

Mesenchymal Stem Cells as Living Bio-drugs: Adding a Novel Dimension to Cardiology and Cardiovascular Sciences

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Keywords

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Abstract

Mesenchymal stem cells (MSCs) are rapidly emerging as living biodrugs with significant potential in regenerative medicine, particularly cardiovascular applications. The recent FDA approval of the first allogenic MSC-based product, Ryoncil (remestemcel-L-rknd), for steroid-refractory acute graft vs. host disease (GvHD), underscores their safety and effectiveness. This paves the way for MSCs to be a safe and effective innovative treatment strategy for acute and chronic ischemic heart disease and cardiomyopathy. Preclinical experiments and translational study data have shown that MSCs have the potential to improve cardiac pump function significantly, opening up a promising avenue for further research. This mini-review explores the promising potential of MSCs as a living drug, offering hope for patients with cardiovascular pathologies.

List of Abbreviations

AD: Adipose tissue

ATMP: Advanced Therapeutic Medicinal Products

Auto: Autologous

Allo: Allogenic

BM: Bone marrow

CABG: Coronary artery bypass grafting

COPD: Chronic obstructive pulmonary disease

CD: Crohn's disease

GVDH: Graft vs. host disease

ISCT: International Society for Cellular Therapy

MI: Myocardial Infarction

MSCs: Mesenchymal stem cells

PTCI: Percutaneous transluminal coronary intervention

UCB: Umbilical cord blood.

Introduction

Cardiovascular pathologies remain the leading cause of morbidity and death globally. According to the recently published Heart Disease and Stroke data by the American Heart Association, cardiovascular pathologies incur high financial costs and health burdens in the USA and worldwide (Martin et al., 2024). Although contemporary patient management strategies combined with pharmacological

and surgical options have immensely progressed, most of these strategies only provide symptomatic alleviation of the disease process. Recent advances in revascularization myocardial strategy, such as coronary artery bypass grafting (CABG) and percutaneous transluminal coronary intervention (PTCI), have been made, but the approaches are invasive. Heart transplantation remains the gold standard surgical intervention, but it suffers from a lack of sufficient donors to fulfill the patients' demand. Hence, an urgent need warrants a search for novel therapeutic options. Cell-based therapy, in general, and mesenchymal stem cell (MSC)-based therapy, in particular, have shown encouraging results in both experimental and clinical settings and provide hope for the critically ill patients with compromised cardiac function via angiomyogenic repair of the damaged myocardium.

Mesenchymal stem cells

Widely present in the mesenchymal tissue in the body, MSCs are non-hematopoietic, multipotent cells with unique differentiation potential to adopt phenotypes of various mesenchymal cell lineages and tissues. They were first identified by Friedenstein in bone marrow as stromal cells in 1966, and they were later named MSCs by Caplan et al. (Caplan et al., 1991). Based on the criteria set by the International Society for Cellular Therapy (ISCT), MSCs must show preferential plastic adherence and trilineage differentiation potential in response to specific cues in vitro culture conditions (Dominici et al., 2006). Additionally, these criteria include the possession of identification markers CD73, CD90, and CD105, the absence of CD45, CD34, CD14, CD11b, CD19, and Human Leukocyte Antigen Complex II, and the expression of transcription factors and plastic-adherence in standard culture conditions (Alvarez-Viejo & Haider, 2022). More recently, these cells have been proposed to be renamed as Medicinal Signaling Cells as they extravasate from their niches in response to the chemical cues and home in on the injured tissue to participate in the repair and regeneration activities (Caplan, 2017). Despite the ISCT criteria, their properties and performance during cell-based therapy are affected by diverse factors encompassing the tissue source from which they are derived to the health status of the donors (Safwan et al., 2024 and 2024).

