isfahan University of Medical Sciences, Isfahan, Iran.

10 Department of Microbiology, Reference health laboratory, Ministry of health and medical education, Tehran, Iran.

ARTICLE INFO

Article type:
Research Article

Article history:

Received	09	May	2025
Revised	30	Jun	2025
Accepted	10	Aug	2025
Published	23	Aug	2025

Keywords:
Antimicrobial, Burn Wound Healing, Mesenchymal Stem Cells.

ABSTRACT

Background: Burn injuries present a considerable global health challenge, characterised by intricate healing processes that are exacerbated by infection and impaired tissue regeneration. Mesenchymal stem cells (MSCs) have emerged as a promising therapeutic option due to their regenerative, immunomodulatory, and antimicrobial properties. MSCs have been shown to secrete AMPs such as LL-37 and hepcidin, which have been found to directly target pathogens including *Pseudomonas aeruginosa* and *Staphylococcus aureus*. In addition to this direct antimicrobial action, MSCs have also been observed to modulate immune responses through the secretion of cytokines such as IL-10 and TGF-β. Their regenerative effects include the promotion of angiogenesis, re-epithelialization, and extracellular matrix (ECM) remodelling via growth factors such as EGF, KGF, and SDF-1. In-vitro and animal studies have demonstrated enhanced wound closure, reduced scarring, and improved antimicrobial efficacy through novel delivery systems such as hydrogels and preconditioning strategies. As demonstrated by clinical trials, the treatment has been shown to facilitate accelerated

*Corresponding Authors: Forouzan Esmaeili Dahaj: Stem Cell Biology Research Center, Yazd Reproductive Science Institute ,Shahid Sadoughi University of Medical Sciences, Yazd, Iran. *Tel*: +98-35-235452578, *E-mail:* forouzan.esmaeili.dahaj@gmail.com.

Mona Mohammadzadeh: Department of Microbiology, Reference health laboratory, Ministry of health and medical education, Tehran, Iran. *Tel*: +98-21-235452578, *E-mail:* monamohammadzadeh@yahoo.com.

Ali Abesi: Student Research Committee, school of medicine,Isfahan University of Medical Sciences, Isfahan, Iran. *Tel*: +98-31-36680239, *E-mail:* abesi755@gmail.com.

Behnam Poureslamfar, Sahar Yadegari were co-first authors.

healing and reduced reliance on antibiotics. However, challenges such as the heterogeneity of mesenchymal stem cells (MSCs), optimisation of dosing, and safety concerns (e.g. coagulopathy, systemic inflammation) persist. Emerging technologies, including synthetic gene circuits, microbiome-targeted engineering, and bioresponsive delivery systems, offer solutions to enhance the efficacy of MSCs.

Conclusion: This review emphasises the potential of MSCs to transform the management of burn wounds, while underscoring the necessity for standardised protocols and advanced engineering to surmount translational barriers.

- ***Please cite this paper as:*** Poureslamfar B, Yadegari S, Rahman Mufazzil K, Karimi M, Misaii B, Tehrani Niya F, Yekani R, Esmaeili Dahaj F, Abesi A, Mohammadzadeh M. Beyond Regeneration: Mesenchymal Stem Cells as Antimicrobial Agents in Burn Wound Healing. *J Med Bacteriol.* 2025; **13** (3): pp.146-168. DOI: 10.18502/jmb.v13i3.19517

Introduction

Burns are a significant public health concern, being among the most common and severe types of trauma. One of the most devastating effects of burn injuries is the number of people affected, especially when skin and tissue are damaged. Depending on the intensity, this can affect an alarming number of people, with close to 11 million cases reported by the World Health Organization (WHO) and millions more receiving medical treatment (1). Such injuries are usually associated with thermal agents, such as fire or hot liquids, but can also be caused by chemical agents, electrical exposure, or radiation. Nevertheless, this may not matter because burn wounds are a complicated type of injury that can cause long-term physical, psychological and social difficulties. The skin, which is the body's main barrier against pathogens, temperature and sensations, is weakened by burns, which increases the risk of infection and impairs the body's ability to repair damaged tissue (2). This makes healing especially difficult. Burns are prone to infection and wound-healing failure, and this aspect remains one of the most clinically interesting areas and a key focus of patient care in the treatment of burns (3).

Infection of a burn wound is one of the most costly complications, often leading to a prolonged hospital stay and delayed healing. After an injury, the protective barrier of the skin is compromised to a large extent, making the underlying tissue vulnerable to microbial penetration. Deep or extensive burn wounds are highly susceptible to bacterial, fungal and viral colonisation. The most common are *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida albicans* (4). These organisms' ability to grow biofilms, which are clumps of bacteria enclosed in an extracellular protective layer, worsens the infection process, as biofilms exhibit lower susceptibility to normal antimicrobial agents. This hinders the regeneration of tissues and maintains the persistence of the infection (5). Burn injuries are also characterised by mixed microbial populations that can interact synergistically, resulting in increased tissue injury and a longer healing period. Consequently, the presence of bacteria growing in a burn wound and the development of biofilms can be considered important causes of slow wound healing and infection (6).

The second challenge in burn wound management is the impaired healing process, which is intrinsic to the nature of the injury itself. Burn wounds disrupt the normal stages of wound healing, which typically include hemostasis, inflammation, proliferation, and remodeling (7). In burns, the initial inflammatory phase is prolonged, which can lead to excessive inflammatory mediators such as cytokines, reactive oxygen species (ROS), and proteases. These factors not only worsen tissue damage but also prevent the wound from progressing to the proliferative and remodeling stages, which are essential for regeneration and closure (8). Further, the wound site is normally inadequately supplied with oxygen and nutrients because of altered blood circulations and inability to grow new blood vessels, known as angiogenesis. Such an inadequacy of blood also makes it even difficult to grow tissues and adds to the problems regarding the restoration of burns (9). The scar tissue that forms can restrict the functionality and the cosmetic appearance of the skin thus causing chronic cosmetic and functional deformity, which seriously compromises the quality of life of a patient (9).

Part of these challenges is met by using conventional treatment strategies of burn wound such as antimicrobial agents, wound debridement, and skin grafting. Nevertheless, they cannot be devoid of their limitations. Antimicrobial agents that play a critical role in infection control might not be more than effective in clearing up biofilms and/or inhibiting resistance (10). Skin grafts despite being a standard procedure in large burns have disadvantages which include immune rejection, donor site morbidity and shortage of donor skin (11). These therapies are also not sufficient to treat the mechanisms of compromised healing or facilitate regeneration of tissues in a manner totally consistent with natural processes of skin healing (12). Thus, the discovery of new treatment strategies that would be able to at once counter infection and promote healing is of greatest significance in the developments of burn treatment.

The regenerative potential is one of the most important characteristics of the MSCs regarding its usage in burn wound healing. MSCs when used on burn wounds have the ability to facilitate tissue repair through production of growth factors and cytokines able to induce angiogenesis, fibroblasts proliferation and deposition of the extracellular matrix (ECM) (13). The process of tissue repair is also considered critical, and herein, the existence of growth factors is vital- namely vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and transforming growth factor-beta (TGF-b). MSCs also have the ability to stimulate collagen deposition and remodelling that is vital in restoring physical integrity of the skin (14). Moreover, MSCs have been demonstrated to shorten wound healing, facilitate the process of epithelialization, and avert the occurrence of hypertrophic scars. MSCs showed that they can enhance the quality and amount of regeneration tissue in animal tests, which means that it has a possibility of being a therapeutic choice in burn patients in the human body (15).

Nevertheless, the repair capabilities of MSCs are not limited to tissue repair. MSCs are also described by their capacity to modulate the immune system so that they lessen irritation and improve the body expertise to heal the infections. Inflammation in burn wounds is in most cases too much and prolonged and this will cause more tissue destruction and slow recovery. MSCs were demonstrated to decrease pro- inflammatory cytokines including TNF-a, IL-1b, and IL-6, and at the same time, they stimulate anti- inflammatory cytokines, including IL-10 (16). This modulatory action has the effect of reducing the chronic levels of inflammation which occur in burn wounds, resulting in a less hostile environment towards tissue repair. MSCs by improving the resolution of inflammation, can hasten the shift in the inflammatory to the proliferative phase of wound healing (17).

Besides the regenerative and the immunomodulatory effect, the MSCs are also notable antimicrobial. The direct fighting against microbial infections by the cells is one of the most

convincing things about the MSC therapy on the burn wounds. MSCs secrete AMPs that are short proteins effective against a multitude of pathogens in a wide-spectrum activity. These peptides lace the bacterial cell membranes and cause bacterial death in a microorganism. It has also been found that MSCs are able to suppress the growth of Pseudomonas aeruginosa, *Staphylococcus aureus* and *Escherichia coli* among others, which are the common growing pathogens in burn wounds (18). One of the most significant ways through which the MSCs are believed to prevent chances of infection of burn wounds hence playing an important part both in inhibiting chances of infection and in promoting healing is the antimicrobial nature of MSCs.

Besides, the activity of immune cells, like macrophages and neutrophil cells, could also be adjusted by MSCs and become reinforced to protect the body against an infection. MSCs have been demonstrated to boost the phagocytic process of the macrophages so that they can better expel the pathogens at the wound site (19). MSCs would facilitate the creation of a workable environment whereby the infection process could be countered more effectively and wound healing executed more efficiently by stimulating the resolution of inflammation as well as the antimicrobial activity of immune cells.

The extent of burn injury as experienced all over the world illustrates the necessity of novel means of treating burn injuries. The effects of burns in patients in most of the low- and middle-income countries, where there is a limited access to the sophisticated healthcare facilities, and treatments, are poor. The outcome of burn injuries that occur in these settings has been attributed to high mortality rates, among them are complications of infections and delayed healing. Consequently, management of the burn wound especially in terms of infection and poor healing is a very important health concern among the global health (20). As a therapeutic option, MSC application presents an opportunity to alleviate the burden of burn injuries on a global scale, which is associated with the superior outcomes of patients who received this treatment and the decreased necessity to resort to severe medical procedures (skin grafts and prolonged anti-infective therapies) (21).

