

Beyond Pluripotency Harnessing Organ Specific Stem Cells for Therapeutic Innovation – A Review

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Abstract

Mesenchymal stem cells (MSCs) have transformed the landscape of regenerative medicine since their discovery in the 1970s, evolving from bone marrow–derived progenitors once regarded as universal repair cells to a diverse family of organ-specific variants adapted to distinct tissue microenvironments. This review traces the historical progression of MSC research—from early focus on trilineage differentiation and generalized therapeutic potential in the 1990s–2000s, through the recognition of source-dependent heterogeneity in the 2010s, to the present paradigm emphasizing organ-resident MSCs. Conventional MSC therapies are limited by poor homing efficiency (<1% engraftment), donor variability, and mismatched microenvironmental cues. In contrast, organ-specific MSCs exhibit enhanced paracrine activity, epigenetic priming, and tissue-aligned functionality that improve therapeutic outcomes. Drawing on transcriptomic, proteomic, and preclinical evidence, this review highlights the advantages of cardiac, hepatic, and endometrial MSCs in targeted applications such as myocardial repair, fibrosis attenuation, and reproductive tissue regeneration. Additionally, perinatal-derived MSCs (e.g., umbilical cord and placenta) demonstrate superior proliferative capacity and immunomodulatory potential compared to adult sources, making them promising candidates for allogeneic therapies. Despite these advances, challenges in standardization, potency assessment, and clinical translation persist.

This synthesis underscores the growing need for precise source–disease matching to optimize MSC efficacy and safety, marking a shift toward personalized regenerative medicine. Organ-specific MSCs thus represent a major step forward in achieving more targeted, efficient, and clinically translatable cell-based therapies for inflammatory, degenerative, and organ-specific disorders.

Keywords: Mesenchymal Stem Cells, Organ-Specific MSCs, Regenerative Medicine, Therapeutic Heterogeneity, Perinatal MSCs, Precision Therapy

1. Introduction

Mesenchymal Stem Cells (MSCs), also known as mesenchymal stromal cells, are a population of multipotent progenitor cells capable of self-renewal and differentiation into multiple mesodermal lineages such as osteoblasts (bone-forming cells), chondrocytes (cartilage cells), and adipocytes (fat cells) [1]. First described in the 1970s by Friedenstein et al. as colony-forming fibroblast-like cells in bone marrow, these cells were later termed “mesenchymal stem cells” by Dr. Arnold Caplan in 1991, highlighting their multilineage differentiation capacity [2].

MSCs have been isolated from a wide range of tissues beyond bone marrow, including **adipose tissue, umbilical cord, placenta, dental pulp, synovial membrane, amniotic fluid, endometrium, and menstrual blood**, suggesting their ubiquitous presence in the perivascular niche of most vascularized tissues [3, 4]. This broad tissue distribution supports the theory that MSCs act as tissue-resident “sentinel” cells that respond to injury by modulating inflammation and facilitating tissue repair [5].

To establish a standard framework for MSC identification, the **International Society for Cellular Therapy (ISCT)** proposed minimal criteria in 2006 [6], which remain widely accepted:

1. **Plastic adherence** when cultured under standard conditions;
2. Expression of surface antigens **CD73, CD90, and CD105**, and **lack of expression** of hematopoietic markers such as **CD45, CD34, CD14 or CD11b, CD79a or CD19, and HLA-DR**;
3. **Tri-lineage differentiation potential** in vitro into **osteoblasts, adipocytes, and chondrocytes**.

While their early therapeutic potential was thought to stem from their ability to differentiate into various cell types, it is now widely accepted that the **primary therapeutic benefits of MSCs** arise from their **paracrine activity**. MSCs secrete a wide array of bioactive molecules—such as growth factors, cytokines, chemokines, and extracellular vesicles—that promote angiogenesis, reduce fibrosis, suppress immune activation, and recruit endogenous repair mechanisms [7, 8].

Moreover, MSCs possess unique **immunomodulatory properties**, which allow them to evade immune detection, modulate T cells, B cells, NK cells, and dendritic cells, and thus make them ideal candidates for **allogeneic cell therapy** applications. These immunomodulatory features have been widely explored in clinical trials targeting autoimmune, inflammatory, and degenerative diseases [3].

Despite their therapeutic promise, MSCs are **not a homogeneous population**. MSCs derived from different tissues demonstrate significant variability in **growth kinetics, surface marker expression, cytokine secretion profiles, differentiation potential, and therapeutic efficacy**.

Challenges of Conventional MSC based therapies

1. **Homing and Engraftment Limitations** – Following systemic infusion, less than 1% of MSCs typically reach the injured organ, with most cells becoming trapped in the lungs [9]. Organ-specific MSCs, by contrast, demonstrate enhanced homing and survival within their native tissue microenvironments.
2. **Heterogeneity and Lack of Standardization** – MSC populations are heterogeneous, with significant inter-donor and inter-tissue variability in potency and function [10]. Organ-specific MSCs may mitigate this by providing functionally specialized populations.

3. **Reduced Therapeutic Specificity** – General MSCs exert broad immunomodulatory and trophic effects, but may not fully recapitulate the specialized regenerative and signaling functions required for certain organs (e.g., cardiac MSCs show superior efficacy in myocardial repair compared to BM-MSCs) [11].
4. **Microenvironmental Mismatch** – MSCs derived from non-resident sources may struggle to adapt to the biochemical and mechanical cues of injured tissue niches, leading to suboptimal integration and therapeutic benefit [8].
5. **Clinical Outcome Variability** – Clinical trial outcomes with general MSCs have been inconsistent, with some reporting strong efficacy while others show modest or no benefit, partly due to the mismatch between cell origin and disease context [12].

These limitations have catalyzed a paradigm shift toward **organ-specific MSCs**, where tissue-resident MSCs are increasingly recognized as being inherently adapted to their native microenvironments, potentially offering superior efficacy, survival, and disease-specific therapeutic outcomes.

2. Historical Evolution of MSCs to Organ-Specific Paradigm

2.1 The Discovery Phase of Mesenchymal Stem Cells (1991–2000s)

Dr. Arnold Caplan Coined the Term “Mesenchymal Stem Cells” (1991)

In 1991, **Dr. Arnold I. Caplan** formally introduced the term *Mesenchymal Stem Cells* to describe a population of **fibroblast-like, plastic-adherent stromal cells** capable of self-renewal and multilineage differentiation [2]. Building on earlier work by **Friedenstein et al. (1970s–1980s)**, who identified colony-forming unit–fibroblasts (CFU-Fs) in bone marrow, Caplan conceptualized MSCs as **progenitor cells** with broad regenerative potential. His vision positioned MSCs as a cornerstone for future **cell-based therapies** in regenerative medicine [13].

Early Studies Emphasized Trilineage Differentiation (Bone, Cartilage, Fat)

Initial experimental studies established **trilineage differentiation**—into **osteoblasts, chondrocytes, and adipocytes**—as the hallmark of MSC identity. **Pittenger et al. (1999)** provided definitive evidence by demonstrating that clonally expanded human bone marrow-derived MSCs could differentiate into these three mesodermal lineages under defined in vitro conditions. This trilineage capacity became a **functional gold standard** in MSC research, forming the basis for later **International Society for Cellular Therapy (ISCT)** criteria [1].

Bone Marrow Was the Dominant Source

During the 1990s and early 2000s, **bone marrow** was considered the **primary and most reliable source** of MSCs. Bone marrow aspirates yielded cells that were:

- Easy to isolate via **density-gradient centrifugation**
- Amenable to **in vitro expansion**
- Well-characterized in terms of phenotype and differentiation potential

Bone marrow MSCs were extensively studied in **orthopedic applications** such as bone defect repair, cartilage regeneration, and treatment of osteonecrosis. Their dominance as the gold standard was partly due to historical precedence (Friedenstein’s work) and the relative scarcity of data on MSCs from other tissues at the time.

MSCs Assumed to Be “Universal” Regenerative Cells

In the early stages of MSC research, it was widely believed that MSCs possessed a **“universal” regenerative capacity**, able to engraft and repair tissues regardless of their origin. This assumption was

based on early preclinical studies showing that **systemically administered bone marrow MSCs** could migrate to various injury sites and contribute to tissue repair via **differentiation** and **paracrine signalling** [14].

This belief drove an initial “one-size-fits-all” approach, where MSCs from a single source—most often bone marrow—were tested for a wide array of unrelated conditions, from myocardial infarction to neurodegenerative disease. However, subsequent research revealed that **tissue-specific microenvironments** influence MSC behavior, leading to the emerging concept of **organ-specific MSCs** with niche-adapted properties [15, 16].

2.2 The Expansion Phase (2000s–2010s)

Following the initial discovery and characterization of mesenchymal stem cells (MSCs) in the 1990s, the first decade of the 21st century marked a period of **rapid expansion in MSC biology**, both in terms of **tissue sources** and **therapeutic applications**.

Key alternative sources identified during this phase included:

- **Adipose Tissue** — Zuk et al. (2001) described adipose-derived stem cells (AD-MSCs) with multilineage potential, easily harvested in high yields via liposuction [17].
- **Umbilical Cord Blood & Wharton’s Jelly** — Romanov et al. (2003) reported isolation of UC-MSCs with robust proliferation and lower immunogenicity [18].
- **Placenta & Amniotic Membrane** — In ’t Anker et al. (2004) demonstrated placental MSCs with both mesodermal and ectodermal differentiation potential [19].
- **Dental Pulp** — Gronthos et al. (2000) isolated dental pulp stem cells (DPSCs) capable of forming dentin-pulp-like complexes [20].
- **Menstrual Blood** — Meng et al. (2007) identified menstrual blood-derived MSCs (MenSCs) with exceptional proliferation and angiogenic factor secretion, representing a non-invasive, repeatable source [21].

The discovery of these varied sources catalyzed the perception of MSCs as **ubiquitous, perivascular progenitors** [22].

Realization of Donor-Site Variability in Therapeutic Performance

As comparative studies emerged, researchers began to notice **functional heterogeneity** among MSCs from different tissues. Although all MSCs met the ISCT’s minimal criteria, they exhibited **source-dependent differences** in:

- **Proliferation rate** (e.g., UC-MSCs > BM-MSCs)
- **Immunomodulatory potency** (e.g., AD-MSCs often higher IL-10 production)
- **Lineage bias** (e.g., synovial MSCs more chondrogenic; dental pulp MSCs more neurogenic)

For example, Strioga et al. (2012) emphasized that MSCs from perinatal sources often displayed superior proliferative and immunosuppressive properties compared to adult tissue-derived MSCs. These findings challenged the earlier assumption of MSCs as “universal” repair cells and underscored the importance of **donor site biology** in determining therapeutic outcomes [23].

Start of Exploring Niche-Specific Properties

By the late 2000s, the concept of **niche-specific MSC properties** began to take shape. Evidence suggested that MSCs retain epigenetic and functional “memory” of their tissue of origin, optimizing them for **organ-specific repair**.

- **Endometrial MSCs (eMSCs)** — Gargett et al. (2009) showed eMSCs have unique angiogenic and reproductive-regenerative properties, making them particularly suited for conditions like Asherman’s

syndrome and endometrial atrophy [24].

- **Synovial MSCs** — Sakaguchi et al. (2005) demonstrated superior chondrogenic capacity compared to BM-MSCs, highlighting their potential in osteoarthritis [25].
- **Cardiac MSCs** — Chong et al. (2011) identified cardiac-resident MSC-like cells with enhanced cardioprotective paracrine secretion [26].

This **shift in research perspective** laid the groundwork for the modern idea of **organ-specific MSC therapy**, where the source is matched to the disease niche to improve efficacy and integration.

2.3 The Paradigm Shift (2010s–Today)

The past decade has marked a **fundamental shift** in mesenchymal stem cell (MSC) research — from viewing MSCs as **universal regenerative cells** to recognizing them as a **heterogeneous family of organ-specific progenitors** with niche-adapted properties. This evolution has been driven by **advances in omics technologies**, better understanding of **tissue microenvironments**, and accumulating clinical evidence favoring **source–disease matching**.

Transcriptomics and Proteomics Reveal Heterogeneity

High-throughput **transcriptomic**, **proteomic**, and **epigenetic** analyses have demonstrated that MSCs from different tissues are not functionally identical. Instead, they display:

- **Distinct gene expression profiles** related to lineage bias and immunomodulatory activity
- **Source-dependent secretomes**, influencing angiogenesis, neuroprotection, or anti-fibrotic effects
- Epigenetic “memory” of their tissue of origin, affecting differentiation potential and niche adaptation

For example, **Pevsner-Fischer et al. (2011)** showed that BM-MSCs express higher osteogenic genes, whereas adipose MSCs are enriched in adipogenesis-related transcripts [27]. Similarly, **Zhou et al. (2019)** reported proteomic signatures unique to endometrial MSCs, correlating with their superior angiogenic capacity [28].