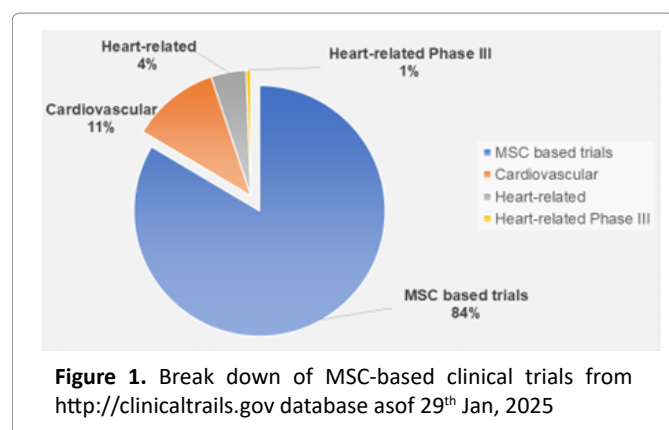
The best thing about MSCs is the ease of their isolation and purification protocols and their considerable ex vivo expansion potential. Several optimized protocols (2D and 3D culture conditions) are now available to efficiently and reproducibly isolate MSCs from diverse tissue sources, each with a specific characteristic despite possessing similar morphology, basic biology, and characteristics. Hitherto, MSCs have been isolated from adult tissues such as adipose tissue, BM, peripheral blood, dental pulp, skin, muscle, endometrium, and ovary, as well as perinatal/fetal sources,

like the placenta, umbilical cord blood (UCB), and umbilical cord (UC) matrix/tissue (Kamal et al., 2022). However, the most important and extensively studied tissue sources for cell-based therapy are bone marrow, Adipose tissue, and Wharton's jelly-derived MSCs (WJ-derived MSCs). Besides tissue sources, their availability from autologous and allogenic sources remains an inconclusive debate regarding their superiority in clinical settings (Ahmed et al., 2025).

Their near-ideal characteristics, cell biology, and multifactorial mechanism of action leading to tissue repair and regeneration have been instrumental in making MSCs one of the most extensively studied cell types (Kamal et al., 2022). They have several functions encompassing multilineage differentiation potential to anti-inflammatory and immunomodulatory properties, allowing them to contribute therapeutically *via* multifactorial mechanisms. These mechanisms include the secretion of bioactive molecules that modulate the local microenvironment, promoting cell survival and proliferation and suppressing immune responses (Mishra et al., 2020). They also release a plethora of bioactive molecules as part of their paracrine activity, including soluble and insoluble components, i.e., secretomes and exosomes, respectively (Xia et al., 2021). More recently, their derivative extracellular vesicles, previously considered "garbage bags," are being extensively studied for theragnostic applications (Mushtaq et al., 2024). These extracellular vesicles serve as signalosomes as they fuse with the recipient cells to deliver their payload of bioactive molecules and initiate specific signaling circuits in the recipient cells to regulate different cellular functions. On the same note, the soluble fraction of the paracrine secretions constitutes a significant mechanism of action by which stem cells incur their therapeutic benefits (Haider and Aziz, 2017). Hence, MSC-derived secretomes and exosomes are emerging as a cell-free therapy approach in regenerative medicine (Haider & Aramini, 2020).

MSCs in Cardiovascular Pharmacology, the Clinical Perspective

MSCs have been extensively characterized in experimental small animal models and translational studies, leading to over 1500 clinical trials (listed on the <http://clinicaltrials.gov> database) across phases I, II, and III. Many more trials may be underway in their respective countries, but not yet listed in this database. These trials have investigated the use of MSCs as a living biodrug for a wide range of clinical conditions, including immune system support, severe COVID-19 symptoms, musculoskeletal injuries and chronic pain, cardiovascular, GIT, ophthalmic, autoimmune diseases, and degenerative diseases such as multiple sclerosis, severe arthritis, Parkinson's disease, and Alzheimer's disease. This extensive research and clinical trials provide a comprehensive understanding of the potential of MSCs in various medical conditions, including



cardiovascular diseases. In the context of cardiovascular diseases, these trials have primarily focused on assessing the safety and efficacy of MSCs in patients with heart and vascular pathologies. Of these, 83 clinical trials have specifically targeted heart diseases, with eleven Phase III trials (all interventional studies) using MSC-based products (Figure 1).