Irrespective of the promising potential of the MSCs in healing burn wounds, there still exist a number of issues to be dealt with before the MSC-based therapies can gain popularity in clinical practice. On the one hand, abundance of research in the effectiveness of MSCs as a means of wound healing and mitigation of infection in animals has been proven valid; on the other hand, evidence in clinical trials is inconclusive. The diverse results of the studies could be explained by the influence of many factors, which include the variability in the source of MSCs, their delivery routes, and the patient background (22). Also of concern is whether MSC-based therapies are safe or not, and whether they have long term effects, whether the treatments cause immune rejection, tumorigenic, and genetic instability effects. This leads to the need of further investigation to streamline MSC-based treatment, find the most promising ways of its administration, and define the guidelines that could keep patients safe.

With the dual burden of infection and poor healing wound injury in burns, it was felt necessary to examine this review on the possibility of MSCs and its potential as both antimicrobial and regenerative techniques in wounds of burns. The main aim will be to critically analyze recent findings made on application of MSCs in burn management with emphasis on its capacity to fight infections and/or to facilitate repair and regeneration of the affected tissues. This article also seeks to explain how the effects of MSCs in burn wound healing take place at the cellular and the molecular level by reviewing the current available literature. In particular, his or her speech will cover the regenerative effects of the MSCs, the immunomodulatory activities of MSCs, and the antimicrobial effect of MSCs. Moreover, the review will assess the preclinical and clinical studies results to identify the efficacy, security predicting the possibility of MSC-based treatments to be.

Antimicrobial mechanisms

MSCs, derived from diverse sources such as bone marrow, adipose tissue, umbilical cord, and placental tissue, have emerged as a promising therapeutic tool in regenerative medicine due to their multifaceted capabilities in tissue repair, immunomodulation, and antimicrobial activity. These cells combat pathogens through direct and indirect mechanisms, with direct mechanisms encompassing the production of antimicrobial factors, phagocytosis, and extracellular trap formation, while indirect mechanisms involve immune modulation and secretion of soluble mediators (23).

Direct antimicrobial mechanisms of MSCs involve the targeted elimination of pathogens without relying on immune system intermediaries (24). A primary mechanism is the secretion of AMPs, such as cathelicidin (LL-37), β-defensins, and hepcidin, which disrupt pathogen membranes through pore formation. human bone marrow-derived MSCs upregulate LL-37 expression in response to Gram-positive bacteria like *Staphylococcus aureus* and Gram-negative bacteria like *Escherichia coli*, leading to membrane disruption and bacterial lysis (25). This broad-spectrum activity is particularly effective against multidrug-resistant pathogens, such as methicillin-resistant *S. aureus* (MRSA). Additionally, MSCs produce hepcidin, which restricts pathogen access to iron, an essential nutrient for microbial growth. adipose-derived MSCs, under inflammatory conditions, enhance hepcidin expression, significantly inhibiting *Pseudomonas aeruginosa* proliferation (26). This iron sequestration mechanism is critical in chronic infections where pathogens rely on iron availability.

Contrary to earlier assumptions that MSCs lack phagocytic capacity, recent evidence suggests that MSCs, particularly those from umbilical cord tissue, exhibit limited phagocytic activity (27). These MSCs internalize and eliminate bacteria such as *Klebsiella pneumoniae* and form NET-like structures analogous to neutrophil extracellular traps (28). These structures, composed of DNA and antimicrobial proteins, effectively ensnare and neutralize pathogens, highlighting MSCs as a direct antimicrobial defense mechanism, particularly in immunocompromised settings.

MSCs also produce antimicrobial metabolites, such as lactic acid and hydrogen peroxide, which create an inhospitable microenvironment for pathogens. Adipose-derived MSCs secrete high levels of lactic acid, lowering local pH and inhibiting the growth of fungi like *Candida albicans* (29). This mechanism is particularly effective against fungi requiring neutral or alkaline environments. Hydrogen peroxide, another MSC-derived metabolite, acts as an oxidative agent, damaging pathogen membranes, although its efficacy varies depending on environmental conditions and pathogen type.

Indirect antimicrobial mechanisms of MSCs are mediated through immunomodulation and the secretion of soluble factors that enhance host immune responses. MSCs secrete anti-inflammatory cytokines, such as IL-10 and TGF-β, and chemokines, like CXCL10 and CCL5, to regulate immune responses and recruit effector cells. A 2025 study demonstrated that bone marrow-derived MSCs in animal models of pulmonary infection increased IL-10 secretion to mitigate excessive inflammation while promoting CXCL10-mediated recruitment of macrophages and neutrophils to infection sites (30). This dual role in dampening inflammation and bolstering antimicrobial defense prevents tissue damage while enhancing immune efficacy.

MSCs also interact with innate immune cells, particularly macrophages and dendritic cells, polarizing them toward antimicrobial phenotypes. MSCs secrete prostaglandin E2 (PGE2), driving macrophages toward an M1 antimicrobial phenotype and increasing nitric oxide (NO) production, which effectively eliminates intracellular bacteria like *Mycobacterium tuberculosis* (31). This interaction is vital in chronic infections requiring sustained immune responses. Additionally, MSCs modulate dendritic cells to produce pro-inflammatory cytokines, such

as IL-12, which enhance Th1-mediated responses against intracellular pathogens and viruses.

In the context of adaptive immunity, MSCs influence T and B lymphocytes to augment pathogen-specific responses (32). A 2019 study found that MSCs, through secretion of vascular endothelial growth factor (VEGF) and IL-6, stimulate T-cell proliferation and enhance B-cell antibody production against viruses like SARS-CoV-2 (33). This mechanism is critical in viral infections requiring robust, coordinated immune responses. Moreover, MSCs produce indoleamine 2,3-dioxygenase (IDO), which suppresses excessive T-cell activity, preventing immunopathology in chronic infections and autoimmune conditions.

The antimicrobial properties of MSCs have significant clinical implications, particularly in treating multidrug-resistant infections and chronic inflammatory conditions (34). A 2024 trial demonstrated that MSC therapy in diabetic patients with chronic wounds significantly improved healing rates and reduced reliance on antibiotics, particularly against pathogens like MRSA and *P. aeruginosa* (35). MSCs have also shown promise in managing respiratory infections, such as bacterial or viral pneumonia. However, challenges, including MSC heterogeneity, source-dependent variability, and variable responses to environmental cues, limit their clinical application. For instance, adipose-derived MSCs may exhibit reduced AMP production compared to bone marrow-derived MSCs (36). Additionally, potential risks of unwanted immune responses or off-target effects underscore the need for standardized production and application protocols.

Future research should focus on optimizing MSC culture conditions to enhance antimicrobial factor production. Genetic engineering, such as CRISPR/Cas9-mediated gene editing, offers potential to augment AMP expression. CRISPR/Cas9-edited MSCs with enhanced LL-37 expression exhibited superior efficacy against S. aureus (34). Combining MSCs with biomaterials, such as biocompatible hydrogels, could improve targeted delivery and cell survival in clinical settings. For example, hydrogel-based MSC delivery to chronic wounds has enhanced therapeutic outcomes.

Another promising avenue is the use of MSC-derived exosomes, extracellular vesicles containing AMPs, microRNAs, and other bioactive molecules. Umbilical cord MSC-derived exosomes, carrying miR-146a, reduced inflammation and inhibited *E. coli* growth, offering a cell-free therapeutic alternative that minimizes risks associated with MSC transplantation (37). This approach could expand the therapeutic utility of MSCs in antimicrobial applications.

Despite these advances, the safety and efficacy of MSCs in clinical settings require further investigation. MSCs may, in some contexts, suppress immune responses excessively, potentially facilitating opportunistic infections. Thus, precise dosing and timing of MSC administration are critical. Moreover, source-specific differences in MSC functionality necessitate comprehensive studies to optimize therapeutic protocols.

The role of MSCs in burn wound repair

MSCs have emerged as a transformative tool in the management of burn wounds, addressing the complex pathophysiology of these injuries through mechanisms that extend beyond their antimicrobial properties. Burn wounds, particularly deep partial- and full-thickness burns, present significant clinical challenges due to extensive tissue destruction, prolonged inflammatory responses, impaired vascularization, and a propensity for hypertrophic scarring (38). MSCs, sourced from bone marrow, adipose tissue, umbilical cord, placenta, and other tissues, contribute to burn wound healing by promoting tissue regeneration, enhancing vascular repair, modulating immune responses, and regulating extracellular matrix (ECM) dynamics to minimize scarring (39).

Burn injuries disrupt the skin’s structural and functional integrity, leading to loss of the epidermal barrier, compromised dermal

architecture, and systemic immune dysregulation (40). MSCs address these challenges by orchestrating a cascade of regenerative processes that restore tissue homeostasis. Unlike their antimicrobial roles, which focus on pathogen elimination, MSCs' regenerative functions in burn wounds center on cellular proliferation, differentiation, and tissue remodeling. Bone marrow-derived MSCs secrete high levels of epidermal growth factor (EGF) and keratinocyte growth factor (KGF), which stimulate keratinocyte proliferation and migration, critical for re-epithelialization (41). These factors enhance the formation of a new epidermal layer, reducing wound exposure and the risk of secondary complications. MSCs also promote fibroblast activation, facilitating the deposition of collagen types I and III, which form the structural scaffold for dermal repair. Unlike previous discussions on growth factors like VEGF, this study highlights the unique role of EGF and KGF in driving epithelial restoration, a process distinct from angiogenesis or antimicrobial activity.

MSCs further contribute to burn wound repair by modulating the wound microenvironment to favor regeneration over fibrosis. Demonstrated that umbilical cord-derived MSCs secrete stromal cell-derived factor-1 (SDF-1), which recruits endogenous progenitor cells to the wound site, enhancing tissue regeneration without relying on external cell transplantation (42). This paracrine effect, distinct from direct cellular engraftment, amplifies the regenerative potential of resident cells, such as dermal fibroblasts and endothelial precursors. SDF-1 also interacts with the CXCR4 receptor on local cells, promoting organized collagen deposition and reducing chaotic ECM remodeling, which is a precursor to hypertrophic scarring. This mechanism, unique from previously discussed cytokine-mediated immunomodulation, underscores MSCs' ability to orchestrate endogenous repair pathways.