Discovery of Organ-Resident MSCs

Evidence from lineage-tracing and perivascular niche studies revealed that MSC-like progenitors exist in **virtually every vascularized tissue**, functioning in local tissue maintenance and repair. These **organ-resident MSCs** are phenotypically similar to conventional MSCs but show **enhanced functional specialization**:

- **Cardiac MSCs** — Identified in epicardium and perivascular niches; secrete higher levels of cardioprotective cytokines (VEGF, HGF, IGF-1) and promote angiogenesis and anti-apoptotic pathways in ischemic myocardium [26].
- **Hepatic MSCs** — Found in perivascular spaces and portal areas; exhibit strong anti-fibrotic activity and hepatocyte-supportive functions via HGF and MMP secretion [29].
- **Pulmonary MSCs** — Located in peribronchiolar and alveolar niches; enhance epithelial repair and reduce fibrosis in lung injury models [30].
- **Renal MSCs** — Reside in perivascular and interstitial compartments; demonstrate superior tubular epithelial repair and modulation of renal inflammation [31].

Functional Advantages in Organ-Matched Therapies

Preclinical and early clinical trials increasingly support the concept that **matching MSC source to target organ** improves therapeutic efficacy:

- **Cardiac MSCs in Heart Failure** — In models of myocardial infarction, cardiac MSCs achieved greater improvement in left ventricular ejection fraction and scar reduction compared to BM-MSCs,

likely due to better survival in the ischemic myocardium and superior secretion of cardioprotective factors [26].

- **Endometrial MSCs in Asherman's Syndrome** — eMSCs have shown remarkable regenerative effects in restoring endometrial thickness, improving vascularization, and enhancing fertility outcomes in patients with intrauterine adhesions [32].
- **Pulmonary MSCs in Lung Injury** — In ARDS models, lung-derived MSCs exhibit superior alveolar epithelial repair compared to BM-MSCs, correlating with their native adaptation to the lung microenvironment [30].

3. Standard Sources of Mesenchymal Stem Cells (MSCs)

Mesenchymal stem cells (MSCs) are distributed across both adult and perinatal tissues, and the **tissue of origin profoundly shapes their biological and therapeutic properties**. Although all MSCs fulfill the minimal ISCT criteria—trilineage differentiation (osteogenic, chondrogenic, adipogenic), plastic adherence, and expression of CD73/CD90/CD105—they diverge considerably in proliferation dynamics, immunomodulatory potential, epigenetic signatures, and paracrine secretome [33, 34].

This diversity has given rise to two broad categories: **adult-derived MSCs**, which are more lineage-committed and often constrained by donor age and invasive harvesting, and **perinatal-derived MSCs**, which are more primitive, proliferative, and immune evasive. Understanding these differences is crucial for aligning MSC sources with **organ-specific therapeutic applications**.

Adult-Derived MSCs are the most established and historically characterized sources, with bone marrow MSCs representing the original prototype [1, 13]. They are well suited for musculoskeletal repair and hematopoietic support but face challenges such as:

- Declining yield and proliferative capacity with donor age [35].
- Invasive harvesting procedures (bone marrow aspiration, liposuction).
- Greater heterogeneity across donors.

Perinatal-Derived MSCs, on the other hand, represent a younger and more primitive population, obtained from tissues normally discarded at birth (umbilical cord, Wharton's jelly, placenta, amnion). These cells offer several inherent advantages:

- **Higher proliferative capacity** and longer telomeres, allowing for more extensive expansion in culture [33].
- **Lower immunogenicity** due to reduced HLA-DR and co-stimulatory molecule expression, making them attractive for allogeneic “off-the-shelf” therapies [36].
- **Ethically uncomplicated procurement**, as tissues are otherwise medical waste and collection is non-invasive [37].
- **Enhanced immunomodulatory potential**, reflecting their natural role in fetomaternal tolerance during pregnancy [38].

As a result, perinatal MSCs are increasingly favored in clinical trials for systemic diseases such as autoimmune disorders, neurological injury, and liver failure, whereas adult-derived MSCs remain the reference standard in orthopedic, dental, and reconstructive applications.

3.1. Bone Marrow-Derived MSCs (BM-MSCs)

Bone marrow was the first identified source of MSCs, discovered as colony-forming fibroblast-like cells [13] and later characterized for their multilineage potential [1, 2]. BM-MSCs exhibit strong osteogenic and chondrogenic differentiation and secrete trophic factors such as VEGF, TGF- β , and IL-10. They also

display immunosuppressive effects through IDO and prostaglandin E2, making them useful in inflammatory disorders and graft-versus-host disease (GVHD). However, their harvest is invasive, and yield declines with donor age [35].

Why: Despite limitations, their robust osteogenic and chondrogenic bias makes them invaluable for musculoskeletal applications where strong differentiation is paramount.

3.2. Adipose Tissue-Derived MSCs (AD-MSCs)

Adipose tissue, accessed via liposuction, provides a plentiful and minimally invasive source of MSCs. Zuk et al. (2001) identified MSC-like cells in the stromal vascular fraction (SVF) [17]. AD-MSCs secrete high levels of IL-6, HGF, VEGF, and TSG-6, supporting immunomodulation and angiogenesis. They proliferate faster than BM-MSCs and retain plasticity across donor ages, though they display weaker osteogenic potential [39].

Why: Their accessibility and superior angiogenic/proliferative profile position them as a leading candidate for therapies requiring vascularization and tissue augmentation.

3.3. Umbilical Cord-Derived MSCs (UC-MSCs) / Wharton's Jelly

UC-MSCs are abundant, non-invasively sourced, and highly proliferative, with fetal-like features including telomerase activity and low immunogenicity [36]. They expand efficiently under GMP conditions and are ideal for allogeneic use. UC-MSCs have been tested in trials for autoimmune disease, diabetes, liver failure, COVID-19 ARDS, and neurological injury [40].

Why: Their unparalleled immunomodulatory and proliferative capacity, combined with ethical sourcing, solidifies their role as a versatile “off-the-shelf” option for systemic inflammatory and immune disorders.

3.4. Placenta-Derived MSCs (P-MSCs)

Placental compartments (amnion, chorion, decidua, villi) harbor MSCs that support fetomaternal tolerance and secrete IL-10, PGE2, and TGF- β 1 [37, 38]. These cells are non-tumorigenic, ethically acceptable, and abundant at birth. They demonstrate plasticity and strong immunosuppressive profiles, with applications in autoimmune disease, fibrosis, and inflammatory disorders.

Why: As a rich source of immune-privileged cells with strong anti-inflammatory properties, P-MSCs are particularly suited for conditions demanding potent immunosuppression and tissue repair, especially in neonatal contexts.

4. Dental Pulp Stem Cells (DPSCs)

DPSCs are isolated from adult dental pulp or exfoliated deciduous teeth (SHED) [41, 42]. They express neural crest markers, show strong neurogenic and angiogenic differentiation, and proliferate rapidly. Their procurement is minimally invasive, enabling banking for pediatric and adult therapies. DPSCs demonstrate potential for neuronal, glial, and dentin regeneration, as well as ischemic tissue repair.

Why: With their innate neurogenic and angiogenic capabilities, DPSCs offer a unique therapeutic avenue for neurological repair and regeneration, leveraging their facile procurement.

Table 1. Comparative Characteristics of Major Mesenchymal Stem Cell (MSC) Sources Highlighting Procurement Ease, Proliferation, Immunogenicity, Secretory Profiles, Therapeutic Potentials, and Limitations.

MSC Source	Ease of Procurement	Proliferation Rate	Immunogenicity	Key Secreted Factors	Primary Therapeutic Strengths	Limitations
BM-MSCs (Bone Marrow)	Invasive aspiration; lower yield	Moderate; declines with donor age	Low (but reduced with age)	VEGF, TGF- β , IL-10, IDO	Osteogenesis, chondrogenesis, GVHD treatment	Painful harvest, aging reduces yield and function
AD-MSCs (Adipose Tissue)	Minimally invasive (liposuction); abundant	High; maintained with age	Low to moderate	IL-6, HGF, VEGF, TSG-6	Angiogenesis, wound healing, soft tissue repair	Lower osteogenic potential; variability with BMI and depot
UC-MSCs (Umbilical Cord/Wharton's Jelly)	Non-invasive; ethically acceptable; plentiful	Very high; primitive phenotype	Very low (HLA-DR negative)	HGF, VEGF, IL-10, PGE2	Systemic immunomodulation, neurological repair, metabolic disorders	Limited osteogenic bias; perinatal tissue availability
P-MSCs (Placenta)	Abundant, collected at birth; ethically acceptable	High; primitive phenotype	Very low; immune privileged	IL-10, TGF- β 1, PGE2	Autoimmune diseases, neonatal therapies, anti-fibrotic effects	Heterogeneity by placental region; less standardization
DPSCs (Dental Pulp/SHED)	Minimally invasive; deciduous and adult teeth	Moderate to high	Low	NGF, BDNF, VEGF, FGF	Neurogenesis, angiogenesis, craniofacial regeneration	Limited availability; not standardized for large-scale use

4. Core Therapeutic Mechanisms of Mesenchymal Stem Cells (MSCs)

Mesenchymal stem cells (MSCs) exert their therapeutic influence through three interrelated mechanisms: **(1) multilineage differentiation, (2) immunomodulation, and (3) paracrine-mediated tissue regeneration.** While early applications emphasized their differentiation capacity, accumulating evidence positions MSCs primarily as “medicinal signaling cells” [5], dynamically interacting with immune and stromal compartments to orchestrate repair and regeneration [43].

4.1. Differentiation into Specialized Lineages

MSCs are multipotent progenitors with the ability to differentiate into osteoblasts, chondrocytes, and adipocytes, with additional reports of transdifferentiation into ectodermal (neurons) and endodermal (hepatocytes) phenotypes under defined conditions [13, 44].

Although their engraftment and long-term persistence in vivo remain limited, direct differentiation remains relevant in **orthopedic, dental, and reconstructive applications**. For example, BM-MSCs transplanted into osteonecrotic femoral heads differentiate into osteoblasts, contributing directly to bone regeneration [45].

Importantly, **organ-derived MSCs often show lineage bias toward their tissue of origin**. Myocardial MSCs preferentially support cardiomyogenesis [46], while endometrial MSCs exhibit a stronger propensity for smooth muscle and stromal differentiation [47]. This **epigenetic memory** reinforces the emerging paradigm of **organ-specific MSCs**.

4.2. Immunomodulation and Anti-Inflammatory Action

MSCs exhibit profound immunomodulatory properties, functioning through both direct cell–cell interactions and the release of soluble mediators. They suppress effector T-cell, B-cell, NK-cell, and dendritic-cell activity, while enhancing regulatory T-cell expansion and driving macrophage polarization toward an anti-inflammatory M2 phenotype [7, 48, 49].

Critical mediators include:

- **Indoleamine 2,3-dioxygenase (IDO)**
- **Prostaglandin E2 (PGE2)**
- **Transforming growth factor- β (TGF- β)**
- **Interleukin-10 (IL-10)**
- **Nitric oxide (NO)** (particularly in rodents)

These immunoregulatory features underlie the success of MSCs in autoimmune and inflammatory disorders. Their **low MHC class I expression and lack of MHC class II/CD80/CD86** further confer hypoimmunogenicity, enabling allogeneic and even off-the-shelf applications with reduced rejection risk [9].

Organ-specific MSCs may further refine this property: e.g., **hepatic MSCs preferentially modulate Kupffer cells**, while **pulmonary MSCs more effectively suppress neutrophilic inflammation** due to niche adaptation.

4.3. Paracrine Signaling and Regenerative Support

Paracrine activity is increasingly regarded as the **principal driver** of MSC-mediated repair. The MSC secretome includes **growth factors, cytokines, extracellular vesicles, and microRNAs**, which collectively:

- Stimulate angiogenesis and vascular remodeling (via VEGF, HGF, FGF2)
- Promote survival and proliferation of resident progenitor cells
- Suppress oxidative stress and apoptosis
- Regulate extracellular matrix turnover and fibrosis

In addition, MSCs can **transfer functional mitochondria** via tunneling nanotubes or extracellular vesicles, restoring cellular bioenergetics and survival in models of ischemic injury and inflammation [50].

Organ-specific MSCs appear to **tailor their paracrine output** toward their native environment. For instance:

- **Cardiac MSCs** secrete elevated SDF-1, VEGF, and IGF-1, boosting cardiomyocyte survival.

- **Liver MSCs** preferentially release HGF and IL-6, enhancing hepatocyte proliferation and antifibrotic repair.
- **Neural MSCs/DPSCs** secrete BDNF, NGF, and GDNF, supporting neuroprotection and synaptic plasticity.

This suggests that **organ-specific MSCs may function as precision “paracrine modulators”**, fine-tuning repair to the demands of their tissue microenvironment.

4.4. Organ-Specific Amplification of MSC Functions

While all MSCs share broad therapeutic mechanisms—such as immunomodulation, trophic support, angiogenesis, and extracellular matrix (ECM) remodeling—**organ-specific MSCs may execute these functions with greater potency or precision in their native environment**. This enhanced performance stems from their **epigenetic imprinting** and **adaptation to local signaling cues**, which influence their transcriptional and secretory profiles.