Vascular repair is a cornerstone of burn wound healing, as burns often cause microvascular damage, leading to ischemia and delayed tissue restoration. MSCs contribute to neovascularization through mechanisms distinct from those previously described, such as the secretion of angiopoietin-2 (Ang-2) and hepatocyte growth factor (HGF) (43). adipose-derived MSCs, when applied to burn wounds in rodent models, upregulated Ang-2 expression, which destabilizes existing vasculature to facilitate sprouting of new capillaries (44). This process, coupled with HGF-mediated endothelial cell proliferation, enhances blood vessel formation in hypoxic wound environments. Unlike VEGF-driven angiogenesis, Ang-2 and HGF work synergistically to remodel vascular networks, ensuring sustained perfusion to support tissue regeneration. Additionally, MSCs' role in stabilizing newly formed vessels is critical. A 2024 study reported that placenta-derived MSCs secrete tissue inhibitor of metalloproteinases-1 (TIMP-1), which prevents excessive degradation of newly formed vascular structures, ensuring their longevity and functionality (45).

The inflammatory microenvironment of burn wounds, characterized by elevated levels of pro-inflammatory mediators like interleukin-1β (IL-1β) and interferon-γ (IFN-γ), poses a significant barrier to healing. MSCs mitigate this by secreting unique anti-inflammatory factors, such as interleukin-1 receptor antagonist (IL-1RA) and tumor necrosis factor-α-stimulated gene-6 (TSG-6). Bone marrow-derived MSCs reduce IL-1β-driven inflammation in burn wounds by upregulating IL-1RA, which competitively inhibits IL-1β signaling (46). This mechanism, distinct from IL-10 or PGE2-mediated immunomodulation, specifically targets the IL-1 pathway, which is overactive in burn injuries. TSG-6, another MSC-derived factor, further suppresses inflammatory cascades by inhibiting neutrophil infiltration and reducing oxidative stress. Unlike previously discussed macrophage polarization, TSG-6 acts directly on the wound microenvironment, creating a pro-regenerative milieu that supports tissue repair.

Scar modulation remains a critical challenge in burn wound management, as excessive collagen deposition and disorganized ECM remodeling lead to hypertrophic scars or keloids, impairing both

function and aesthetics (47). MSCs address this through novel mechanisms involving the regulation of myofibroblast activity and ECM dynamics. Found that adipose-derived MSCs secrete decorin, a small leucine-rich proteoglycan that binds to collagen fibrils, preventing excessive cross-linking and promoting organized ECM architecture (48). This process reduces scar stiffness and enhances tissue flexibility, distinct from MMP-mediated ECM degradation discussed previously. Additionally, MSCs modulate the Wnt/β-catenin signaling pathway, which is implicated in fibrogenesis. Umbilical cord-derived MSCs downregulate β-catenin expression in fibroblasts, reducing myofibroblast differentiation and collagen overproduction, thereby minimizing scar formation (49). This pathway-specific approach offers a targeted strategy for scarless healing, distinct from TGF-β isoform regulation.

MSCs' paracrine signaling extends beyond growth factors and cytokines to include extracellular vesicles, particularly exosomes, which deliver bioactive cargo to modulate wound healing. Unlike the antimicrobial roles of exosomes, their regenerative functions in burn wounds involve unique molecular payloads. Exosomes from bone marrow-derived MSCs, enriched with miR-29a, suppress fibroblast activation by downregulating collagen type I expression, reducing fibrotic tissue formation (50). Additionally, MSC-derived exosomes carry long non-coding RNAs (lncRNAs), such as lncRNA MALAT1, which promote endothelial cell migration and proliferation, enhancing vascular repair. A 2023 study demonstrated that placenta-derived MSC exosomes containing MALAT1 accelerated re-epithelialization in burn wounds by upregulating keratinocyte motility (51). These exosome-mediated mechanisms, distinct from direct cellular effects, highlight the potential for cell-free therapies in burn wound management.

The clinical translation of MSCs for burn wound repair has shown significant promise, with studies demonstrating improved outcomes in both acute and chronic burns (52). A 2023 clinical trial involving patients with third-degree burns reported that topical application of adipose-derived MSCs embedded in a fibrin scaffold reduced wound healing time by 20% compared to standard care, with improved skin elasticity and reduced contracture (53). This approach, distinct from hydrogel-based delivery, leverages fibrin's biocompatibility to enhance MSC retention and activity at the wound site. Another 2023 study explored the use of MSC spheroids, three-dimensional aggregates that enhance cell-cell interactions and secretome production. These spheroids, when applied to burn wounds, increased the expression of angiogenic and regenerative factors, such as HGF and FGF-2, leading to faster wound closure and reduced scarring (54). These clinical advancements highlight MSCs' versatility in addressing the multifaceted challenges of burn wound repair.

Despite their potential, several obstacles limit the widespread adoption of MSC-based therapies for burn wounds (55). MSC heterogeneity, influenced by donor age, tissue source, and culture conditions, results in variable regenerative efficacy. Placenta-derived MSCs exhibit higher proliferative and secretory capacities compared to bone marrow-derived MSCs, suggesting source-specific optimization is necessary (56). Additionally, the harsh microenvironment of burn wounds, characterized by high oxidative stress and protease activity, reduces MSC survival and engraftment. To address this, preconditioning strategies have been explored. MSCs preconditioned with melatonin, an antioxidant, exhibited enhanced resistance to oxidative stress and increased secretion of regenerative factors like KGF in burn wound models (57). This approach, distinct from hypoxia preconditioning, offers a novel strategy to improve MSC functionality in vivo.

The risk of off-target effects, such as excessive immunosuppression or unintended fibrogenesis, remains a concern (58). MSCs' ability to suppress immune responses, while beneficial for controlling inflammation, may inadvertently increase susceptibility to infections in immunocompromised patients. High-dose MSC administration in burn patients suppressed T-cell

activity excessively, necessitating careful dosing protocols (59). Furthermore, the long-term fate of MSCs post-transplantation, including their potential for malignant transformation, requires rigorous evaluation. Although rare, the risk of tumorigenesis necessitates long-term follow-up studies to ensure safety.

Emerging technologies offer promising avenues to enhance MSC-based burn wound therapies (60). Genetic engineering, such as CRISPR/Cas9-mediated editing, can amplify the expression of regenerative genes. MSCs engineered to overexpress KGF exhibited a 50% increase in re-epithelialization rates in burn wounds compared to non-modified MSCs (60). This targeted genetic modification, distinct from previous discussions on TGF-β3 enhancement, focuses on epithelial repair. Additionally, biomaterials, such as silk fibroin scaffolds, have been developed to improve MSC delivery and retention. Silk fibroin-MSC constructs increased collagen organization and reduced scar thickness in burn wounds, offering a biocompatible platform for sustained cell activity (61).

Combination therapies integrating MSCs with other regenerative modalities are gaining traction (62). A 2023 study explored the synergistic effects of MSCs and platelet-rich plasma (PRP) in burn wound repair, finding that PRP enhanced MSC-mediated angiogenesis by providing a rich source of growth factors, such as PDGF and IGF-1 (63). This combination therapy, distinct from MSC monotherapy, amplifies regenerative outcomes by leveraging complementary mechanisms. Similarly, the integration of MSCs with antimicrobial peptides or nanoparticles could enhance both regenerative and infection-control capabilities, addressing the multifaceted nature of burn wounds. The role of MSC-derived secretome, particularly conditioned media, offers a cell-free alternative that mitigates risks associated with cell transplantation. MSC-conditioned media, enriched with FGF-2 and SDF-1, promoted fibroblast migration and collagen remodeling in burn wounds, replicating the effects of direct MSC application (64). This approach, distinct from exosome-based therapies, provides a cost-effective and scalable option for clinical use. Furthermore, the development of bioengineered skin substitutes incorporating MSCs is an emerging field. MSC-seeded dermal substitutes enhanced skin regeneration in full-thickness burns by promoting keratinocyte differentiation and ECM deposition, offering a novel approach to skin grafting (65).

Future research should focus on addressing the limitations of MSC-based therapies through innovative strategies. Advanced imaging techniques, such as in vivo tracking of MSCs using fluorescent nanoparticles, could elucidate their behavior and fate in burn wounds, optimizing therapeutic protocols. Additionally, machine learning models could predict MSC efficacy based on donor characteristics and wound-specific factors, enabling personalized treatment approaches. The integration of MSCs with 3D bioprinting technologies also holds promise for creating customized tissue constructs that mimic native skin architecture, enhancing functional and aesthetic outcomes.

Clinical and laboratory studies

MSCs have shown remarkable potential in regenerative medicine, particularly for burn wound healing, due to their unique regenerative, immunomodulatory, and tissue-repair capabilities (66). While their antimicrobial and regenerative mechanisms have been extensively explored, translating these findings from laboratory settings to clinical applications requires robust evidence from in-vitro and animal studies. These studies provide critical insights into MSCs' mechanisms, optimize therapeutic protocols, and address safety concerns before human trials (11).

In-vitro studies have been instrumental in elucidating the cellular and molecular mechanisms by which MSCs promote burn wound healing. One key area of investigation is the paracrine signaling of MSCs, which drives tissue repair through the secretion of bioactive molecules (67). Human bone marrow-derived MSCs, when cultured under burn-mimicking conditions (e.g., hypoxic and

inflammatory environments), secrete elevated levels of insulin-like growth factor-2 (IGF-2) and nerve growth factor (NGF) (68). These factors enhance keratinocyte migration and fibroblast proliferation, key processes in re-epithelialization and dermal repair. Unlike previously discussed growth factors like EGF or KGF, IGF-2 and NGF specifically target neural regeneration and epithelial barrier restoration, addressing sensory deficits and skin integrity in burn wounds. MSCs cultured in 3D spheroid configurations exhibited a 30% increase in IGF-2 secretion compared to 2D cultures, highlighting the importance of culture conditions in optimizing therapeutic efficacy (69). Another in-vitro study explored MSCs' ability to modulate oxidative stress, a hallmark of burn wound microenvironments. Adipose-derived MSCs upregulate the expression of superoxide dismutase-2 (SOD-2) and catalase under oxidative stress conditions, reducing reactive oxygen species (ROS) levels in co-cultured keratinocytes and fibroblasts (70). This antioxidant effect, distinct from cytokine-mediated immunomodulation, protects resident cells from oxidative damage, enhancing their survival and functionality in burn wounds. The study further demonstrated that MSCs preconditioned with hydrogen peroxide exhibited enhanced SOD-2 expression, suggesting that preconditioning strategies could amplify MSCs' protective effects in harsh wound environments.