- **Cardiac MSCs:** Compared to AD-MSCs, cardiac-resident MSCs often upregulate **cardioprotective and pro-angiogenic factors** such as **VEGF, HGF, and IGF-1**, enabling them to more effectively limit cardiomyocyte apoptosis and promote neovascularization in ischemic tissue. Their secretome also shows higher levels of **SDF-1**, which enhances cardiomyocyte recruitment and survival [51, 52].
- **Liver MSCs:** Hepatic MSCs display elevated expression of **hepatocyte growth factor (HGF)** and **IL-6**, directly supporting hepatocyte proliferation, antifibrotic remodeling, and liver regeneration. Their immunomodulatory profile tends to favor **Kupffer cell and Treg modulation**, making them uniquely suited for hepatic inflammatory and fibrotic disorders [53, 54].
- **Neural MSCs:** MSCs from brain or dental pulp sources often secrete higher levels of **BDNF, NGF, and GDNF**, supporting neuroprotection and axonal repair. This neurotrophic enrichment makes them more potent in neurodegenerative or spinal cord injury contexts compared to BM-MSCs [55].
- **Pulmonary MSCs:** Lung-resident MSCs adapt to the respiratory microenvironment by secreting elevated **FGF-10** and anti-fibrotic mediators, facilitating epithelial repair and dampening alveolar inflammation more effectively than systemic MSC sources [56, 57].
- **Renal MSCs:** Kidney-derived MSCs express higher levels of **CXCR4 and VEGF**, enhancing homing to ischemic renal tissue and promoting microvascular stabilization, which is less pronounced in UC-MSCs or BM-MSCs [58, 59].

5. Application of Organ-Specific MSCs in Disease Models and Clinical Translation

5.1. Clinical Applications of MSCs

Mesenchymal Stem Cells (MSCs) have emerged as powerful tools in regenerative and reparative medicine due to their multipotency, paracrine effects, and immunomodulatory potential. Since the initial discovery of bone marrow-derived MSCs, their use has expanded into numerous therapeutic domains. As of 2024, over **1,200 MSC-based clinical trials** are registered on ClinicalTrials.gov, targeting indications ranging from inflammatory and autoimmune disorders to cardiovascular, orthopedic, hepatic, and neurological diseases [3, 12].

Current Clinical Indications for MSC Therapy

5.1.1. Graft-versus-Host Disease (GvHD)

Graft-versus-Host Disease (GvHD) is a potentially life-threatening complication that can occur after **allogeneic hematopoietic stem cell transplantation (HSCT)**, where donor immune cells attack the recipient’s tissues. It is most commonly seen in **bone marrow and peripheral blood transplants** and

affects organs like the **skin, liver, and gastrointestinal tract**. While corticosteroids are the first-line treatment, **up to 50% of patients develop steroid-refractory GvHD (SR-GvHD)**, which is associated with high mortality and limited therapeutic options [60].

The factors create a local immunosuppressive microenvironment that helps **reduce tissue damage** while preserving the beneficial graft-versus-leukemia (GvL) effect [9, 61].

Clinical Evidence and Trials

The **pioneering work by Le Blanc et al. (2004, 2008)** demonstrated that MSCs could be safely infused into patients with **steroid-resistant acute GvHD**, resulting in **complete or partial responses in a majority of treated patients**. These studies laid the foundation for subsequent large-scale trials and commercial product development [62, 61]

One of the most prominent MSC products, **Remestemcel-L (Prochymal®)**—an **off-the-shelf, allogeneic bone marrow-derived MSC therapy** developed by Mesoblast Ltd.—has been evaluated in multiple international trials:

- In a **Phase III randomized, placebo-controlled trial**, Remestemcel-L showed **notable improvements in survival and response rate** in children with steroid-refractory acute GvHD, particularly for gastrointestinal involvement [63].
- Although the trial narrowly missed its primary endpoint in adults, secondary analyses showed **higher overall response and durability**, especially in **pediatric cohorts**.
- As a result, Remestemcel-L received **conditional approval in Canada and New Zealand** for the treatment of **pediatric SR-GvHD**, making it **one of the first MSC products to reach market authorization**.

A **10-year retrospective analysis** further confirmed the **long-term safety and efficacy** of MSCs in SR-GvHD, showing favorable outcomes with minimal adverse events and no tumorigenicity [64].

Key Advantages of MSC Therapy in GvHD

- **Allogeneic Use Feasibility:** Due to low expression of MHC-II and costimulatory molecules, MSCs are immune evasive, allowing third-party transplantation.
- **Safety:** Clinical trials consistently show **low adverse event rates**, even with repeated dosing.
- **Rapid Action:** Many patients demonstrate **clinical improvement within a few infusions**, especially in GI and skin GvHD.

Challenges and Considerations

- **Variable Response:** Not all patients respond equally; underlying inflammation, MSC source, and timing of infusion may influence outcomes.
- **Manufacturing Consistency:** Batch-to-batch variation remains a concern, necessitating rigorous potency and identity assays.

5.1.2. Orthopaedic and Musculoskeletal System

Musculoskeletal disorders, including osteoarthritis (OA), cartilage defects, and bone injuries, are among the most common targets for MSC-based therapies. Conventional MSCs—primarily **BM-MSCs** and **AD-MSCs**—have shown therapeutic promise through their osteogenic and chondrogenic differentiation potential, combined with paracrine-mediated anti-inflammatory and trophic effects [65].

General MSC Applications

- **BM-MSCs:** Considered the “gold standard” for musculoskeletal repair due to their strong osteogenic bias. They are widely used in bone regeneration, fracture healing, and spinal fusion. However, BM aspiration is invasive, yields decline with donor age, and expansion potential is limited [35].

- **AD-MSCs:** Readily available in large quantities via liposuction, with robust proliferation and angiogenic potential. They are effective for soft-tissue repair and OA management but exhibit relatively weaker chondrogenic differentiation compared to BM-MSCs [39].

Synovial Membrane-Derived MSCs (SM-MSCs): Organ-Specific Advantage

The synovial membrane of joints is a rich and accessible source of MSCs, particularly relevant for **cartilage and joint repair**. SM-MSCs have attracted attention due to their **superior chondrogenic differentiation capacity** compared with BM-MSCs and AD-MSCs [25].

Key Characteristics of SM-MSCs

- **Source & Accessibility:** Obtained via arthroscopic biopsy, relatively low morbidity compared to BM aspiration.
- **Proliferation:** High proliferative potential, enabling efficient expansion in vitro.
- **Chondrogenesis:** Demonstrated **higher expression of SOX9, COL2A1, and aggrecan** during differentiation compared to BM-MSCs, suggesting intrinsic adaptation to the joint environment [66].
- **Immunomodulation:** Strong anti-inflammatory properties via IL-10 and TSG-6 secretion, supporting joint homeostasis and reducing OA progression.
- **Tissue Adaptation:** Reside naturally in the joint niche, making them inherently responsive to cartilage and synovial injury signals.

Comparative Evidence: SM-MSCs vs. BM-MSCs and AD-MSCs

- **Chondrogenic Potential:** SM-MSCs > BM-MSCs > AD-MSCs [25].
- **Osteogenesis:** BM-MSCs remain superior for bone formation, while SM-MSCs are better suited for cartilage repair.
- **Clinical Utility:** SM-MSCs demonstrate **enhanced cartilage regeneration and integration with native cartilage**, making them ideal for OA and focal cartilage defects.

Preclinical and Clinical Insights

- **Animal Studies:** SM-MSCs have shown superior outcomes in rabbit and goat models of cartilage repair compared to BM-MSCs, with improved cartilage thickness, matrix production, and biomechanical strength [67].
- **Clinical Trials:**
 - Early-phase clinical studies using intra-articular injections of SM-MSCs in OA patients report **pain reduction, improved joint function, and MRI evidence of cartilage regeneration** [68].
 - Autologous SM-MSC implantation for focal cartilage defects demonstrated **long-lasting hyaline-like cartilage repair**, superior to microfracture techniques [69].

Emerging Role of SM-MSCs in Orthopaedic Therapy

SM-MSCs exemplify how **organ-specific MSCs outperform conventional MSCs** by leveraging **epigenetic memory and niche adaptation**. Their high chondrogenic propensity makes them uniquely suited for **cartilage repair in OA, meniscal injuries, and focal defects**, where BM-MSCs or AD-MSCs may yield fibrocartilaginous rather than hyaline-like repair.

5.1.3. Cardiovascular System

Cardiovascular disease (CVD) remains the leading global cause of morbidity and mortality, with myocardial infarction (MI) and ischemic cardiomyopathy posing major therapeutic challenges. Conventional pharmacological and surgical interventions often fail to restore lost cardiomyocytes or reverse fibrosis, creating a strong rationale for MSC-based regenerative approaches.

General MSC Applications

BM-MSCs and AD-MSCs have been widely studied in preclinical and clinical settings for cardiac repair. Their benefits include **angiogenesis promotion, anti-apoptotic effects, modulation of post-MI inflammation, and improved left ventricular function** [46, 70]. Despite these effects, their **low cardiac engraftment rate, poor homing, and modest long-term benefits** have limited clinical impact.

Cardiac-Specific MSC Approaches

To address these challenges, researchers have focused on **organ-specific strategies** tailored to the heart:

1. Cardiac-Specific MSCs (CSCs)

- Derived from cardiac tissue, these cells demonstrate a **strong inherent cardiomyogenic and angiogenic bias**.
- They secrete higher levels of **VEGF, IGF-1, and SDF-1**, supporting **endogenous cardiomyocyte survival and neovascularization**.
- Preclinical models demonstrate superior **reduction in infarct size and improvement in contractility** compared to BM-MSCs [71].

2. Cardiosphere-Derived Cells (CDCs)

- Isolated from myocardial biopsies and cultured as "cardiospheres."
- Exhibit **enhanced regenerative signaling**, including **exosome-mediated cardioprotection and angiogenesis**.
- In the **CADUCEUS trial**, CDCs were shown to **reduce scar size and increase viable myocardium**, though functional improvements were modest [72].

3. MSC Preconditioning and Genetic Engineering for Cardiac Repair

- Hypoxia-preconditioned MSCs upregulate **HIF-1 α** and **VEGF**, enhancing angiogenesis and survival in ischemic tissue.
- Genetically modified MSCs expressing **Akt, SDF-1, or connexin-43** demonstrate improved **cardiomyocyte coupling, engraftment, and paracrine potency**.

Clinical Trials of MSCs in Cardiac Repair

Several landmark clinical trials have evaluated MSC therapy in ischemic cardiomyopathy and heart failure:

- **POSEIDON Trial (Hare et al., 2012)**: Compared autologous vs. allogeneic BM-MSCs in ischemic cardiomyopathy. Both were safe, improved quality of life, and reduced scar size, with allogeneic MSCs being equally effective [70].
- **TAC-HFT Trial (Heldman et al., 2014)**: Autologous BM-MSCs and BM mononuclear cells were tested in ischemic cardiomyopathy. MSCs improved functional capacity and reduced infarct size [73].
- **MSC-HF Trial (Bartunek et al., 2017)**: Intramyocardial injection of BM-MSCs in chronic heart failure patients improved left ventricular ejection fraction (LVEF) and reduced adverse remodeling [74].

Emerging Role of Cardiac-Specific MSCs

While traditional BM- and AD-MSCs show safety and modest efficacy, **cardiac-specific MSC approaches (CSCs, CDCs, preconditioned MSCs)** may overcome limitations by providing **tissue-adapted paracrine signaling, better myocardial retention, and enhanced reparative effects**. Early-phase clinical findings suggest that **scar reduction and angiogenesis** are achievable, though functional recovery remains a key challenge.

4. Autoimmune and Inflammatory Conditions

Mesenchymal stem cells (MSCs) have emerged as promising therapeutic agents for a wide range of **autoimmune and inflammatory disorders**, due to their potent **immunomodulatory and anti-inflammatory properties**. Unlike conventional immunosuppressive drugs that carry the risk of systemic immune suppression, MSCs offer **targeted immune regulation** with reduced side effects and long-term immunological tolerance.

MSCs exert their effects through:

- Suppression of **effector T cells (Th1, Th17)**
- Induction of **regulatory T cells (Tregs)**
- Inhibition of **B cell proliferation and antibody production**
- Polarization of **macrophages** from pro-inflammatory M1 to anti-inflammatory M2 phenotype
- Modulation of **dendritic cell maturation and antigen presentation**

A. Systemic Lupus Erythematosus (SLE)

SLE is a chronic multisystem autoimmune disease characterized by immune complex deposition, widespread inflammation, and organ damage. **Bone marrow-derived MSCs (BM-MSCs)** and **umbilical cord-derived MSCs (UC-MSCs)** have shown efficacy in **refractory SLE** by suppressing aberrant immune responses and restoring immune homeostasis.

- **Wang et al., 2013** conducted a clinical trial showing that **UC-MSC infusion** led to reduced disease activity (measured by SLEDAI score), improved renal function, and decreased autoantibody levels in SLE patients [58].
- The effect was associated with increased **Treg frequency** and decreased **Th17 activity**.

B. Multiple Sclerosis (MS)

MS is an autoimmune demyelinating disorder of the central nervous system. **MSCs**, particularly **BM-MSCs**, have shown promise in experimental autoimmune encephalomyelitis (EAE) models and early clinical trials.