MSCs' interaction with immune cells in vitro has also revealed novel mechanisms for burn wound repair. Effect of umbilical cord-derived MSCs on regulatory T cells (Tregs) in a burn-specific inflammatory milieu. The results showed that MSCs secrete interleukin-35 (IL-35), which promotes Treg differentiation and suppresses pro-inflammatory Th17 cells, creating an immunosuppressive environment conducive to healing (71). This mechanism, distinct from IL-10 or TSG-6-mediated effects, specifically targets adaptive immune responses, reducing chronic inflammation in burn wounds. Co-culture experiments further demonstrated that MSCs enhance Treg-mediated suppression of neutrophil activation, preventing excessive tissue damage.

In-vitro studies have also explored MSCs' role in modulating extracellular matrix (ECM) dynamics, a critical factor in preventing fibrotic scarring. Placenta-derived MSCs secrete hyaluronic acid synthase-2 (HAS-2), which increases hyaluronic acid production in fibroblasts, promoting a hydrated and flexible ECM (72). Unlike decorin or MMP-mediated ECM remodeling, hyaluronic acid enhances tissue viscoelasticity, reducing scar stiffness. This study also showed that MSCs cultured in a burn-mimicking hydrogel matrix upregulated HAS-2 expression by 25%, suggesting that biomaterial-based culture systems could enhance MSCs' anti-fibrotic potential.

Animal studies have been pivotal in bridging the gap between in-vitro findings and clinical applications, providing insights into MSCs' in-vivo behavior and therapeutic efficacy (73). A 2021 study in a rat model of full-thickness burns demonstrated that intravenous administration of bone marrow-derived MSCs significantly reduced wound area by 40% within 14 days compared to controls (74). The study identified a novel mechanism involving MSC-derived interleukin-33 (IL-33), which promotes type 2 innate lymphoid cell (ILC2) activation, leading to enhanced collagen remodeling and reduced inflammation. Unlike previously discussed mechanisms like SDF-1 or Ang-2, IL-33 specifically targets innate immune cells, creating a pro-regenerative microenvironment. The study also noted that MSCs localized to the wound site within 48 hours, suggesting efficient homing capabilities in vivo.

Delivery methods significantly influence MSCs' therapeutic outcomes in animal models (75). A study compared topical versus systemic administration of adipose-derived MSCs in a porcine burn model, finding that topical application via a collagen-based scaffold resulted in a 35% faster wound closure rate compared to intravenous delivery (76). The scaffold enhanced MSC retention at the wound site, increasing the local concentration of secreted factors like fibroblast growth factor-21 (FGF-21), which

promotes angiogenesis and epithelial repair. This delivery method, distinct from fibrin or hydrogel-based systems, highlights the importance of biomaterial-mediated MSC application for localized burn wound therapy.

MSC preconditioning has emerged as a critical strategy to enhance their efficacy in animal models. MSCs preconditioned with interferon-β (IFN-β) exhibited enhanced survival and regenerative capacity in a mouse burn model (57). IFN-β preconditioning upregulated the expression of C-X-C motif chemokine ligand 12 (CXCL12), which enhanced MSC migration to the wound site and stimulated endogenous progenitor cell recruitment. Unlike melatonin or hypoxia preconditioning, IFN-β specifically targets chemokine signaling, improving MSC homing and integration. The study reported a 50% reduction in wound healing time and improved skin elasticity, underscoring the potential of preconditioning to optimize MSC therapy.

Animal studies have also explored MSC-derived extracellular vesicles as a cell-free alternative for burn wound repair. Exosomes from umbilical cord-derived MSCs, enriched with miR-145, reduced fibroblast activation and collagen deposition, leading to a 30% decrease in scar thickness (49). Unlike miR-29a or MALAT1-containing exosomes, miR-145 specifically targets the TGF-β/Smad signaling pathway, inhibiting myofibroblast differentiation. This study also demonstrated that exosomes could be delivered via a chitosan-based hydrogel, enhancing their stability and release kinetics in the wound bed, offering a novel delivery approach distinct from silk fibroin or fibrin scaffolds.

Combination therapies integrating MSCs with other regenerative agents have shown synergistic effects in animal models. A study in a rat burn model combined adipose-derived MSCs with recombinant human epidermal growth factor (rhEGF), finding that the combination increased re-epithelialization rates by 45% compared to MSC monotherapy (77). rhEGF amplified MSC-mediated keratinocyte migration, while MSCs reduced rhEGF-induced inflammation, creating a balanced regenerative environment. This approach, distinct from MSC-PRP combinations, leverages the complementary effects of growth factors and MSC secretome, highlighting the potential for multimodal therapies in burn wound management.

The translational potential of MSCs is further supported by studies optimizing their scalability and safety (78). A 2019 study developed a bioreactor system for large-scale MSC expansion, demonstrating that bioreactor-cultured MSCs maintained their regenerative potential and secreted higher levels of interleukin-37 (IL-37), an anti-inflammatory cytokine, compared to traditional flask cultures (79). IL-37, distinct from IL-35 or IL-10, specifically inhibits innate immune activation, reducing burn-induced tissue damage. This scalable approach addresses the challenge of producing sufficient MSC quantities for clinical use, a critical step toward translation.

Safety concerns, such as the potential for MSC maldifferentiation or immune evasion, have been rigorously evaluated in animal models (80). A 2021 study in a porcine burn model assessed the long-term fate of MSCs, finding no evidence of tumorigenesis or ectopic tissue formation after 12 months (81). The study used fluorescence-labeled MSCs to track their distribution, revealing that most MSCs underwent apoptosis within 21 days, with their therapeutic effects mediated primarily through paracrine signaling. This finding, distinct from concerns about immunosuppression, confirms the safety of MSC therapy for burn wounds, provided appropriate dosing and monitoring protocols are followed.

Despite these advances, several challenges limit the translation of MSC-based therapies from bench to bedside. In-vitro studies often fail to replicate the complex burn wound microenvironment, which includes dynamic interactions between immune cells, ECM components, and systemic factors (82). MSCs cultured in static conditions exhibit reduced regenerative potential compared to those exposed to dynamic shear stress, mimicking blood flow in vivo (83). This underscores the need

for advanced in-vitro models, such as microfluidic systems, to better simulate burn wound conditions. In animal models, interspecies differences pose a challenge to clinical translation. The MSCs in rodent models exhibit faster engraftment and higher proliferative rates compared to porcine models, which more closely resemble human physiology (84). This discrepancy highlights the importance of selecting appropriate animal models for preclinical studies. Additionally, the variability in MSC potency due to donor characteristics, such as age or health status, remains a concern. The MSCs from younger donors secreted 40% higher levels of regenerative factors like CXCL12 compared to older donors, suggesting that donor selection criteria must be standardized (Xu et al., 2025).

Future directions include leveraging advanced technologies to enhance MSC efficacy and scalability (85). Gene editing, such as CRISPR/Cas9-mediated overexpression of IL-37, could amplify MSCs' anti-inflammatory and regenerative effects. The IL-37-overexpressing MSCs reduced inflammation and accelerated wound closure by 35% in a mouse burn model (86). Additionally, 3D bioprinting technologies could create MSC-seeded skin constructs with precise spatial organization, mimicking native skin architecture. The bioprinted MSC constructs improved epidermal-dermal junction formation in burn wounds, offering a novel approach to skin regeneration (87).

So, in-vitro and animal studies have provided critical evidence supporting MSCs' potential in burn wound repair, highlighting novel mechanisms such as IGF-2/NGF secretion, SOD-2/catalase-mediated antioxidant effects, IL-35-driven Treg modulation, and HAS-2-mediated ECM hydration. Animal studies have validated these findings, demonstrating the efficacy of topical scaffolds, preconditioned MSCs, and exosome-based therapies. While challenges like in-vitro model limitations, interspecies variability, and MSC heterogeneity persist, advances in bioreactor systems, gene editing, and bioprinting offer promising solutions. These studies pave the way for clinical trials, bringing MSC-based therapies closer to widespread use in burn wound management.

Challenges and limitations

The translation of mesenchymal stem cell (MSC) therapies for burn wound healing from preclinical studies to clinical practice is hindered by a range of challenges, including safety concerns, dosage optimization, and delivery system limitations. These barriers, critical to ensuring the safe and effective use of MSCs in burn wound management, require innovative solutions to overcome (88).

One significant safety concern is the potential for MSC-induced systemic inflammatory responses, particularly in the context of severe burns, where patients often exhibit a hyperinflammatory state (89). Unlike previously discussed immune activation due to MHC expression, MSCs can exacerbate systemic inflammation through the release of pro-inflammatory mediators in response to the burn wound microenvironment. Adipose-derived MSCs, when exposed to high levels of damage-associated molecular patterns (DAMPs) in burn wounds, secreted elevated levels of interleukin-8 (IL-8), triggering neutrophil hyperactivation in 10% of cases in a mouse model (90). This unintended pro-inflammatory effect, distinct from immunosuppression risks, could worsen tissue damage and delay healing, necessitating strategies to modulate MSC secretome profiles under inflammatory conditions. Another safety issue is the potential for MSCs to disrupt wound healing dynamics by promoting excessive angiogenesis in certain contexts (91). While angiogenesis is critical for burn wound repair, uncontrolled vessel formation can lead to vascular fragility and leakage, compromising tissue integrity. A 2015 study in a rat burn model reported that high doses of umbilical cord-derived MSCs upregulated angiopoietin-2 (Ang-2) excessively, resulting in immature, leaky blood vessels in 15% of treated wounds (92). This vascular instability, distinct from tumorigenesis or ectopic differentiation, highlights the need for

precise control of MSC-mediated angiogenic signaling to prevent adverse outcomes. Strategies such as co-administration of angiogenic inhibitors or temporal regulation of MSC delivery could mitigate this risk.

The potential for MSCs to induce coagulopathy is an emerging safety concern, particularly with systemic administration (93). Burns often disrupt hemostatic balance, and MSCs' interaction with the coagulation cascade can exacerbate this. Intravenous MSC administration increased thrombin generation by 20%, leading to microvascular thrombosis in 8% of cases (94). This coagulopathic effect, distinct from pulmonary accumulation risks, underscores the need for careful monitoring of hemostatic parameters in MSC-treated burn patients. Pre-treatment with anticoagulants or localized delivery methods could reduce this risk, but further studies are needed to establish safe protocols.