- MSCs reduce **neuroinflammation**, **preserve axons**, and promote **oligodendrocyte differentiation**, aiding **remyelination** [76].
- In a phase I/II study, **BM-MSC infusion** in MS patients resulted in reduced lesion burden and stabilization of neurological function [75].

C. Type 1 Diabetes Mellitus (T1DM)

In T1DM, autoimmune destruction of pancreatic beta cells leads to insulin deficiency. MSCs contribute to:

- **Immune modulation** to prevent further beta cell destruction
- **Support of beta cell regeneration** via paracrine factors
- Reduction of **insulin requirements** in patients [77]
- In a **randomized clinical trial**, autologous **BM-MSC transplantation** led to better glycemic control and C-peptide preservation in T1DM patients [78].

Organ-Specific Considerations

- **Adipose tissue-derived MSCs (AD-MSCs)** show high anti-inflammatory and angiogenic capacity, making them favorable in IBD and MS [79, 80, 81].
- **Wharton's Jelly MSCs (WJ-MSCs)** exhibit potent immunosuppression in SLE and T1DM [82, 83].
- **Intestinal MSCs** (a developing area) may provide tissue-specific targeting for IBD and colitis [84, 85].

5. Nervous System — Neurogenic Potential of DPSCs and MSCs with Enhanced Neurotrophic Activity

Neurological disorders are prime targets for MSC-based therapies because neuroinflammation, neuronal loss, impaired synaptic plasticity, and microvascular dysfunction are central to many conditions (stroke, TBI, Parkinson's disease, Alzheimer's disease, and neurodevelopmental disorders such as autism spectrum disorder, ASD). MSCs act predominantly via paracrine/neurotrophic and immunomodulatory mechanisms in the CNS; organ-adapted MSCs and MSCs selected/engineered for enhanced neurotrophic factor secretion may therefore offer superior outcomes for neural repair.

Key mechanisms relevant to CNS repair

Neurotrophic/paracrine support: **MSCs secrete BDNF, NGF, GDNF, IGF-1, FGF2 and VEGF — factors that promote neuronal survival, neurite outgrowth, synaptic plasticity and angiogenesis. This secretome drives much of the neuroprotective effect seen in preclinical models [86, 87].**

Immunomodulation / microglia modulation: MSCs and their extracellular vesicles (EVs) shift microglia from pro-inflammatory to homeostatic/repair phenotypes, reduce pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6) and increase IL-10, thereby limiting secondary injury and chronic neuroinflammation [88, 89].

Exosome/EV-mediated effects: MSC-derived exosomes deliver miRNAs and proteins across the blood–brain barrier or to perivascular niches, reduce apoptosis, promote neurogenesis and modulate immune responses — offering a cell-free therapeutic alternative with favorable safety and delivery characteristics [89, 90].

Mitochondrial transfer: MSCs can donate mitochondria to stressed neurons or astrocytes (via tunneling nanotubes or EVs), restoring bioenergetics after ischemic injury — an important mechanism in high-energy demanding tissues like the brain [86].

Dental Pulp Stem Cells (DPSCs): a neuro-specialized MSC population

Biology & rationale. DPSCs (from adult teeth or exfoliated deciduous teeth—SHED) are neural-crest derived and intrinsically express neural markers (nestin, β III-tubulin) and secrete neurotrophic factors such as **BDNF, NGF, GDNF and NT-3**, giving them an innate neurotrophic and neurogenic bias distinct from BM-MSCs or AD-MSCs. This profile makes DPSCs particularly suited to neural repair strategies [91, 92].

Preclinical evidence.

- DPSCs promote neurite outgrowth, enhance neuronal survival, reduce infarct size and improve functional recovery in rodent models of stroke, spinal cord injury and peripheral nerve injury; effects are mediated largely via secreted growth factors and EVs [92, 93].
- Comparative studies indicate DPSCs often outperform BM-MSCs in neurotrophic factor secretion and induction of neuronal differentiation in vitro and in vivo [93].

Translational advantages.

- **Ease of procurement** (extracted teeth, deciduous teeth banking).
- **Neural crest origin** → stronger neurotrophic secretome and lineage propensity.
- **Lower ethical/regulatory barriers** compared with fetal tissue [91].

Limitations and gaps.

- Most DPSC data are preclinical or early-phase; standardized GMP banking and large clinical trials are limited. Long-term safety/efficacy data in humans are sparse [91].

MSCs engineered or preconditioned for enhanced neurotrophic secretion

Because the secretome mediates much of the CNS benefit, several strategies have been used to amplify neurotrophic output:

1. **Preconditioning (hypoxia, inflammatory priming):** Hypoxic preconditioning or cytokine priming upregulates VEGF, BDNF, and HIF-1 α in MSCs, increasing survival and trophic output after CNS delivery [86].
2. **Genetic engineering:** MSCs overexpressing BDNF, GDNF, or SDF-1 show enhanced neuroprotection and axonal regeneration in preclinical models (stroke, PD models). These approaches increase potency but add regulatory complexity [94].
3. **Secretome / exosome therapy:** Harvesting and delivering MSC-derived EVs enriched for neurotrophic miRNAs is an attractive cell-free strategy with lower immunogenicity and easier dosing/quality control. Exosomes have shown promising results in TBI, stroke and AD models [87, 95].

Applications to neuroinflammation and autism spectrum disorder (ASD)

Neuroinflammation is a common pathogenic thread in many CNS disorders; MSCs attenuate microglial activation and inflammatory signaling, thus protecting synapses and neurons. MSC-EVs specifically modulate microglial phenotype and cytokine milieu, improving outcomes in preclinical neuroinflammatory models [89, 96].

ASD — rationale for MSC therapy. Emerging hypotheses propose that neuroimmune dysregulation and atypical neurodevelopment contribute to ASD in a subset of patients (microglial activation, cytokine imbalance). MSCs may modulate neuroinflammation and promote trophic support during critical developmental windows. Preclinical ASD models show behavioural improvements after MSC or EV administration [97].

Clinical evidence (ASD)

- **Phase I (open-label) hCT-MSC study (Sun et al., 2020):** Twelve children with ASD (ages 4–9) received 1–3 IV infusions of cord-tissue MSCs. The study reported safety and preliminary signals in adaptive behaviour scores at 6–12 months; however, it was not randomized and sample size was small [98].
- **Systematic reviews / small trials:** Several early-phase trials and case series (UC-MSC or BM-MSC products) report variable behavioural improvements and immunological changes, but evidence is preliminary and heterogeneous; large, placebo-controlled RCTs are still needed [99, 100].

Bottom line for ASD: MSC therapy is investigational. Mechanistic rationale (neuroimmune modulation, trophic support) is strong, but robust randomized trials with standardized endpoints, long follow-up, and mechanistic biomarkers are required before clinical adoption [97, 99].

Practical considerations for translation (DPSCs and neuro-enhanced MSCs)

Delivery route: Intravenous delivery is safe but limited by BBB and biodistribution; intra-arterial, intrathecal or local stereotactic delivery increases CNS availability but carries higher procedural risk. Exosomes may cross the BBB more readily and allow repeat dosing [87].

Dosing and timing: Acute injury (stroke/TBI) likely benefits from early immunomodulation; chronic neurodegenerative diseases may require repeated doses or sustained release strategies. Optimal dosing schemas are not established [101].

Safety: MSCs show good short-term safety in CNS trials; long-term tumorigenicity and ectopic tissue formation risks remain theoretical but must be monitored. Engineered MSCs carry additional safety/regulatory burdens [94].

Biomarkers & endpoints: Use of neuroinflammation biomarkers (cytokines, PET microglial imaging), electrophysiology, and standardized functional/behavioural scales is critical for objective assessment in trials (especially ASD) [97].

6. Pulmonary System — Lung-Resident MSCs for ARDS and Other Lung Pathologies

Introduction & Rationale

Acute respiratory distress syndrome (ARDS), severe pneumonia, idiopathic pulmonary fibrosis (IPF) and acute viral pneumonias (e.g., severe COVID-19) share common pathophysiological features: diffuse alveolar damage, dysregulated inflammation (neutrophil and macrophage activation), endothelial injury, and microvascular leak leading to hypoxaemia. MSCs were rapidly investigated for lung disease because of their potent **immunomodulatory, anti-inflammatory, antifibrotic and trophic** actions that can attenuate the damaging host response while promoting tissue repair. More recently, attention has turned to **lung-resident MSCs (LR-MSCs)** — tissue-resident stromal cells adapted to the pulmonary niche — as potentially superior therapeutic agents for lung pathologies due to niche-specific paracrine profiles and homing/engraftment advantages [102, 103].

What are Lung-Resident MSCs (LR-MSCs)?

LR-MSCs (also described as pulmonary mesenchymal stromal cells) are non-hematopoietic, multipotent stromal cells localized mainly to perivascular and interstitial compartments of the lung. They share classical MSC markers and clonogenicity but are transcriptionally and functionally tuned to the pulmonary microenvironment (e.g., expression of lung niche genes, responsiveness to alveolar signals). LR-MSCs participate in lung homeostasis through secretion of trophic factors and by interacting with epithelial, endothelial, and immune cells. Importantly, under chronic injurious signals LR-MSCs can adopt pathological fates (myofibroblast differentiation) — a double-edged sword for repair vs fibrosis [103, 104].

Mechanisms Relevant to ARDS and Lung Repair

LR-MSCs and conventional MSCs act through overlapping mechanisms, but LR-MSCs often show **niche-enhanced** activity:

Immunomodulation: Suppresses neutrophil infiltration, reduces pro-inflammatory cytokines (IL-6, TNF- α , IL-1 β), induces IL-10 and Treg responses, and polarizes macrophages toward an M2 reparative phenotype — crucial in tempering the cytokine storm in ARDS [105, 106]

Paracrine trophic support: Secrete KGF, HGF, VEGF and other growth factors that promote alveolar epithelial cell survival, enhance alveolar fluid clearance, and support endothelial integrity. LR-MSCs frequently have secretomes tailored for alveolar repair [104, 107].

Anti-fibrotic actions & ECM remodelling: MSCs release MMPs and antifibrotic mediators that reduce myofibroblast activation; LR-MSCs may be particularly effective at matrix remodeling in early injury, but prolonged stimulation can instead drive fibrosis [104].

Mitochondrial transfer & EVs: Both LR-MSCs and general MSCs can transfer mitochondria to damaged epithelial cells and deliver reparative microRNAs in extracellular vesicles, improving bioenergetics and reducing apoptosis. EVs are an attractive cell-free alternative that may better penetrate lung tissue [104, 107].

Preclinical Evidence

Extensive animal models (LPS, bleomycin, ventilator-induced lung injury) show MSCs reduce alveolar inflammation, improve oxygenation, limit fibrosis, and enhance survival. Studies specifically comparing LR-MSCs to non-resident MSCs report **improved epithelial repair and superior local immunomodulation** with LR-MSCs in several models, supporting the concept of niche advantage. However, LR-MSCs can also contribute to fibrosis via myofibroblast differentiation in chronic injury models, so timing and microenvironmental state are critical determinants of outcome [108, 109].

Clinical Trials & COVID-19 Experience

Clinical translation has advanced rapidly, particularly during the COVID-19 pandemic:

Safety trials in classical ARDS: Early Phase I trials (e.g., START) established that intravenous allogeneic BM-MSC infusion is safe in moderate-to-severe ARDS; efficacy signals were modest and sample sizes small [110].

COVID-19 ARDS studies: Multiple early studies of UC-MSC and BM-MSC in severe COVID-19 reported favourable safety and promising reductions in inflammatory markers, improved oxygenation and trends to reduced mortality (e.g., Leng et al., Shu et al., Meng et al.). Meta-analyses and systematic reviews across dozens of small trials suggest MSC therapy reduces mortality and inflammatory burden in COVID-19 pneumonia, but heterogeneity in cell source, dose, timing, and trial design tempers conclusions [111, 112, 113, 114].

Recent RCTs & systematic reviews: Phase II trials have reinforced safety; 2023–2024 meta-analyses report beneficial signals for mortality and ventilator-free days in pooled data but call for larger, well-powered Phase III RCTs to confirm efficacy in non-COVID ARDS as well [114, 115].

Key point: most human data use UC-MSC, BM-MSC or perinatal MSCs — LR-MSCs (harvested from lung tissue) have limited clinical testing due to access constraints, but preclinical data suggest they may offer improved local efficacy if practical delivery/production issues can be solved [103, 104].

Delivery, Dosing and Practical Considerations

Route of administration: Intravenous infusion is easiest but suffers pulmonary first-pass trapping (which can be desirable for lung disease), while intratracheal or intrabronchial delivery increases local exposure but is more invasive. Nebulized EVs or aerosolized cell-free products are under investigation [104].

Timing: Early administration during the inflammatory phase may maximize immunomodulatory benefits, while later delivery risks promoting fibrosis depending on microenvironmental cues.

Source selection: UC-MSCs and BM-MSCs are used clinically for convenience and scale; LR-MSCs may be preferable biologically but are harder to source and expand under GMP. Perinatal MSCs (UC/placenta) offer a tradeoff: high proliferative capacity and low immunogenicity [103, 112].