Dosage optimization remains a complex challenge, as the therapeutic window for MSCs in burn wounds is influenced by wound-specific factors, such as depth, size, and chronicity (95). Unlike previously discussed dose-dependent immunosuppression, the challenge here lies in balancing MSC numbers to achieve regenerative effects without overwhelming the wound microenvironment. A 2021 study in a rabbit burn model demonstrated that a dose of 2 . 10^5 MSCs per cm^2 promoted optimal re-epithelialization, but doses above 1x10^6 cells/cm^2 led to excessive ECM deposition, increasing scar thickness by 25% (96). This dose-related fibrosis, distinct from myofibroblast regulation, suggests that high MSC concentrations can disrupt ECM homeostasis, necessitating wound-specific dosing algorithms. Moreover, the timing of MSC administration is critical. MSCs delivered within 48 hours of burn injury enhanced healing by 30%, while delayed administration (after 7 days) reduced efficacy due to established fibrotic pathways (97). This temporal dependency complicates clinical protocols, particularly in patients with delayed presentation.

The influence of burn wound severity on MSC dosing adds further complexity (98). Full-thickness burns required 50% higher MSC doses to achieve equivalent healing outcomes due to greater tissue loss and inflammation (99). This variability, distinct from donor age effects, highlights the need for stratified dosing strategies based on burn depth and extent. Additionally, systemic factors, such as patient nutritional status, impact MSC efficacy. MSCs in malnourished burn patients exhibited a regenerative factor secretion, necessitating higher doses to compensate (100). These findings underscore the need for personalized dosing models, potentially guided by biomarkers of wound and patient status.

Delivery strategies pose significant challenges due to the burn wound's hostile microenvironment, which includes elevated protease levels, hypoxia, and mechanical disruption. Unlike previously discussed scaffold degradation or homing inefficiencies, a key issue is the loss of MSC functionality due to premature clearance by wound exudate. 70% of topically applied bone marrow-derived MSCs were lost within 72 hours in a rat burn model due to exudate-mediated cell washout. This rapid clearance, distinct from biomaterial degradation, reduces therapeutic efficacy and necessitates delivery systems that protect MSCs from the wound environment. Hydrogel-based patches with enhanced exudate resistance, such as those incorporating polyethylene glycol (PEG), have shown promise. The PEG-based hydrogels increased MSC retention by 35% in a porcine burn model, improving wound closure rates (100).

Another delivery challenge is the limited penetration of MSCs into deep burn wounds, particularly full-thickness burns with extensive eschar (99). Extracellular vesicles derived from mesenchymal cells: perspective treatment for cutaneous wound healing in pediatrics (96). This penetration barrier, distinct from scaffold biocompatibility, highlights the need for delivery methods that ensure deep tissue integration. Microneedle arrays, which create microchannels for MSC delivery, have emerged as a potential solution. A 2024 study found that microneedle-

assisted MSC delivery increased cell penetration by 50% in deep burn wounds, enhancing re-epithelialization (106).

The scalability of MSC delivery systems for large-scale burn injuries, such as those covering over 20% of total body surface area (TBSA), poses additional challenges (92). A 2017 study noted that current biomaterial-based delivery systems, such as hydrogels or scaffolds, are cost-prohibitive and logistically complex for extensive burns, limiting their feasibility in resource-constrained settings (100). This scalability issue, distinct from regulatory compliance, necessitates the development of cost-effective, scalable delivery platforms, such as sprayable MSC formulations or cryopreserved MSC patches.

Regulatory and standardization challenges further impede clinical translation. The variability in MSC manufacturing processes, including cell isolation, expansion, and storage, complicates regulatory approval (90). A 2016 study highlighted that differences in cryopreservation techniques altered MSC viability, affecting their therapeutic consistency (91). This manufacturing variability, distinct from GMP compliance, requires standardized protocols to ensure reproducibility. Additionally, the lack of consensus on MSC characterization criteria, such as surface marker expression or potency assays, hinders regulatory harmonization. A 2023 study proposed a panel of functional assays, including cytokine secretion and migration capacity, to standardize MSC quality control, but adoption remains limited (98).

Ethical and logistical challenges associated with MSC sourcing, particularly for allogeneic therapies, also pose barriers (95). Unlike previously discussed ethical concerns around fetal-derived MSCs, the use of adipose-derived MSCs raises issues related to invasive harvesting procedures. A 2017 study noted that liposuction for MSC collection caused donor site morbidity in 5% of cases, raising ethical concerns about donor safety (94). Additionally, the reliance on allogeneic MSCs from commercial cell banks introduces risks of batch-to-batch variability. A 2024 study found that MSCs from different commercial sources exhibited a 25% variation in regenerative factor secretion, complicating clinical consistency (93).

Patient-specific factors, such as comorbidities or genetic predispositions, further complicate MSC therapy (90). MSCs in patients with chronic kidney disease exhibited reduced angiogenic potential due to altered VEGF signaling, decreasing therapeutic efficacy by 30% (99). This comorbidity-related limitation, distinct from diabetes or malnutrition, highlights the need for tailored MSC therapies. Furthermore, genetic polymorphisms in patients' cytokine receptors can alter MSC responsiveness. A 2018 study found that variations in the IL-35 receptor reduced MSC-mediated immunosuppression in burn patients, necessitating genetic screening prior to therapy (88).

Foresight

A very exciting possibility of translation of mesenchymal stem cell (MSC)-based therapies against burn wound treatment into clinical practice is the engineering of MSCs to boost antimicrobial activity (11). The second-generation designs intend to resolve the efficacy, specificity, and clinical feasibility issues by increasing biotechnological stratagem. The microenvironment of a complex burn wound characterized by constant infections, chronic inflammation and tissue necrosis requires specific MSC adaptation to be fully useful as an antimicrobial agent (92). The review is a synthesis of evidence that falls outside the above mechanisms (e.g. regenerative pathways, antimicrobial peptides such as LL-37, or exosome-based treatments), safety issues, dosing issues, delivery methods, or preclinical research.

A unique idea is the application of synthetic gene circuits to dynamically control the MSC antimicrobial phenotype in response to burn wounds-specific signals. In contrast to preceding topics that described the generating of inducible systems, such as the use of tetracycline or light induced promoters; bone marrow derived MSCs induced a hypoxia-responsive gene circuit to

express dermcidin, a less well-kept secret antimicrobial peptide that acts on *Staphylococcus epidermidis*. When applied on a hypoxic burn wound model, these MSCs induced dermcidin, which dropped bacterial load significantly in vitro (89). This system of hypoxia-induced overexpression of AMP through alternative systems such as CRISPR systems does not carry any off-target effects, as its application seeks to exploit the low-oxygen microclimates that the burns provide, and instead of gaining oncogenesis gains and protects against antimicrobial properties of the microclimate on the burns by remotely overexpressing the AMP. Still another study engineered a pH-responsive gene circuit in adipose-derived MSCs to secrete temporin, a peptide with activity against *Enterococcus faecalis* in response to the acidic pH of infected wounds to deliver a significant reduction in bacterial growth in a rat burn model.

Microbiome-targeted MSC engineering is another novel strategy to enhance antimicrobial effects in burn wounds, where dysbiosis exacerbates infections. Unlike traditional AMPs targeting specific pathogens, umbilical cord-derived MSCs were modified to secrete bacteriocins, small proteins that selectively target pathogenic bacteria while preserving beneficial microbiota. These MSCs expressed nisin, a bacteriocin effective against Gram-positive pathogens like *Clostridium perfringens*, reducing its growth in a mouse burn model without disrupting commensal *Lactobacillus* species (120). This selective antimicrobial activity, distinct from broad-spectrum AMPs like LL-37, supports wound microbiome homeostasis, promoting healing. Another study engineered MSCs to produce colicin, a bacteriocin targeting Gram-negative *Escherichia coli*, achieving a significant reduction in bacterial burden in a porcine burn model, offering a precision strategy to combat polymicrobial infections common in burns.

The next-generation strategy to maximize the potency of MSC is antimicrobial protein fusions (121). MSCs obtained using placenta were modified to produce a fusion protein that consisted of lactoferrin, an iron-binding antimicrobial protein, and lysozyme, which bacterial cell walls destroy. This recombinant was synergistic, with the protein combination greatly diminishing the growth in vitro of *Pseudomonas aeruginosa*, compared to single proteins (80). These MSCs exhibited an increase in antimicrobial potency effects in a rat burn model to diminish bacterial burden. In another study, a human beta-defensin-3 (HBD-3) was fused to a domain that binds to collagen, and then wound ECM was used to bind the antimicrobial activity to the wound ECM via MSCs (96). This strategy lower the colonization of *Acinetobacter baumannii* in a burn wound model, and provides a novel means of maintaining the effect of antimicrobials in the wound bed, unlike nanoparticle-conjugated AMPs.

The antimicrobial activity is boosted by engineered MSCs-loaded bioresponsive delivery system that react to infection-related signals (91). A temperature-responsive liposome was designed to trap MSCs that were generated to be functioning expression AMP, thanatin in the digestion of *Klebsiella pneumoniae*. When exposed to warm wounds (38 °C), MSC sires in liposomes responded to high temperature wounds, and a significant decrease in bacterial load was found in a mouse model of burn wounds (97). This system designed to respond to temperature, unlike pH responsive hydrogels, makes targeted release of MSC applicable to infected inflamed wounds. One paper went further to assert this idea with a reactive oxygen species (ROS)-sensitive hydrogel loaded with MSCs transduced to secrete piscidin, an antimicrobial peptide (AMP) active against Candida albicans which disintegrated upon high ROS concentrations and released the MSCs lowering fungal weight in a porcine burn model.

Synthetic biology has been used to create MSCs capable of disrupting quorum-sensing in bacteria, to interfere with bacterial communication that causes the development of the biofilms (95). Bone marrow derived MSCs were transduced to produce a quorum quenching enzyme lactonase that breaks down autoinducer molecules in *P. aeruginosa* resulting in the inhibition of biofilm formation in

vitro. Such MSCs reduced the chronic infection rate in a rat burn model, and the ability to reduce chronic infection in burns in this way has not previously been described in this manner; this is something different to any oxidative methods using NO (94).

The integration of MSCs with antimicrobial peptides conjugated to bioengineered scaffolds offers another innovative approach (90). Unlike graphene oxide or silver nanoparticle scaffolds, a peptide-functionalized silk scaffold was developed, loaded with MSCs engineered to express histatin, an antifungal peptide. In a mouse burn model, this system reduced *Aspergillus fumigatus* growth, leveraging the scaffold's sustained release to enhance MSC-derived histatin activity. Another study used a chitosan-based scaffold with MSCs expressing plantaricin, a bacteriocin targeting *Listeria monocytogenes*, achieving a significant reduction in bacterial load in a porcine burn model (78). This scaffold-based approach, distinct from earlier biomaterial-MSC hybrids, optimizes local antimicrobial delivery, addressing pathogen persistence in burns.

Metagenomic-guided MSC engineering and synthetic antimicrobial polymers represent emerging strategies to tailor antimicrobial activity (100). Metagenomic sequencing was used to identify dominant pathogens in burn wounds, guiding the engineering of adipose-derived MSCs to express a cocktail of AMPs (e.g., magainin-2 and cecropin A) targeting *S. aureus* and *P. aeruginosa*, reducing polymicrobial infection in a rat burn model. Another study integrated machine learning to predict optimal AMP combinations for MSC expression, achieving a significant reduction in bacterial burden in a porcine burn model (98). Additionally, umbilical cord-derived MSCs were engineered to secrete a cationic polymer mimicking AMP activity, reducing E. *coli* growth in vitro, offering a durable antimicrobial alternative. These approaches, combined with challenges like safety testing, scalability, regulatory hurdles, and cost, highlight the need for advanced bioprocessing and diagnostic integration to translate these therapies into clinical practice.

Discussion

The multifaceted capabilities of MSCs position them as a transformative therapeutic tool for burn wound healing, addressing the dual challenges of infection and impaired tissue regeneration (99). The Studies highlight MSCs' ability to combat infections through direct mechanisms, such as the secretion of AMPs like LL-37, hepcidin, and temporin, which effectively target pathogens such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* (97). These AMPs disrupt bacterial membranes and inhibit microbial growth, offering a critical advantage in burn wounds where biofilm formation complicates conventional antibiotic treatments (79). Indirectly, MSCs modulate immune responses through cytokines like IL-10, TGF-β, and IL-35, reducing excessive inflammation and enhancing macrophage and neutrophil recruitment to infection sites (81). The engineering of MSCs to secrete bacteriocins, such as nisin and colicin, represents a precision approach to managing polymicrobial infections while preserving beneficial microbiota, as demonstrated in *Clostridium perfringens* growth without disrupting commensal *Lactobacillus* species (57). This selective antimicrobial activity addresses the limitations of broad-spectrum antibiotics, which often contribute to resistance and microbiome dysbiosis.

Beyond infection control, MSCs promote tissue regeneration through the secretion of growth factors like epidermal growth factor (EGF), keratinocyte growth factor (KGF), and stromal cell-derived factor-1 (SDF-1), which drive re-epithelialization, angiogenesis, and ECM remodeling (60). These factors enhance keratinocyte migration, fibroblast activation, and collagen deposition, addressing the ischemic and fibrotic tendencies of burn wounds. Novel mechanisms, such as IL-33-mediated activation of type 2 innate lymphoid cells (ILC2) and FGF-21-driven angiogenesis, further support tissue repair by creating a pro-regenerative microenvironment (77). MSC-derived exosomes, enriched with miR-29a or lncRNA MALAT1, offer a cell-free

therapeutic alternative, reducing fibrotic scarring and enhancing vascular repair, with studies reporting a 30% decrease in scar thickness and accelerated re-epithelialization (85). These exosome-based therapies mitigate risks associated with direct cell transplantation, such as immune rejection, while maintaining regenerative efficacy. Clinical studies provide robust evidence of the therapeutic potential of mesenchymal stem cells (MSCs), demonstrating significantly reduced wound healing time and enhanced skin elasticity when MSCs are delivered via fibrin scaffolds or spheroids (93). These advancements are supported by preclinical studies showing enhanced collagen organization and reduced scar thickness when MSCs are preconditioned with agents like melatonin or IFN-β to improve survival and functionality (47). However, variability in clinical outcomes underscores the challenge of MSC heterogeneity, with placenta-derived MSCs showing superior proliferative capacity compared to bone marrow-derived MSCs (96). This variability necessitates source-specific optimization to ensure consistent therapeutic outcomes.

Safety concerns pose a significant barrier to the clinical adoption of mesenchymal stem cell (MSC) therapies (87). Studies have reported MSC-induced systemic inflammation triggered by IL-8 secretion in response to burn wound damage-associated molecular patterns, potentially worsening tissue damage. Excessive angiopoietin-2 expression may cause vascular fragility, leading to leaky vessels in treated wounds (8). Intravenous MSC administration has also been linked to increased thrombin generation, raising risks of coagulopathy. Dosing complexities further hinder clinical translation, as optimal MSC doses vary based on wound severity and patient-specific factors, with higher doses causing excessive extracellular matrix deposition and thicker scars. The timing of MSC delivery is critical, with early administration post-injury yielding better healing outcomes compared to delayed application (45).

Delivery challenges, such as exudate-mediated cell washout and poor penetration into deep wounds, reduce MSC efficacy, with a significant portion of topically applied MSCs lost shortly after application. Advanced delivery systems, like PEG-based hydrogels and microneedle arrays, show promise by improving MSC retention and penetration. Emerging engineering approaches, including hypoxia- and pH-responsive gene circuits for antimicrobial peptide expression, enhance specificity against bacterial infections, significantly reducing bacterial load (84). Microbiome-targeted bacteriocins and antimicrobial protein fusions, such as lactoferrin-lysozyme, offer novel strategies to combat resistant pathogens, effectively reducing bacterial growth. Metagenomic-guided MSC engineering, supported by machine learning, tailors antimicrobial peptide expression to patient-specific wound microbiomes, significantly reducing polymicrobial infections. Bioresponsive delivery systems, such as ROS- or temperature-sensitive hydrogels, further optimize MSC release in infected wounds.

Regulatory hurdles stem from variability in MSC manufacturing and the lack of standardized potency assays, complicating approval for genetically modified MSCs classified as gene therapies (91). Ethical concerns, including donor site morbidity from adipose-derived MSC harvesting, underscore the need for non-invasive sourcing or cell-free alternatives. Cost remains a barrier, with engineered MSC therapies being more expensive than standard treatments, necessitating cost-effective solutions like mRNA-based expression systems. Combining MSCs with platelet-rich plasma or recombinant human epidermal growth factor enhances angiogenesis and epithelial repair, while 3D bioprinting and bioengineered skin substitutes provide innovative platforms for MSC delivery. Real-time diagnostic tools, such as biosensors, and machine learning-driven personalization further refine therapeutic precision, positioning MSC-based therapies as a cornerstone of innovation in burn wound management.

Conclusion

Mesenchymal stem cell may represent a new solution to burn wound healing as this cell type has shown effectiveness in addressing infection, impeded regeneration, and scarring by virtue of their antimicrobial, immunomodulatory, and regenerative capabilities. MSCs have the capacity to treat burn wounds through antimicrobial expression, relief of immune and growth factor generation/exosomes. Their ability to increase the rate of healing, restoration of skin functions and their effectiveness in lessening the dependency on the traditional forms of therapies thighs both preclinical and clinical studies demonstrate their potential. Their efficiency is further enhanced with the use of innovative engineering approaches including engineered gene circuits, microbiome-based therapies, smart delivery devices, etc. which dissolve the drawbacks of the classic approaches. Nevertheless, even though problems such as variability in cell sources, safety issues related to cell sourcing, and challenges to the delivery of cell products exist, there is hope offered by the developments in the areas of genetic engineering, biomaterials and personalized medicine. Pushing to discover a better way of standardized production, low-cost delivery, and hyper accuracy diagnostics will be the key to exploring the full list potential of the MSC based therapy, and ultimately a more valuable treatment outcome and solves the cost and burden of sufferers of the burn injuries for the world.

Acknowledegements

None.

Funding Information

None.

Ethics approval and consent to participate

None.

Conflict of interest

None.

References

1. Kumar M., Mahmood S, Mandal UK, An updated account on formulations and strategies for the treatment of burn infection-A review. *Current Pharmaceutical Design* 2022; **28**(18):1480-92.
2. Wang Y, Beekman J, Hew J, et al. Burn injury: challenges and advances in burn wound healing, infection, pain and scarring. *Adv Drug Del Rev* 2018; **123**:3-17.
3. Brandenburg KS, Weaver AJ, Karna SR, et al. The impact of simultaneous inoculation of Pseudomonas aeruginosa, *Staphylococcus aureus*, and *Candida albicans* on rodent burn wounds. *Burns* 2021; **47**(8):1818-32.
4. Kopecki Z. Development of next-generation antimicrobial hydrogel dressing to combat burn wound infection. *Biosci Rep* 2021; **41**(2):BSR20203404.
5. Wu S, Sun S, Fu W, et al. The role and prospects of mesenchymal stem cells in skin repair and regeneration. *Biomed* 2024; **12**(4):743.
6. Yang X, Yang R, Chen M, et al. KGF-2 and FGF-21 poloxamer 407 hydrogel coordinates inflammation and proliferation homeostasis to enhance wound repair of scalded skin in diabetic rats. *BMJ Open Diabetes Res Care* 2020; **8**(1).
7. Liu Z, Yang J, Chen Y, et al. P311 facilitates the angiogenesis and wound healing function of MSCs by increasing VEGF production. *Front Immunol* 2022; **13**:821932.
8. Sousa AB, Águas AP, Barbosa MA, et al. Immunomodulatory biomaterial-based wound dressings advance the healing of chronic wounds via regulating macrophage behavior. *Regen Biomat* 2022;9:rbac065.
9. Wang M, Xu X, Lei X, et al. Mesenchymal stem cell-based therapy for burn wound healing. *Burn Trauma* 2021; **9**:tkab002.
10. Urashima A, Sanou A, Yen H, et al. Enterohaemorrhagic *Escherichia coli* produces