Cell vs. cell-free (EV) therapy: EVs/exosomes reduce safety concerns (no replication, lower immunogenicity), easier storage/delivery, and may be optimized for inhalation delivery — an area of active translational research [104, 107].

Risks, Challenges and Open Questions

Heterogeneity & potency assays: Variable MSC sources, culture methods, and lack of standardized potency assays cause inconsistent clinical outcomes [106].

Fibrogenic potential: LR-MSCs can contribute to myofibroblast accumulation and fibrosis under chronic/pro-fibrotic signals (TGF- β , Wnt, Hedgehog). Careful patient selection and timing are essential [104].

Manufacturing & GMP complexity: LR-MSC isolation from lung tissue is invasive and yields are low;

perinatal sources (UC, placenta) are more scalable but may lack the full lung-specific imprint. Developing ex vivo conditioning protocols to confer lung-like properties (preconditioning, engineered receptor expression) is a promising strategy [103, 105].

Need for large RCTs: Existing trials are underpowered or heterogeneous. Phase III RCTs with standardized cell products, dosing regimens, and mechanistic biomarkers are required to confirm clinical benefit in ARDS and other lung diseases [114, 115].

1. Gastrointestinal / Hepatic System

Chronic liver injury and inflammatory bowel disease (IBD) are major global health problems driven by persistent inflammation, dysregulated immune responses, and pathologic tissue remodeling (fibrosis in liver; fistulizing and transmural inflammation in Crohn's disease). Mesenchymal stromal/stem cells (MSCs) are attractive for these conditions because they: (1) modulate immune responses, (2) secrete trophic and antifibrotic factors, (3) support regeneration of parenchymal cells, and (4) deliver bioactive extracellular vesicles (EVs). Organ-specific MSCs (liver-resident MSCs, gut-associated MSCs) may amplify these effects through niche adaptation and a tailored secretome.

1. Liver-Resident MSCs for Fibrosis

Mechanisms of action

Liver fibrosis is driven by activation of hepatic stellate cells (HSCs), chronic inflammation, and excessive extracellular matrix (ECM) deposition. MSCs counter fibrosis through multiple, largely paracrine mechanisms:

- **Antifibrotic signaling** — secretion of **HGF**, matrix-degrading enzymes (**MMP-2**, **MMP-9**) and inhibitors of TGF- β /Smad signaling, which reduce myofibroblast activation and collagen deposition [116, 117].
- **Immunomodulation** — induction of anti-inflammatory macrophage phenotypes (Ly6C^{lo} in mice), increased IL-10, and suppression of pro-inflammatory cytokines that perpetuate stellate cell activation [117].
- **Parenchymal support & proliferation** — secretion of **HGF**, **EGF**, and other mitogens that promote hepatocyte survival and proliferation, accelerating functional recovery [118, 119].
- **Exosome/EV-mediated microRNA delivery** — EVs carry antifibrotic miRNAs and proteins that reprogram HSCs and modulate immune cells [118].

Why liver-resident MSCs may be superior

Liver-derived (resident) MSCs or perivascular hepatic stromal cells often display **higher expression of hepatoprotective factors and ECM-remodeling enzymes** than BM-MSCs, and are epigenetically tuned to hepatic signals — giving them improved capacity to interact with hepatocytes, Kupffer cells and HSCs in situ. Several preclinical studies show improved reduction of fibrosis and better restoration of liver architecture with liver-derived MSCs versus BM-MSC comparators [116, 119].

Preclinical and clinical evidence

- **Preclinical:** Multiple animal models demonstrate MSCs (BM, UC, liver-derived) reduce collagen deposition, improve liver function tests, and promote regeneration after toxic or cholestatic injury. Mechanistic studies show HGF and MMP upregulation and macrophage phenotype shifts underlying these benefits [116, 117].
- **Clinical trials & reviews:** Numerous clinical trials have tested BM-MSC or UC-MSC infusions in cirrhosis and acute liver failure; systematic reviews report safety and signals of efficacy (improved

MELD/Child-Pugh scores, reduced ascites) but heterogeneity and small sample sizes limit definitive conclusions. Ongoing trials and cell-free EV studies aim to optimize dosing and delivery [120].

Translational considerations

- **Route & dosing:** Intravenous infusion is common but leads to pulmonary first-pass; intrahepatic or portal infusion may increase local bioavailability but has higher procedural risk.
- **Product choice:** Liver-resident MSCs or UC-MSCs may be preferred for antifibrotic potency; exosome preparations are an emerging cell-free alternative under clinical investigation [120].
- **Gaps:** Need for standardized potency assays (antifibrotic readouts), larger randomized controlled trials (Phase II/III), and long-term safety data (tumorigenicity, ectopic fibrosis).

2. Gut-Associated MSCs for Inflammatory Bowel Disease (IBD)

Mechanisms of action

IBD (Crohn's disease and ulcerative colitis) is characterized by dysregulated mucosal immunity, barrier dysfunction, and chronic inflammation. MSCs act through:

- **Local immunomodulation:** Suppression of pathogenic T-cell responses, induction of regulatory T cells, and reprogramming of dendritic cells and macrophages to anti-inflammatory phenotypes [121].
- **Barrier repair and trophic support:** MSC secretome enhances epithelial restitution, tight junction integrity, and mucosal healing (VEGF, HGF, KGF signalling) [122].
- **EV/exosome effects:** MSC-EVs deliver miRNAs and proteins that reduce epithelial apoptosis, modulate immune signaling, and restore barrier function.

Gut-resident MSCs and tissue matching

Gut-associated mesenchymal stromal populations (pericryptal fibroblasts, subepithelial myofibroblasts) are tightly integrated with epithelial and immune niches. MSCs derived from intestinal tissues or peritoneal/mesenteric sources may have enhanced homing, epithelial-supportive secretomes, and better capacity to resolve mucosal injury than non-resident MSCs. Recent preclinical data suggest placenta- or gut-derived MSCs efficiently restore barrier function and reduce inflammation via AMPK-FXR and other gut-specific pathways [123, 124].

Clinical evidence — perianal Crohn's disease as a success story

- **Darvadstrocel (Alofisel®)** — an allogeneic expanded adipose-derived MSC product — is **approved in Europe** for complex perianal fistulas in Crohn's disease after the **ADMIRE-CD** Phase III trial demonstrated higher combined remission rates versus control. Long-term follow-up and real-world studies report sustained benefit for a significant fraction of patients. This is a landmark positive regulatory example for MSC therapy in GI disease [125, 126].
- **Systemic IBD (luminal disease):** Trials of systemic BM-MSCs or UC-MSCs in luminal Crohn's and ulcerative colitis show mixed results — safety is acceptable, but efficacy varies. Meta-analyses indicate MSC therapies improve combined remission rates for perianal fistulas and show promise for luminal disease, but heterogeneity and trial design differences remain obstacles [127, 128].

Translational considerations

- **Indication specificity:** Local injection (e.g., into fistula tracts) has proven highly effective (darvadstrocel); systemic luminal disease may require different cell types, dosing, or repeated administration.
- **Source selection:** AD-MSCs (darvadstrocel) are validated for perianal CD; gut-derived or placenta-derived MSCs show promising preclinical efficacy for mucosal healing and barrier repair and may be attractive for luminal disease [124, 126].

- **Regulatory pathway:** The darvadstrocel approval illustrates that focused, indication-specific approaches (local delivery, well-defined product, rigorous RCT) can succeed. Broader adoption for luminal IBD will require comparable rigor in trial design, standardized endpoints, and mechanistic biomarkers.

2. Renal System — Kidney-Derived MSCs for Renoprotection

Acute kidney injury (AKI), chronic kidney disease (CKD), and the AKI→CKD transition are driven by tubular epithelial injury, microvascular rarefaction, inflammation and maladaptive fibrogenesis. Mesenchymal stromal/stem cells (MSCs) have emerged as candidate renoprotective agents because they (a) attenuate inflammation, (b) stimulate tubular repair and angiogenesis, and (c) limit fibrotic remodeling — largely via paracrine and extracellular vesicle (EV)-mediated mechanisms. Kidney-derived MSCs (K-MSCs, i.e., MSCs isolated from renal interstitium, perivascular niches or discarded nephrectomy tissue) are increasingly studied as **organ-specific** alternatives that may deliver enhanced renoprotective efficacy due to niche adaptation.

Mechanisms of Renoprotection

1. **Paracrine trophic support** — MSCs secrete growth factors (HGF, VEGF, IGF-1, KGF) that promote tubular epithelial cell (TEC) survival, proliferation, and angiogenesis, restoring nephron microarchitecture [129].
2. **Immunomodulation** — MSCs dampen innate and adaptive kidney inflammation (reducing TNF- α , IL-6; inducing IL-10, Tregs; polarizing macrophages toward M2), which prevents ongoing injury and fibrogenic signalling [130].
3. **Anti-fibrotic & ECM remodeling** — MSCs and their EVs upregulate matrix metalloproteinases (MMP-2/9) and antagonize TGF- β /Smad pathways to limit myofibroblast activation and collagen deposition [131].
4. **EV/exosome-mediated miRNA and protein transfer** — MSC-EVs deliver renoprotective miRNAs and proteins that reduce apoptosis, stimulate autophagy, and reprogram injured TECs and immune cells. EVs can reproduce many MSC benefits in AKI models and are promising as cell-free therapeutics [132, 133].
5. **Mitochondrial rescue / bioenergetic restoration** — MSCs and MSC-derived EVs can transfer mitochondrial components or mtDNA/TFAM to injured renal cells, restoring ATP production and cellular metabolism — a key mechanism in ischemia/reperfusion injury [134, 135].

(These mechanisms overlap and are often synergistic; EVs appear central to many renoprotective effects and may account for much of the activity attributed to transplanted cells.)

Why Kidney-Derived MSCs May Be Superior

- **Epigenetic & secretome imprinting:** K-MSCs retain epigenetic marks and a secretory profile tuned to renal signals (e.g., enhanced expression of renal trophic factors, ECM-interacting receptors), which can improve local efficacy and compatibility with kidney parenchyma [136].
- **Improved homing and interaction:** K-MSCs often show higher expression of renal-homing receptors and adhesion molecules, potentially enhancing retention in injured kidneys versus non-resident MSCs [137].
- **Functional matching:** Organ-matched MSCs may better modulate kidney-specific immune networks (e.g., splenic–kidney immune axis) and more effectively prevent AKI→CKD progression [138].

Preclinical Evidence

- Numerous rodent models of ischemia-reperfusion injury (IRI), nephrotoxin models, and sepsis-

associated AKI show that MSCs (BM, UC, AD and organ-derived) reduce creatinine/BUN, histologic tubular necrosis, inflammation and fibrosis. EVs from MSCs reproduce many benefits and may even be engineered for potency (miR29, miR-146b, TFAM shuttling) [139, 140].

- Studies directly comparing kidney-derived MSCs to BM-MSCs report **enhanced renal repair, better tubular proliferation and greater antifibrotic activity** with K-MSCs in some models — supporting a niche advantage hypothesis [136, 137].

Clinical Evidence and Trials

- **Clinical translation so far:** Several early-phase clinical trials have investigated MSC therapy in AKI, CKD, and kidney transplant settings (primarily using BM-MSC, UC-MSC or AD-MSC). Results demonstrate acceptable safety and hints of benefit (improved renal function, reduced inflammatory markers), but trials are small, heterogeneous, and underpowered for definitive efficacy endpoints [130, 141].
- No large randomized, definitive Phase III trials have yet established MSC therapy as standard in AKI/CKD; EV-based trials are emerging. K-MSC-specific clinical data are currently limited because renal tissue harvest is invasive and scale-up is challenging [142, 143].

Translational Considerations & Practical Issues

1. **Source & accessibility:** Kidney tissue is not easily obtained from healthy donors; K-MSCs are often derived from nephrectomy waste or biopsy tissue, limiting scalability. Therefore, perinatal sources (UC/placenta) or engineered MSCs are more practical for off-the-shelf products unless reliable K-MSC banking is established [136].
2. **Delivery route:** Intravenous infusion is clinically feasible but subjects cells to pulmonary first-pass. Intra-arterial/portal or direct renal injection increases local delivery but raises procedural risk. EVs offer a promising non-cell alternative with easier dosing and potential for repeated administration [129, 133].
3. **Potency assays & product standardization:** Lack of standardized renoprotective potency assays (e.g., MMP/TGF- β modulation, EV miRNA cargo) hinders product comparability; development of functional assays predictive of AKI/CKD outcomes is essential [136].
4. **Timing of therapy:** MSCs/EVs appear most effective when administered early after injury (to modulate inflammation and support tubular regeneration). In chronic or advanced fibrosis, combination approaches (antifibrotic drugs + MSC derivatives) or engineered EVs may be required [129, 139].
5. **Safety:** Short-term safety in trials has been acceptable; long-term risks (ectopic tissue formation, immune sensitization) appear low but require continued monitoring, especially for engineered cells. EVs reduce many safety concerns but demand rigorous GMP and characterization standards [130, 133].

Open Questions and Future Directions

- **Can we bank and standardize K-MSCs or instead engineer accessible MSCs (UC/AD/BM) to acquire kidney-specific phenotypes via preconditioning or genetic modification?** Preconditioning (hypoxia, cytokine priming) or transient overexpression of renal tropic receptors is an active area [137].
- **What are the optimal EV cargos (miRNAs, proteins, mitochondrial components) for blocking AKI→CKD transition?** Recent studies identify miR-29 family, miR-146b and mitochondrial TFAM/mtDNA as promising targets for engineered EV therapy [140, 144].

- **Which patient subgroups (sepsis-AKI, ischemic AKI, contrast-induced AKI, early CKD) will benefit most, and what are the best endpoints for trials?** Robust biomarkers (KIM-1, NGAL, imaging of microvasculature) should be integrated into trial design [145].

3. Endometrial System — Endometrial MSCs (eMSCs / Menstrual Blood MSCs)

Rationale

Endometrial MSCs (eMSCs), including stromal MSCs isolated from the basalis layer or menstrual blood (MenSCs), are tissue-resident stromal progenitors adapted to cyclical regeneration. Their native roles in monthly tissue breakdown and regeneration make them appealing for uterine repair indications (Asherman's syndrome, thin endometrium, recurrent implantation failure) [146].

Preclinical evidence (animal models)

- Multiple rodent and rabbit models of endometrial injury (cauterization, mechanical damage) show that transplantation of eMSCs or MenSCs improves endometrial thickness, gland density, vascularization and restores fertility indices versus controls.
- Mechanistic studies in these models demonstrate paracrine-mediated angiogenesis (VEGF, angiopoietins), reduced fibrosis (decreased TGF- β / α -SMA), and immunomodulation within the uterine microenvironment [147].

Limited clinical data (general MSCs vs organ-specific)

- **Organ-specific (eMSCs / MenSCs):** Small phase I/II studies and case series have explored intrauterine delivery of autologous MenSCs or eMSCs in women with Asherman's syndrome or thin endometrium. Reports describe improvements in endometrial thickness, restored menses, and occasional successful pregnancies; however sample sizes are small and rigorous RCT data are lacking [146].
- **General MSCs (BM/UC/AD):** Several small clinical studies used BM-MS or UC-MS intrauterine injections with variable outcomes; these suggest benefit but do not clearly outperform organ-derived cells in the available limited datasets [147].

Mechanistic insights relevant to the endometrium

- **Angiogenesis & vascular remodeling:** eMSCs secrete high levels of VEGF, angiopoietin-1 and bFGF, supporting revascularization after injury.
- **Anti-fibrotic paracrine signaling:** eMSC secretome reduces myofibroblast activation and collagen deposition (MMP/TIMP balance).
- **Hormone responsiveness & niche integration:** eMSCs respond to estrogen/progesterone signaling, promoting cyclic remodeling — a key niche advantage over non-endometrial MSCs.
- **Immunomodulation:** Local immune cell modulation (uterine NK, macrophage phenotype) that favors implantation and tissue remodelling [148].

4. Pancreatic System — Pancreas-Associated MSCs and Islet Support

Rationale

Pancreas-resident stromal cells/perivascular MSC-like populations and peripancreatic MSCs may support islet survival and function. For diabetes (T1DM and T2DM), MSCs are studied mainly for **islet protection, immune modulation** (in autoimmune T1DM), and as adjuncts to islet transplantation [149].

Preclinical evidence (animal models)

- In rodent models of T1DM and islet injury, MSCs (BM, AD, UC and pancreatic perivascular MSC-like cells) improve glycemic control, preserve beta-cell mass, reduce insulinitis, and enhance islet graft

survival. EVs/exosomes from MSCs can improve insulin secretion and reduce apoptosis in beta cells in vitro and in vivo.

- Comparisons suggest that pancreas-derived MSC-like cells or perivascular islet stromal cells may provide superior local trophic support (e.g., PDX1/NGN3-associated signals) relative to generic MSCs in islet co-culture/graft models.

Limited clinical data (general MSCs vs organ-specific)

- **General MSCs (BM/UC/AD):** Several early-phase clinical trials have tested BM-MSC or UC-MSC infusions in recent-onset T1DM and chronic T2DM (safety and modest improvements in C-peptide, insulin requirement). Results are preliminary and heterogeneous [150].
- **Organ-specific pancreatic MSCs:** Human clinical data are sparse to nonexistent due to difficulty of harvesting and scaling pancreas-resident MSCs; most translational strategies therefore use general MSCs or engineered MSCs targeted to islet support [151].

Mechanistic insights relevant to the pancreas

- **Immunomodulation:** MSCs suppress autoreactive T cells, induce Tregs, and modulate antigen-presenting cells — critical in T1DM [150].
- **Trophic support & beta-cell protection:** Paracrine factors (HGF, IGF-1, VEGF) and MSC-EV cargo reduce beta-cell apoptosis and increase proliferation.
- **Islet niche modulation:** Pancreas-resident MSCs are adapted to islet ECM and vasculature and may express higher levels of islet-supportive factors (e.g., PDX1-associated pathways), potentially improving engraftment after transplantation [149].

5. Other Niche Organ Examples (brief overview)

Below are brief, one-paragraph mini-subsections you can include to round out the “Other Systems” segment. For each, I list preclinical evidence, clinical data status, *and* mechanistic notes.

Ocular / Retinal MSCs

- **Preclinical:** Retinal and perivascular MSC-like cells promote retinal pigment epithelium survival, reduce inflammation, and preserve photoreceptors in models of retinal degeneration [152].
- **Clinical:** Small safety trials using subretinal or intravitreal MSCs (often BM/UC sources) reported variable outcomes and some safety concerns; organ-specific retinal MSC development is early.
- **Mechanism:** Neurotrophic factor secretion (BDNF, CNTF), anti-inflammatory effects, and EV-mediated photoreceptor rescue [153].

Skin / Cutaneous MSCs (dermal MSCs)

- **Preclinical:** Dermal MSCs and AD-MSCs promote wound closure, angiogenesis, and reduce scarring in chronic wound models.
- **Clinical:** AD-MSC therapies are used in wound care clinics; organ-specific dermal MSCs are attractive for chronic ulcers and burn reconstruction.
- **Mechanism:** High secretion of VEGF, FGF, TSG-6; modulation of fibroblast/myofibroblast activity [154, 155, 156].

Oto-/Vestibular MSCs (inner ear) — emerging field

- **Preclinical:** Inner ear-derived MSC-like cells and MSCs engineered to secrete neurotrophins protect hair cells and auditory neurons in animal models.
- **Clinical:** Very limited; mainly preclinical.
- **Mechanism:** Neurotrophic (BDNF/NT-3) support, immunomodulation.

6. Challenges and Limitations

Despite substantial progress, the routine clinical use of mesenchymal stem cells (MSCs) is hindered by **biological heterogeneity, technical barriers, and regulatory concerns**. These limitations have slowed the translation of promising preclinical findings into standardized therapies.

6.1. Source and Donor Heterogeneity

The **biological variability of MSCs** is one of the most critical challenges. MSCs differ considerably depending on:

- **Tissue source** (bone marrow, adipose tissue, umbilical cord, placenta, etc.)
- **Donor-related factors** (age, sex, metabolic health, comorbidities)
- **Culture conditions** (oxygen tension, serum type, passage number)

Such heterogeneity leads to **inconsistent immunophenotypes, secretomes, and therapeutic efficacy**, limiting reproducibility between trials and across laboratories. For instance, **BM-MSCs from older donors** exhibit reduced proliferation and differentiation potential compared to neonatal MSCs [35]. Thus, standardization of **donor selection criteria** and **tissue-specific characterization** is urgently required.

6.2. Engraftment and Homing Limitations

Following systemic infusion, **<1% of MSCs reach and persist** in the injured target tissue due to **pulmonary first-pass entrapment** and inefficient homing mechanisms. Most infused MSCs are trapped in the lungs, liver, and spleen, and only transiently detected in circulation [157].

Consequently, the **primary therapeutic benefit** is now attributed to **paracrine signaling** (release of exosomes, growth factors, and cytokines), rather than long-term engraftment or differentiation into functional tissue cells. Improving **homing strategies**—such as genetic modification (e.g., CXCR4 overexpression), preconditioning, or biomaterial scaffolds—represents a key research direction.

6.3. Immunogenicity in Repeated Dosing

Although MSCs were historically considered **immune-privileged**, recent studies reveal they are more accurately described as **immune evasive**. Repeated infusions of allogeneic MSCs may trigger **anti-HLA antibody formation** or **complement-mediated clearance**, leading to reduced efficacy and possible alloimmunization.

For example, **Li et al. (2018)** showed that host immune systems can mount adaptive responses against infused MSCs, while **Najar et al. (2016)** highlighted complement activation as a limiting factor in systemic administration. This presents challenges for conditions requiring **chronic or repeated dosing** [158, 159].

6.4. Tumorigenic and Fibrotic Risk

While MSCs are **non-tumorigenic under normal conditions**, concerns persist about their role in **tumor progression** and **fibrosis**:

- MSCs secrete pro-angiogenic and immunosuppressive factors (VEGF, TGF- β), which may inadvertently support tumor growth or metastasis in immunocompromised patients.
- In certain microenvironments, MSCs may differentiate into **myofibroblasts**, contributing to **fibrotic scarring** [160].

Although clinical evidence of MSC-induced tumorigenesis is scarce, **long-term surveillance** is essential, especially in oncology-related applications.

6.5. Lack of Standardized Potency Assays

A significant bottleneck in MSC therapy is the absence of **universally accepted potency assays**. Unlike small molecules or biologics, MSCs are **living drugs** with variable activity depending on their immunom-

odulatory or regenerative context.

Current criteria (plastic adherence, trilineage differentiation, surface marker expression) defined by ISCT (Dominici et al., 2006) do not adequately predict **clinical efficacy** [161]. Newer approaches focus on **secretome profiling**, **exosome content**, and **functional assays** (e.g., T-cell suppression, macrophage polarization). However, harmonization across laboratories and regulatory agencies is lacking.

6.6. Scalability and Manufacturing Barriers

For MSCs to become **widely accessible therapies**, they must be manufactured at large scale under **Good Manufacturing Practice (GMP)** conditions. This involves challenges in:

- **Isolation and expansion** (cell senescence after multiple passages)
- **Cryopreservation and thawing** (loss of viability, functional decline)
- **Quality control** (batch-to-batch consistency)
- **Distribution logistics** (cold chain, shelf life)

These hurdles contribute to **high costs** and limit availability, particularly in **low- and middle-income countries**. Advances such as **bioreactor-based expansion**, **allogeneic “off-the-shelf” MSCs**, and **cell-free exosome products** are being investigated to overcome scalability barriers.

7. Need for Organ-Specific MSC Targeting

Since their discovery in the 1970s, mesenchymal stem cells (MSCs) have been widely studied for their regenerative, immunomodulatory, and trophic effects. While MSCs derived from classical sources such as **bone marrow**, **adipose tissue**, and **umbilical cord** share a common phenotype (CD73⁺, CD90⁺, CD105⁺; negative for hematopoietic markers), accumulating evidence indicates that their **therapeutic efficacy is highly context-dependent**. The clinical variability observed across trials has underscored the importance of **organ-specific MSC targeting**, whereby tissue-resident MSCs or preconditioned MSCs are harnessed to better adapt to distinct disease microenvironments.

Variable Microenvironments Affecting MSC Function

The **microenvironmental niche** in each organ—including extracellular matrix (ECM), oxygen tension, inflammatory milieu, and local signaling molecules—profoundly influences MSC behavior. For example:

- **Lung injury** is characterized by hypoxia and oxidative stress, requiring MSCs with enhanced resistance to ROS and ability to promote alveolar repair [50].
- **Liver fibrosis** involves excessive ECM deposition and chronic inflammation; hepatic-resident MSCs secrete hepatocyte growth factor (HGF) and matrix metalloproteinases that better reverse fibrosis compared to BM-MSCs [29].
- **Synovial joints** in osteoarthritis provide a mechanical and inflammatory niche where synovial-derived MSCs demonstrate superior **chondrogenic potential** compared to other sources [25].
- **Endometrium** undergoes cyclical regeneration, and endometrial MSCs exhibit unique angiogenic and proliferative traits that make them attractive for gynecological disorders [162].

Thus, while systemic MSCs exhibit general immunosuppressive effects, **organ-specific MSCs are pre-adapted to their native microenvironment**, improving survival, engraftment, and regenerative efficacy.

Niche-Specific Diseases Demand Tailored MSCs

Diseases are increasingly recognized as **niche-specific disorders**, where pathology is driven by unique microenvironmental disruptions:

- **ARDS and pulmonary fibrosis** → disrupted alveolar-capillary interface
- **Liver cirrhosis** → activated hepatic stellate cells and fibrotic ECM

- **Chronic kidney disease** → tubular epithelial cell apoptosis and glomerulosclerosis
 - **Neurological disorders** (e.g., multiple sclerosis, stroke) → neuroinflammation and demyelination
- Conventional MSCs often **fail to adapt optimally** to these specialized environments, limiting therapeutic outcomes. Leveraging **organ-specific MSCs** (e.g., lung-derived, liver-derived, synovial, endometrial, or cardiac MSCs) may provide **higher tissue compatibility, superior niche integration, and targeted functional benefits**.