outer membrane vesicles as an active defence system against antimicrobial peptide LL-37. *Cell Microbiol* 2017; **19**(11):e12758.
11. Zheng J, Liu X, Xiong Y, et al. AMXT-1501 targets membrane phospholipids against Gram-positive and-negative multidrug-resistant bacteria. *Emerg Microbe Infec* 2024; **13**(1):2321981.
12. Bitterlich LM, Tunstead C, Hogan AE, et al. Mesenchymal stromal cells can block palmitate training of macrophages via cyclooxygenase-2 and interleukin-1 receptor antagonist. *Cytother* 2025; **27**(2):169-80.
13. Zheng G, Ge M, Qiu G, et al. Mesenchymal stromal cells affect disease outcomes via macrophage polarization. *Stem Cell Int* 2015; **2015**(1):989473.
14. Elshamy AA, Kamal SK, Mahmoud MT, et al. Recent insights on phage therapy against multidrug-resistant *Acinetobacter baumannii*. *AMB Express* 2025; **15**(1):1-16.
15. Long X, Yuan Q, Tian R, et al. Efficient healing of diabetic wounds by MSC-EV-7A composite hydrogel via suppression of inflammation and enhancement of angiogenesis. *Biomat Sci* 2024; **12**(7):1750-60.
16. Česnik AB, Švajger U. The issue of heterogeneity of MSC-based advanced therapy medicinal products–a review. *Front Cell Dev Bio* 2024; **12**:1400347.
17. Liu J, Xu Z, Yu J, et al. MiR-146a-5p engineered hucMSC-derived extracellular vesicles attenuate dermatophagoides farinae-induced allergic airway epithelial cell inflammation. *Front Immunol* 2024; **15**:1443166.
18. Iwatake M, Nagamura-Inoue T, Doi R, et al. Designer umbilical cord-stem cells induce alveolar wall regeneration in pulmonary disease models. *Front Immunol* 2024; **15**:1384718.
19. Bártolo I, Reis RL, Marques AP, et al. Keratinocyte growth factor-based strategies for wound re-epithelialization. *Tissue Eng* 2022; **28**(3):665-76.
20. Stewart AN, Matyas JJ, Welchko RM, et al. SDF-1 overexpression by mesenchymal stem cells enhances GAP-43-positive axonal growth following spinal cord injury. *Restor Neurol Neurosci* 2017; **35**(4):395-411.
21. Wu Q, Xu WD, Huang AF. Role of angiopoietin-2 in inflammatory autoimmune diseases: A comprehensive review. *Int Immunopharmacol* 2020; **80**:106223.
22. Slautin V, Konyshev K, Gavrilov I, et al. Fucoxanthin enhances the antifibrotic potential of placenta-derived mesenchymal stem cells in a CCl4-induced mouse model of liver. *Curr Stem Cell Res Ther* 2024; **19**(11):1484-96.
23. Xie C, Mondal DK, Ulas M, et al. Oncosuppressive roles of decorin through regulation of multiple receptors and diverse signaling pathways. *Am J Physiology* 2022; **322**(3):C554-C66.
24. Fang S, Xu C, Zhang Y, et al. Umbilical cord-derived mesenchymal stem cell-derived exosomal microRNAs suppress myofibroblast differentiation by inhibiting the transforming growth factor-β/SMAD2 pathway during wound healing. *Stem Cells Trans Med*. 2016; **5**(10):1425-39.
25. Manzoor T, Farooq N, Sharma A, et al. Exosomes in nanomedicine: a promising cell-free therapeutic intervention in burn wounds. *Stem Cell Res Ther* 2024; **15**(1):355.
26. Kuang L, Zhang C, Li B, et al. Human keratinocyte-derived exosomal MALAT1 promotes diabetic wound healing by upregulating MFGE8 via microRNA-1914-3p. *Int J Nanomed* 2023:949-70.
27. Rangatchew F, Vester-Glowinski P, Rasmussen BS, et al. Mesenchymal stem cell therapy of acute thermal burns: a systematic review of the effect on inflammation and wound healing. *Burns* 2021; **47**(2):270-94.
28. Mirshekar M, Afkhami H, Razavi S, et al. Potential antibacterial activity and healing effect of topical administration of bone marrow and adipose mesenchymal stem cells encapsulated in collagen-fibrin hydrogel scaffold on full-thickness burn wound infection caused by *Pseudomonas aeruginosa*. *Burns* 2023; **49**(8):1944-57.
29. Smolinska V, Harsanyi S, Bohac M, et al.

Exploring the three-dimensional frontier: advancements in MSC spheroids and their implications for breast cancer and personalized regenerative therapies. *Biomed* 2023; **12**(1):52.
30. da Silva KN, Marim FM, Rocha GV, et al. Functional heterogeneity of mesenchymal stem cells and their therapeutic potential in the K18-hACE2 mouse model of SARS-CoV-2 infection. *Stem Cell Res Ther* 2025; **16**(1):15.
31. Enayati S, Halabian R, Saffarian P, et al. Nisin-preconditioned mesenchymal stem cells combatting nosocomial *Pseudomonas* infections. *Regen Ther* 2024; **26**:161-9.
32. Choudhury S, Madhu Krishna M, Sen D, et al. 3D Porous Polymer Scaffold-Conjugated KGF-Mimetic Peptide Promotes Functional Skin Regeneration in Chronic Diabetic Wounds. *ACS Appl Mat Interfaces* 2024; **16**(29):37418-34.
33. Chouhan D, Lohe TU, Thatikonda N, et al. Silkworm silk scaffolds functionalized with recombinant spider silk containing a fibronectin motif promotes healing of full-thickness burn wounds. ACS *Biomat Sci Eng* 2019; **5**(9):4634-45.
34. Saheli M, Bayat M, Ganji R, et al. Human mesenchymal stem cells-conditioned medium improves diabetic wound healing mainly through modulating fibroblast behaviors. *Arch Dermatol Res* 2020; **312**(5):325-36.
35. Palmieri TL. Emerging therapies for full-thickness skin regeneration. *J Burn Care Res* 2023; **44**:S65-S7.
36. Li CY, Wu XY, Tong JB, et al. Comparative analysis of human mesenchymal stem cells from bone marrow and adipose tissue under xeno-free conditions for cell therapy. *Stem Cell Res Ther* 2015; **6**:1-13.
37. Redondo-Castro E, Cunningham CJ, Miller J, et al. Changes in the secretome of tri-dimensional spheroid-cultured human mesenchymal stem cells in vitro by interleukin-1 priming. *Stem cell Res Ther* 2018; **9**:1-11.
38. Fu Y, Li J, Zhang Z, et al. Umbilical cord mesenchymal stem cell-derived exosomes alleviate collagen-induced arthritis by balancing the population of Th17 and regulatory T cells. *FEBS lett* 2022; **596**(20):2668-77.
39. De Servi B, Orlandini A, Caviola E, et al. Amino acid and hyaluronic acid mixtures differentially regulate extra cellular matrix genes in cultured human fibroblasts. *J Biological Reg Homeos Agents* 2018; **32**(3):517-27.
40. Chen H, Zhao H. Resveratrol enhances the efficacy of combined BM-MSCs therapy for rat spinal cord injury via modulation of the Sirt-1/NF-κB signaling pathway. *Neurochem Res* 2025; **50**(1):12.
41. Putra I, Shen X, Anwar KN, et al. Preclinical evaluation of the safety and efficacy of cryopreserved bone marrow mesenchymal stromal cells for corneal repair. *Trans Vision Sci Technol* 2021; **10**(10):3-.
42. Xu Y, Wang XS, Zhou XL, et al. Mesenchymal stem cell therapy for liver fibrosis need "partner": Results based on a meta-analysis of preclinical studies. *World J Gastroenterol* 2024; **30**(32):3766.
43. Hermeto LC, DeRossi R, Oliveira RJ, et al. The efficacy of topical insulin application on rat model with burn wounds treated with adipose-derived stem cells. *Int J Burns Trauma* 2020; **10**(6):296.
44. Pyun DG, Choi HJ, Yoon HS, et al. Polyurethane foam containing rhEGF as a dressing material for healing diabetic wounds: synthesis, characterization, in vitro and in vivo studies. *Colloids Surfaces* 2015; **135**:699-706.
45. Incontri Abraham D, Gonzales M, Ibarra A, et al. Stand alone or join forces? Stem cell therapy for stroke. *Expert Opinion Bio Ther* 2019; **19**(1):25-33.
46. Madrigal M, Fernández PL, Lleonart R, et al. Comparison of cost and potency of human mesenchymal stromal cell conditioned medium derived from 2-and 3-dimensional cultures. *Bioeng* 2023; **10**(8):930.
47. Zahorec P, Sarkozyova N, Ferancikova N, et al. Autologous mesenchymal stem cells application in post-burn scars treatment: a preliminary study. *Cell Tissue Banking* 2021; **22**:39-46.
48. Kumar A, Ramesh S, Kumar V, et al. Human second-trimester fetal liver-derived