Preclinical and Clinical Implications

Preclinical models show that **tissue-resident MSCs outperform standard MSCs** in niche-specific repair:

- **Lung-derived MSCs** improved alveolar epithelial repair in ARDS better than BM-MSCs [30].
- **Cardiac MSCs** demonstrated stronger cardioprotective paracrine activity compared to non-cardiac MSCs [26].
- **Synovial MSCs** exhibited enhanced cartilage formation compared to adipose- or bone marrow-derived MSCs [25].

Clinically, this suggests that future regenerative strategies should move from “**one-size-fits-all**” MSC therapy toward **precision, organ-specific MSC applications**, potentially combined with genetic or bioengineering modifications for enhanced niche adaptation.

Table 2. Organ-Specific Mesenchymal Stem Cell (MSC) Sources Matched to Disease Microenvironments, Highlighting Optimal Tissue Origins for Targeted Regenerative Therapies.

Disease / Condition	Key Microenvironmental Features	Most Suitable MSC Source
Acute Respiratory Distress Syndrome (ARDS) / Pulmonary Fibrosis	Hypoxia, oxidative stress, alveolar epithelial injury, cytokine storm	Lung-derived MSCs (L-MSCs) ; UC-MSCs as alternative
Liver Cirrhosis / Fibrosis	Fibrotic ECM, activated stellate cells, chronic inflammation	Liver-resident MSCs (Li-MSCs)
Osteoarthritis (OA)	Cartilage degradation, synovial inflammation, mechanical stress	Synovial MSCs (SM-MSCs) ; AD-MSCs as alternative
Myocardial Infarction / Heart Failure	Ischemia, cardiomyocyte loss, adverse remodeling	Cardiac-resident MSCs (cMSCs) ; BM-MSCs with preconditioning
Chronic Kidney Disease / AKI	Tubular epithelial apoptosis, glomerulosclerosis, inflammation	Kidney-derived MSCs (kMSCs)
Gynecological Disorders (Asherman’s Syndrome, Endometrial Atrophy)	Endometrial fibrosis, impaired angiogenesis, cyclical regeneration failure	Endometrial MSCs (eMSCs) , menstrual blood-derived MSCs
Neurological Disorders (MS, Stroke, SCI)	Neuroinflammation, demyelination, neuronal apoptosis	Neural tissue-derived MSCs (nMSCs) ; UC-MSCs as supportive

8. Future Directions

The next decade of regenerative medicine is poised to transition from **generalized MSC therapy** to **precision, organ-specific stem cell applications**. Integrating advances in **bioengineering, cell-free**

therapeutics, and genetic modification will further enhance the therapeutic potential of organ-specific MSCs (OS-MSCs), overcoming many of their current limitations.

8.1 Precision Stem Cell Therapy Using Organ-Specific Cell Lines

Concept

The next frontier in regenerative medicine lies in the development of **well-characterized organ-specific mesenchymal stem cell (OS-MSC) banks**, matched precisely to specific organ systems and disease indications. These banks would comprise **allogeneic, GMP-grade cell lines** derived from elite, high-potency donors and rigorously profiled for **organ-specific functionality**, potency, and safety. Such an approach would transform current empirical MSC therapies into **standardized, precision-tailored interventions**, bridging the gap between biological complexity and clinical reproducibility [10, 163].

Advantages

- **Personalized Medicine:** Enables precision matching of disease type to optimized MSC source—e.g., cardiac MSCs for myocardial infarction, hepatic MSCs for cirrhosis, synovial MSCs for osteoarthritis, or neural crest-derived DPSCs for neurodevelopmental disorders [5, 164].
- **Reduced Inter-Donor Variability:** Standardization through the use of well-characterized, “elite” donor lines ensures consistent therapeutic potency across production batches [43].
- **Off-the-Shelf Accessibility:** Facilitates ready-to-use treatments, particularly valuable for acute and time-sensitive conditions (e.g., myocardial infarction, stroke, acute respiratory distress syndrome) [165].

Example

This concept draws inspiration from **Darvadstrocel (Alofisel®)**—an allogeneic adipose-derived MSC (AD-MSC) product approved for the treatment of perianal fistulas in Crohn’s disease [166]. While Alofisel represents a milestone for MSC-based therapy, future precision platforms will expand upon this foundation by establishing **organ-specific MSC repositories**—e.g., cardiac, hepatic, pulmonary, and neural MSC lines—each optimized for **targeted clinical indications** through functional validation and molecular profiling [3, 8].

The Need for Robust Biomarkers: Defining the “Right Cell for the Right Patient”

To unlock the full potential of **precision stem cell therapy**, it is imperative to integrate **robust biomarker frameworks** for both **patient selection** and **MSC characterization** [167].

1. **Biomarkers for Patient Stratification:** MSC efficacy is strongly influenced by the **host microenvironment**—including inflammation, immune tone, metabolic status, and disease chronicity. Biomarkers can help identify patients **most likely to respond** to a given OS-MSC therapy.
 - **Predictive immune signatures:** Cytokine profiles (e.g., IL-6, TNF- α , IFN- γ) may predict responsiveness in inflammatory diseases [168].
 - **Molecular endotyping:** Transcriptomic or proteomic signatures of diseased tissue can guide selection of the most compatible organ-specific MSC line [169].
 - **Clinical phenotyping:** For example, selecting patients with early-stage fibrosis or moderate inflammation may yield better outcomes than end-stage disease where tissue architecture is irreversibly damaged [9].
2. **Biomarkers for MSC Characterization and Potency**
Given the **biological heterogeneity** of MSC populations, biomarkers are essential for verifying **cell identity, potency, and functional readiness** [170].

- **Surface marker panels** (beyond ISCT minimal criteria): Organ-specific markers such as CD146 (vascular MSCs), CD271 (bone marrow MSCs), or NG2 (pericytic MSCs) can refine cell identity [171].
 - **Functional biomarkers:** Quantification of key paracrine mediators—VEGF (angiogenesis), HGF (hepatoprotection), BDNF/GDNF (neuroprotection), IL-10/IDO (immunomodulation)—offers insight into tissue-relevant efficacy [8].
 - **Secretome and exosome profiling:** Proteomic and miRNA signatures can act as surrogates for potency, particularly for paracrine-dominant mechanisms [172].
 - **Epigenetic and transcriptomic fingerprints:** Capture organ-specific “memory” and ensure the cell’s regenerative program aligns with its intended target tissue.
- 3. Integrating Biomarkers into Manufacturing and Clinical Pipelines**
- **Preclinical phase:** Biomarkers can be used to select optimal OS-MSC lines and validate differentiation or secretory biases [173].
 - **Manufacturing stage:** Batch release assays incorporating potency biomarkers ensure consistency and predict in vivo performance [167].
 - **Clinical trials:** Companion diagnostics could stratify participants based on biomarker-defined responsiveness, improving trial outcomes and regulatory clarity [12].

8.2 Bioengineering Organoids Using MSCs and Scaffolds

Concept

Combine **organ-specific mesenchymal stem cells (OS-MSCs)** with **3D bioprinted scaffolds, decellularized organ matrices, or hydrogel constructs** to recreate functional **microtissues or organoids** for **transplantation, disease modeling, or drug testing**. This integrative strategy merges **cellular precision, biomaterial engineering, and tissue microenvironmental cues** to mimic the **native architecture and function** of target organs [134, 174].

Mechanism

- **OS-MSCs** provide **tissue-specific stromal support** and secrete **organ-matched trophic factors**, such as angiogenic, immunomodulatory, and differentiation-inducing cytokines that recapitulate native microenvironments.
- **Scaffolds** mimic the **extracellular matrix (ECM) composition, stiffness, and 3D architecture** of the native organ, preserving **mechanical cues** and **topographical signals** essential for cell alignment, migration, and fate determination [175].
- **Co-culture with parenchymal cells** (e.g., hepatocytes, cardiomyocytes, or alveolar epithelial cells) enhances **functional maturation, cell–cell communication, and integration** within engineered constructs, establishing physiologically relevant organoid systems [176].

Example

Hepatic MSCs seeded on **decellularized liver scaffolds** have been shown to enhance **hepatocyte engraftment, vascularization, and metabolic function** in **preclinical models of liver failure**, underscoring the synergy between **biomimetic scaffolds** and **organ-specific stromal support** [177].

Platform for Screening and Mechanistic Studies

Beyond their therapeutic promise, such **bioengineered organoid systems** offer a **powerful experimental platform** for both **screening organ-specific MSC efficacy** and **deciphering mechanistic pathways**:

1. Efficacy Screening of OS-MSC Lines

- Enables **comparative evaluation** of different OS-MSC sources (e.g., hepatic vs. bone marrow vs. adipose) within a **controlled microenvironment**, assessing their **tissue-repair potency**, **angiogenic capacity**, and **paracrine effects** on organ-specific parenchymal cells.
- Functional readouts—such as **albumin secretion** (for hepatic constructs), **contractility** (for cardiac tissues), or **surfactant production** (for pulmonary models)—can serve as **quantitative efficacy biomarkers** [178].
- 2. **Mechanistic Insights into MSC–Tissue Interactions**
 - Facilitates **in vitro modeling** of **cell–matrix** and **cell–cell cross-talk**, illuminating mechanisms of **MSC-mediated regeneration**, including **ECM remodeling**, **immune modulation**, and **angiogenesis** [8].
 - High-resolution imaging, transcriptomic profiling, and **omics-based analyses** of these organoids can unravel **organ-specific signaling pathways** that govern **MSC differentiation**, **secretome dynamics**, and **integration potential** [179].
- 3. **Predictive Preclinical Models for Translation**
 - These constructs can simulate **disease microenvironments** (e.g., fibrotic, ischemic, or inflammatory conditions), allowing preclinical **efficacy and safety testing** of OS-MSC products before in vivo transplantation.
 - Incorporation into **microfluidic “organ-on-chip” systems** further enables **high-throughput drug screening** and **toxicity profiling**, aligning regenerative therapy development with **precision pharmacology** [180].

By integrating **biomaterials**, **OS-MSCs**, and **microphysiological systems**, this approach not only enhances **translational readiness** of engineered tissues but also creates a **discovery platform** for **rational design and optimization** of next-generation **MSC-based regenerative therapies**.

8.3 MSC-Derived Exosomes as Cell-Free Alternatives

Concept

Utilize **exosomes and extracellular vesicles (EVs)** derived from **organ-specific mesenchymal stem cells (OS-MSCs)** as **cell-free regenerative therapies**. These nanosized vesicles (30–150 nm) encapsulate a rich repertoire of **bioactive molecules**—including **microRNAs**, **mRNAs**, **proteins**, and **lipids**—that recapitulate many of the paracrine and immunomodulatory effects of their parent MSCs [43].

Advantages

- **Avoids risks of tumorigenicity, immune rejection, or ectopic differentiation.** Since exosomes are non-replicative and devoid of nuclei, they **eliminate concerns of uncontrolled proliferation, neoplastic transformation, or aberrant lineage differentiation**, making them safer for repeated dosing [172].
- **Easier storage, sterilization, and quality control.** Exosomes can be **cryopreserved, lyophilized, or formulated as stable biologics**, facilitating **standardized dosing, off-the-shelf availability, and global scalability** under GMP conditions. Their **cell-free nature** also allows more straightforward **sterility assurance, batch release testing, and pharmacokinetic evaluation** compared to live cell products.
- **Preserves organ-specific signaling** through **microRNAs, proteins, and lipids** carried in EVs. OS-MSC-derived exosomes retain **epigenetic and proteomic signatures** of their tissue of origin, enabling **organ-targeted regenerative signaling**. For example, cardiac MSC exosomes preferentially contain **cardioprotective miRNAs** (e.g., miR-21, miR-210, miR-22), whereas hepatic MSC exosomes

are enriched with **anti-fibrotic and metabolic regulators** such as **miR-122** and **HGF mRNA** [181, 182].

Example

- **Cardiac MSC-derived exosomes**, enriched in **miR-210** and **miR-22**, have been shown to **enhance angiogenesis, suppress apoptosis, and improve post-myocardial infarction (MI) cardiac function** in preclinical studies [183].
- **Liver MSC exosomes** containing **miR-122** reduced **fibrosis, downregulated collagen deposition, and restored hepatic enzyme homeostasis** in experimental models of **chronic hepatic injury** [182].

Future Direction

Advancing this field will rely on **engineering exosomes** with **enhanced targeting peptides, surface ligands, or payload delivery systems** to improve **tissue specificity and therapeutic potency**. For example, conjugation with **RGD peptides** or **organ-homing motifs** can improve **endothelial or parenchymal uptake**, while **nanocarrier hybridization** may extend **circulatory half-life and controlled release** at the target site [184].

Emphasis on Organ-Specific Delivery Advantages

The **organ-specific origin** of exosomes offers a **biological targeting mechanism** unmatched by generic MSC-derived vesicles. By leveraging **inherent tropism** and **microenvironmental adaptation**, OS-MSC exosomes can:

- **Enhance homing** to injured tissues through **integrin-ligand interactions** reflective of their native niche.
- Deliver **precisely tuned cargo** (e.g., organ-relevant miRNAs, growth factors, transcriptional regulators) optimized for **local repair pathways**.
- Enable **systemic administration** with **reduced off-target accumulation, minimized immune activation, and improved biodistribution efficiency**, particularly for **cardiac, hepatic, or neurological applications**.

Thus, **cell-free, organ-specific exosome therapy** bridges the gap between **cellular complexity and pharmacologic control**, offering a **scalable, safe, and precision-guided regenerative platform** for next-generation therapeutics.

8.4 Integration with CRISPR Gene Editing for Targeted Repair

Concept

Apply **CRISPR/Cas9-based gene editing** to **organ-specific mesenchymal stem cells (OS-MSCs)** to:

- **Enhance survival under stress** (e.g., upregulating anti-apoptotic genes like *BCL2*).
- **Boost regenerative factor secretion** (e.g., *VEGF* overexpression for angiogenesis).
- **Knock out pro-fibrotic genes** (e.g., *TGF-β receptors*) to limit scar formation.
- **Correct disease-causing mutations** in autologous OS-MSCs before re-implantation.

Example

In **preclinical cardiac models**, **CRISPR-enhanced cardiac MSCs** with **overexpressed CXCR4** improved **homing** to ischemic myocardium and **boosted functional recovery** [185].

Enhancing Organ-Specific MSC Functionality

CRISPR-mediated genetic modification offers a **precision toolkit** to **optimize OS-MSCs for their native tissue microenvironment**, addressing the limitations of conventional MSC therapy (poor engraftment, heterogeneity, and transient efficacy). By tailoring **gene circuits to organ-specific needs**, researchers can **amplify intrinsic advantages** of OS-MSCs:

- **Improved Homing and Retention**
Upregulation of **chemokine receptors** such as *CXCR4*, *CCR2*, or *CXCR7* can enhance **chemotactic migration** toward injury sites rich in **SDF-1** gradients [185]. For example, **CXCR4-edited cardiac MSCs** demonstrated **2–3× greater myocardial retention**, augmenting **angiogenesis** and **left ventricular ejection fraction recovery** compared to unmodified MSCs.
- **Enhanced Survival under Oxidative or Ischemic Stress**
Editing OS-MSCs to **overexpress anti-apoptotic genes** (*BCL2*, *HIF-1α*, *AKT1*) or **silence pro-apoptotic regulators** (*BAX*) improves **cell viability** in harsh microenvironments such as **ischemic myocardium, fibrotic liver, or hypoxic cartilage**. This is particularly relevant for cardiac and hepatic MSCs, which face **high ROS burden** and **metabolic stress** post-transplantation.
- **Optimized Secretome for Organ-Specific Regeneration**
CRISPR activation (CRISPRa) systems can **upregulate paracrine mediators** tailored to each organ’s repair pathway:
 - *VEGF*, *FGF2*, and *ANGPT1* → **Cardiac and vascular repair**
 - *BDNF*, *GDNF*, *NGF* → **Neuroregeneration** in DPSCs or neural MSCs
 - *HGF*, *IL-10*, *IDO1* → **Hepatic and anti-inflammatory effects**
 These modifications create **“designer OS-MSCs”** with **enhanced trophic signaling** and **microenvironmental adaptation** [186].
- **Reduction of Fibrotic or Pro-Inflammatory Potential**
Deletion of *TGFBR1*, *CCN2* (*CTGF*), or *COL1A1* can reduce **fibroblast-like differentiation** and **ECM overproduction**, mitigating risks of **scar formation** in chronic injury models. This approach supports **regenerative healing** over fibrosis, particularly in **hepatic, renal, and pulmonary applications**.
- **Correction of Patient-Specific Genetic Defects**
In autologous settings, **CRISPR-corrected OS-MSCs** derived from patients with **monogenic disorders** (e.g., *COL1A1* mutations in osteogenesis imperfecta, *G6PC* in glycogen storage disease) can restore **normal function** and serve as **autologous gene-corrected grafts**, minimizing immunogenic risk.

Strategic Outlook

Integrating **CRISPR precision editing** with **organ-specific MSC therapy** represents a paradigm shift toward **next-generation regenerative medicine**—enabling **tailored, durable, and mechanistically predictable outcomes**. Combining **multi-gene editing** with **epigenetic tuning** may further refine **lineage stability, immunomodulatory potency, and contextual responsiveness** of OS-MSCs, paving the way for **“smart” cell therapeutics** that can dynamically adapt to their repair milieu.

8.5 Artificial Niches or Hydrogels to Mimic Organ Environments

Concept

Precondition or maintain OS-MSCs in bioengineered microenvironments that simulate the target organ’s ECM composition, stiffness, and biochemical cues.

Benefits

- Maintains organ-specific phenotype and secretome during ex vivo expansion.
- Increases survival and engraftment upon transplantation.

- Allows disease-specific preconditioning (e.g., hypoxia for cardiac MSCs, cyclic stretch for lung MSCs).

Example

Hydrogel scaffolds functionalized with cardiac ECM peptides enhanced VEGF secretion and contractile support by cardiac MSCs in MI models [187].

Further

Perspective

These artificial niches or hydrogels can serve as **ex vivo preconditioning platforms** to reinforce the **functional fidelity and therapeutic potency** of organ-specific MSCs. By exposing cells to **biophysical cues** (e.g., shear stress, stiffness gradients, oxygen tension) and **biochemical signals** (e.g., organ-derived ECM proteins, growth factors, cytokines), researchers can fine-tune the **epigenetic memory, metabolic activity, and secretory profile** of OS-MSCs before clinical use [188, 189].

For instance, **cardiac MSCs** cultured in **myocardial-mimicking hydrogels** demonstrate enhanced **angiogenic** and **anti-apoptotic** activity through upregulated expression of *VEGF*, *HGF*, and *ANGPT1*, thereby improving myocardial repair post-transplantation (Huang et al., 2020; Zhang et al., 2016). Similarly, **hepatic MSCs** preconditioned within **liver-like matrices** enriched with **collagen IV** and **laminin** show augmented **anti-fibrotic, hepatoprotective, and metabolic support** properties, attributed to preserved niche-specific signaling pathways [177, 190].

This **organ-mimetic preconditioning** ensures that OS-MSCs retain **tissue-specific functional traits** and enhances their ability to **integrate, survive, and modulate host immune and inflammatory responses** following transplantation. Moreover, these engineered microenvironments can serve as **predictive ex vivo screening tools** for assessing MSC potency, enabling optimization of ECM composition, stiffness, and oxygenation levels tailored to each **organ system**. Such approaches accelerate **precision regenerative medicine**, bridging the gap between preclinical promise and clinical efficacy.

8.6 Artificial Intelligence and Machine Learning for MSC Optimization

Concept

Artificial Intelligence (AI) and Machine Learning (ML) technologies are increasingly being applied to optimize stem cell-based regenerative therapies. In the context of organ-specific MSCs (OS-MSCs), AI/ML can serve as **powerful tools for source selection, potency prediction, patient stratification, and mechanistic insights** by integrating multi-omics, imaging, and clinical outcome data.

Applications

- **Identifying Optimal MSC Sources:**

AI-driven pattern recognition applied to **transcriptomic, proteomic, and metabolomic profiles** can classify MSCs based on functional potency, differentiation potential, and organ-specific signatures. This enables researchers to select elite donors and the most suitable tissue source (e.g., cardiac vs. hepatic MSCs) for specific indications [191].

- **Predicting Therapeutic Outcomes:**

ML algorithms can analyze **preclinical and clinical datasets** to identify predictive biomarkers (e.g., secretome factors, surface markers) that correlate with favorable therapeutic responses, thereby enhancing **patient selection and precision therapy design** [192].

- **Analyzing Complex Omics Data:**

Integrative AI frameworks, such as **deep learning** and **graph-based neural networks**, can unravel complex interactions between **genomic, epigenetic, and metabolic pathways**, providing insights into **mechanisms of action and organ-specific differentiation** [193].

- **Quality Control and Manufacturing:**

AI-based image analysis tools are increasingly used for **non-invasive MSC quality monitoring**, tracking morphological changes, senescence, and viability during **ex vivo expansion** to ensure GMP-grade consistency [194].

Future Perspective

The integration of AI/ML into OS-MS-C research marks a step toward **data-driven regenerative medicine**, enabling the creation of **digital twins** of MSC behavior under different microenvironmental conditions, predicting **therapy outcomes** before clinical application. As multi-omics databases expand, **AI-powered decision support systems** may become indispensable for designing **personalized, organ-specific stem cell therapies** with enhanced safety, potency, and reproducibility.

9. Conclusion

Over the past three decades, the field of mesenchymal stem/stromal cell (MSC) research has witnessed a paradigm shift — from the early view of **bone marrow-derived MSCs** as universal regenerative cells to the current recognition of **organ-specific, tissue-resident MSC populations** with distinct biological identities. Insights from **transcriptomics, proteomics, and niche biology** have revealed that MSCs are not uniform but exhibit **microenvironment-driven specialization**, enabling improved survival, integration, and functional performance within their native tissues.

This evolution has profound clinical implications. **Endometrial MSCs** have shown targeted regenerative potential for intrauterine disorders such as **Asherman's syndrome** and **thin endometrium**; **cardiac MSCs**, characterized by a **cardioprotective secretome** and **hypoxia tolerance**, demonstrate superior outcomes in **myocardial infarction** and **heart failure**; and **liver-resident MSCs** exhibit robust **anti-fibrotic** and **immunomodulatory** properties, redefining therapeutic strategies for **cirrhosis** and **acute liver injury**. Comparable benefits are emerging from **pulmonary, renal, and pancreatic** MSC studies, collectively underscoring the importance of **matching MSC origin to disease context** for optimal therapeutic efficacy.

Despite these advances, **routine clinical translation** of MSC-based therapies remains limited by several challenges, including:

- **Donor and source heterogeneity**, leading to variable therapeutic outcomes,
- **Limited engraftment and homing efficiency**,
- **Inconsistent potency assays** that fail to predict in vivo performance, and
- **Regulatory and manufacturing barriers** to scalable, GMP-compliant production.

To bridge these gaps, the field must prioritize:

- Development of **potency and identity assays** tailored to specific organ-derived MSCs,
- Establishment of **standardized, GMP-grade production pipelines** that preserve organ-specific traits, and
- Execution of **head-to-head clinical trials** comparing **organ-specific** and **conventional MSCs** in defined disease settings.

Collectively, these efforts converge toward the vision of **precision stem cell therapy** — selecting the **right MSC type**, from the **right source**, for the **right disease**. **Organ-specific MSCs (OS-MS-Cs)** thus represent a significant advancement toward **personalized, targeted, and more effective regenerative therapies**, offering superior **tissue integration, functional relevance, and reduced off-target effects**.

However, their **widespread clinical adoption** will depend on overcoming **translational bottlenecks**, ensuring **long-term safety**, and integrating **regulatory harmonization** across global frameworks. Looking forward, the fusion of **bioengineering**, **CRISPR-based enhancement**, **exosome-based cell-free therapies**, **AI-driven cell profiling**, and **artificial niche technologies** is expected to accelerate the clinical maturity of organ-specific MSC platforms. With these innovations, **organ-specific MSCs hold transformative potential** to revolutionize regenerative medicine — ushering in a new era of **precision, predictability, and patient-specific therapy** for complex diseases across multiple organ systems.

Table 3. Overview of Organ-Specific Diseases and Corresponding Mesenchymal Stem Cell (MSC) Sources Utilized for Targeted Regenerative and Therapeutic Applications.

Organ Affected	Associated Disease(s)	MSCs Used
Heart	Myocardial infarction, ischemic cardiomyopathy	Cardiac MSCs, Bone marrow-derived MSCs (BM-MSCs)
Liver	Liver cirrhosis, acute liver failure, NAFLD	Liver-derived MSCs, Umbilical cord MSCs (UC-MSCs)
Lung	COPD, Pulmonary fibrosis, Acute Respiratory Distress Syndrome (ARDS)	Lung-derived MSCs, Adipose-derived MSCs (AD-MSCs)
Kidney	Acute kidney injury (AKI), Chronic kidney disease (CKD), Diabetic nephropathy	Kidney-derived MSCs, UC-MSCs, BM-MSCs
Endometrium	Asherman’s syndrome, Thin endometrium, Infertility	Endometrial MSCs (eMSCs), Menstrual blood MSCs (MenSCs)
Pancreas	Type 1 & Type 2 Diabetes mellitus	Pancreatic MSCs, AD-MSCs, BM-MSCs
Intestine	Crohn’s disease, Perianal fistula	Adipose-derived MSCs (e.g., Darvadstrocel)
Joint (Cartilage)	Osteoarthritis, Rheumatoid arthritis	BM-MSCs, AD-MSCs
Brain/Neuro	Autism Spectrum Disorder, Stroke, Multiple sclerosis	BM-MSCs, UC-MSCs, Neural tissue MSCs
Eye (Retina)	Retinitis pigmentosa, Diabetic retinopathy	Retinal MSCs, BM-MSCs, UC-MSCs

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