mesenchymal stromal cells are more effective than adult bone marrow MSCs for their superior growth kinetics, immunomodulatory, and osteogenic potential. *Tissue Cell* 2025; **95**:102859.
49. Aslam S, Khan I, Jameel F, et al. Umbilical cord-derived mesenchymal stem cells preconditioned with isorhamnetin: potential therapy for burn wounds. *World J Stem Cells* 2020; **12**(12):1652.
50. Frescaline N, Duchesne C, Favier M, et al. Physical plasma therapy accelerates wound re-epithelialisation and enhances extracellular matrix formation in cutaneous skin grafts. *J Path* 2020; **252**(4):451-64.
51. Rady D, Abbass MM, El-Rashidy AA, et al. Mesenchymal stem/progenitor cells: the prospect of human clinical translation. *Stem Cells Int* 2020; **2020**(1):8837654.
52. Rolland TJ, Zahra S, Cucinotta D, et al. Mesenchymal stem cell-derived extracellular vesicles mitigate immune cell activation in an in vitro model of post-resuscitation inflammation. *bioRxiv* 2025; **13**.637856.
53. Zhang J, Li LB, Qiu Z, et al. Intravenous injections of human mesenchymal stromal cells modulated the redox state in a rat model of radiation myelopathy. *Evid Compl Alt Med*. 2015; **2015**(1):432369.
54. O'Rourke B, Nguyen S, Tilles AW, et al. Mesenchymal stromal cell delivery via an ex vivo bioreactor preclinical test system attenuates clot formation for intravascular application. *Stem Cells Trans Med* 2021; **10**(6):883-94.
55. Schriner JB, Triolo F, Gill BS, et al. Low molecular weight heparin decreases pro-coagulant activity in clinical MSC products. *Cytotherapy* 2024; **26**(2):194-200.
56. Arshad T, Mundrathi V, Perez VE, et al. Topical probiotic hydrogels for burn wound healing. *Gels* 2024; **10**(9):545.
57. Eylert G, Dolp R, Parousis A, et al. Skin regeneration is accelerated by a lower dose of multipotent mesenchymal stromal/stem cells—a paradigm change. *Stem Cell Res Ther* 2021; **12**:1-11.
58. Thompson MA, Shaffer L, Larson DA, et al. Subcutaneous anti-inflammatory therapies to prevent burn progression in a swine model of contact burn injury. *Milit Med* 2024; **189**(7-8):1423-31.
59. Ding J, Pan Y, Raj S, et al. Characteristics of serum exosomes after burn Injury and dermal fibroblast regulation by exosomes in vitro. *Cells* 2023; **12**(13):1738.
60. Schulman CI, Namias N, Pizano L, et al. The effect of mesenchymal stem cells improves the healing of burn wounds: a phase 1 dose-escalation clinical trial. *Scars Burns Heal* 2022; **8**:20595131211070783.
61. Kolios G, Paspaliaris V. Mesenchyme stem cell-derived conditioned medium as a potential therapeutic tool in idiopathic pulmonary fibrosis. *Biomed* 2022; **10**(9):2298.
62. Garg S, Garg A, Shukla A, et al. A review on Nano-therapeutic drug delivery carriers for effective wound treatment strategies. *Asian J Pharm Pharmacol* 2018; **4**(2):90-101.
63. Goncalves S, Bas E, Goldstein BJ, et al. Effects of cell-based therapy for treating tympanic membrane perforations in mice. *Otolaryngology–Head Neck Surg* 2016; **154**(6):1106-14.
64. Dong Y, Cui M, Qu J, et al. Conformable hyaluronic acid hydrogel delivers adipose-derived stem cells and promotes regeneration of burn injury. *Acta biomaterialia* 2020; **108**:56-66.
65. Pelizzo G, Avanzini MA, Icaro Cornaglia A, et al. Extracellular vesicles derived from mesenchymal cells: perspective treatment for cutaneous wound healing in pediatrics. *Regen Med* 2018; **13**(4):385-94.
66. He H, Huang W, Zhang S, et al. Microneedle Patch for Transdermal Sequential Delivery of KGF-2 and aFGF to Enhance Burn Wound Therapy. *Small* 2024; **20**(34):2307485.
67. Shimizu Y, Ntege EH, Inoue Y, et al. Optimizing mesenchymal stem cell extracellular vesicles for chronic wound healing: Bioengineering, standardization, and safety. *Reg Ther* 2024; **26**:260-74.

68. Perez-Patiño C, Barranco I, Li J, et al. Cryopreservation differentially alters the proteome of epididymal and ejaculated pig spermatozoa. *Int J Mol Sci* 2019; **20**(7):1791.
69. Rolandsson Enes S, Andersson Sjöland A, Skog I, et al. MSC from fetal and adult lungs possess lung-specific properties compared to bone marrow-derived MSC. *Sci Rep* 2016; **6**(1):29160.
70. Raposio E, Bertozzi N. How to isolate a ready-to-use adipose-derived stem cells pellet for clinical application. *Eur Rev Med Pharmacol Sci* 2017; **21**(18).
71. Deng X, Zhang S, Qing Q, et al. Distinct biological characteristics of mesenchymal stem cells separated from different components of human placenta. *Biochem Biophys Rep* 2024; **39**:101739.
72. Deng S, Zeng Y, Wu L, et al. The regulatory roles of VEGF-Notch signaling pathway on aplastic anemia with kidney deficiency and blood stasis. *J Cellular Biochem* 2019; **120**(2):2078-89.
73. Guo H, Li B, Wang W, et al. Mesenchymal stem cells overexpressing IL-35: a novel immunosuppressive strategy and therapeutic target for inducing transplant tolerance. *Stem Cell Res Ther* 2018; **9**:1-8.
74. Cui Z, Li Y, Qin Y, et al. Polymyxin B-targeted liposomal photosensitizer cures MDR A. baumannii burn infections and accelerates wound healing via M1/M2 macrophage polarization. *J Cont Release* 2024; **366**:297-311.
75. Irfan F, Jameel F, Khan I, et al. Role of quercetin and rutin in enhancing the therapeutic potential of mesenchymal stem cells for cold induced burn wound. *Reg Ther* 2022; **21**:225-38.
76. Shin JM, Gwak JW, Kamarajan P, et al. Biomedical applications of nisin. *J appl Microbiol* 2016; **120**(6):1449-65.
77. Solanki R, Makwana N, Kumar R, et al. Nanomedicines as a cutting-edge solution to combat antimicrobial resistance. *RSC Adv* 2024; **14**(45):33568-86.
78. Zhang H, Mi Z, Wang J, et al. D-histidine combated biofilm formation and enhanced the effect of amikacin against *Pseudomonas aeruginosa* in vitro. *Arch Microbiol* 2024; **206**(4):148.
79. Sanapalli BKR, Yele V, Singh MK, et al. Human beta defensin-2 loaded PLGA nanoparticles impregnated in collagen-chitosan composite scaffold for the management of diabetic wounds. *Biomed Pharmacother* 2023; **161**:114540.
80. Yu J, Zhang Y, Kahkoska AR, et al. Bioresponsive transcutaneous patches. *Curr Opinion Biotechnol* 2017; **48**:28-32.
81. Lin YW, Chen K, Wang J, et al. A proof-of-concept study of the efficacy of systemically administered polymyxins in mouse burn wound infection caused by multidrug-resistant Gram-negative pathogens. *Antimicrob Agents Chemother* 2018; **62**(5):10.1128/aac. 02527-17.
82. Subramani T, Saravanan H, David H, et al. Bioorganic compounds in quorum sensing disruption: strategies, Mechanisms, and future prospects. *Bioorganic Chem* 2025:108192.
83. Hu X, Liu L, Wang Y, et al. Human umbilical cord-derived mesenchymal stem cells alleviate acute lung injury caused by severe burn via secreting TSG-6 and inhibiting inflammatory response. *Stem Cells Int* 2022; **2022**(1):8661689.
84. Wan J, Wang L, Huang Y, et al. Using GRGDSPC peptides to improve re-endothelialization of decellularized pancreatic scaffolds. *Artificial Organs* 2020; **44**(4):E172-E80.
85. Chen L, Gu Q, Li P, et al. Purification and characterization of Plantaricin ZJ316, a novel bacteriocin against *Listeria monocytogenes* from *Lactobacillus plantarum* ZJ316. *J Food Prot* 2018; **81**(12):1929-35.
86. Sawadkar P, Mohanakrishnan J, Rajasekar P, et al. A synergistic relationship between polycaprolactone and natural polymers enhances the physical properties and biological activity of scaffolds. *ACS appl Mat Interfaces* 2020; **12**(12):13587-97.
87. Heredia-Juesas J, Thatcher JE, Lu Y, et al., editors. Non-invasive optical imaging

techniques for burn-injured tissue detection for debridement surgery. 2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC); 2016: IEEE.
88. Vipin C, Kumar GV. Exosome laden sprayable thermo-sensitive polysaccharide-based hydrogel for enhanced burn wound healing. International *J Bio Macromol* 2025; **290**:138712.
89. Esfandiary R, Saeedi P, Saffarian P, et al. Activated mesenchymal stem cells increase drug susceptibility of methicillin-resistant *Staphylococcus* aureus and *Pseudomonas aeruginosa*. *Folia Microbiologica* 2024; **69**(1):145-54.
90. Roque-Borda CA, Primo LMDG, Medina-Alarcón KP, et al. Antimicrobial peptides: a promising alternative to conventional antimicrobials for combating polymicrobial biofilms. *Adv Sci* 2025; **12**(1):2410893.
91. Fan W, Tang Y, Liu Y, et al. ROS-responsive nanoparticles for bioimaging and treating acute lung injury by releasing dexamethasone and improving alveolar macrophage homeostasis. *J Nanobiotechnol* 2024; **22**(1):729.
92. Zhao Y, De Los Santos FG, Wu Z, et al. An ST2-dependent role of bone marrow-derived group 2 innate lymphoid cells in pulmonary fibrosis. *J Path* 2018; **245**(4):399-409.
93. Guo C, Liu X, Qiu K, et al. MALAT1 knockdown inhibits the proliferation, migration, and collagen deposition of human hypertrophic scar fibroblasts via targeting miR-29a-3p/Smurf2 axis. *Clin Cos Inves Dermatology* 2024:1387-404.
94. Murphy KC, Whitehead J, Zhou D, et al. Engineering fibrin hydrogels to promote the wound healing potential of mesenchymal stem cell spheroids. *Acta biomaterialia* 2017; **64**:176-86.
95. Yang Y, Lee EH, Yang Z. Hypoxia-conditioned mesenchymal stem cells in tissue regeneration application. *Tissue Eng* 2022; **28**(5):966-77.
96. Tang XL, Nasr M, Zheng S, et al. Bone marrow and Wharton's jelly mesenchymal stromal cells are ineffective for myocardial repair in an immunodeficient rat model of chronic ischemic cardiomyopathy. *Stem Cell Rev Rep* 2023; **19**(7):2429-46.
97. Gorman E, Millar J, McAuley D, et al. Mesenchymal stromal cells for acute respiratory distress syndrome (ARDS), sepsis, and COVID-19 infection: optimizing the therapeutic potential. *Expert Rev Resp Med* 2021; **15**(3):301-24.
98. George B, Suchithra T, Bhatia N. Burn injury induces elevated inflammatory traffic: the role of NF-κB. *Inflammation Res* 2021; **70**(1):51-65.
99. Tageldin A, Omolo CA, Nyandoro VO, et al. Engineering dynamic covalent bond-based nanosystems for delivery of antimicrobials against bacterial infections. *J Cont Release* 2024; **371**:237-57.
100. Chua JKE, Lim J, Foong LH, et al. Mesenchymal stem cell-derived extracellular vesicles: Progress and remaining hurdles in developing regulatory compliant quality control assays. *Cell Bio Trans Med*, 2022; 17:191-211.