It all started with an industry-sponsored Phase III assessment of Rexlemestrocel-L (under the trade name of Prochymal® and containing cryopreserved allogenic MSCs) in 2009 when Orisis Therapeutics (USA) conducted the first allogenic MSC-based trials to treat patients with steroid-refractory GvHD (Daly et al., 2012). These data led to the approval of Prochymal® for use in children with GvHD (Martin et al., 2010). Subsequently, Rexlemestrocel-L has also been trialed for patients with diabetes type-I (NCT 00690066) and heart failure (NCT02032004). Since then, MSC-based clinical trials have exponentially grown (Galderisi et al., 2022). Table I outlines the summary of phase III clinical trials in heart patients. Data from most of these clinical trials is still awaited. As new kids on the block, little is known about their pharmacokinetic behavior post-engraftment. From the route of administration (Jihwprani et al., 2024) to the primary pharmacokinetic parameters, including optimum dose and volume of distribution (Vd), all the parameters still need to be established for their optimal use and establish them for routine applications in the clinic (Kalou et al., 2023; Ahmed et al., 2024). On the same note, efforts are still underway in clinical settings to achieve a mechanistic understanding of their efficacy, which, in most cases, is considered multifactorial. Lacking this vital information has led to modest outcomes in clinical settings for their use in heart-related pathologies.

Researchers have also ascribed the modest outcome of the previous clinical data from MSCs-based treatment to the unfavorable inflammatory milieu of the ischemic myocardium infiltrated by the pro-immunomodulatory cells. This has led to cell priming strategies before use in the clinic (Haider, 2024). Advancing their cardiopoietic conditioning approach reported in CHART-I in 39 centers

(n= 484 patients) (Bartunek et al., 2017), Yamada et al. have recently reported the most extensive Phase III CHART-1 (Congestive Heart failure cArdiopoietic Regenerative Therapy-1) trial using cardiopoietically conditioned BM-derived MSCs (Yamada et al., 2024).

Data from Phase III trials is anticipated to answer unresolved issues facing MSC-based therapy treating cardiovascular pathologies. Another important consideration for the success of MSC-based living biodrugs is their off-the-shelf availability, which necessitates their use from allogenic tissue sources. Although many MSC-based commercial products use allogenic cells, the superiority debate between allogenic and autologous cells remains inconclusive (Ahmed et al., 2025). The situation is accentuated by the donor-related factors affecting their biology and functional heterogeneity, especially for long-term benefits, thus raising their post-transplantation performance.

MSCs as Living Biodrugs

As we enter the era of Advanced Therapy Medicinal Products (ATMP) (Mello et al., 2024), MSC-based products are amongst the earliest entrants into the pharmaceutical market after completing extensive characterization in experimental settings and safety and efficacy assessment during advanced phases of clinical evaluation. This novel class of viable drugs in pharmacology is in the early phase of development, as these drugs deviate entirely from contemporary pharmaceuticals and biopharmaceuticals. Reparability and regeneration of the damaged remain the unique discriminating characteristics of ATMP, which distinguish them from other contemporary drug classes. Their viability remains the primary factor that determines their efficacy. To date, nine commercially available MSC-based products have been approved by the respective drug agencies of South Korea, India, the EU, Japan, Canada, and New Zealand (Table II).

Among the S. Korean MSC-based products, MEDIPOST's product Cartistem was the first commercially launched product for knee osteoarthritis. More recently, on 18th December 2024, the FDA, USA also approved the first Allo^{BM}-MSC-based product Ryoncil (Mesoblast Inc.) to treat steroid-refractory acute graft versus host disease after the successful completion of a multicenter clinical trial (NCT02336230). Cellgram® was the first stem cell-based drug product approved by the Ministry of Food and Safety, South Korea, in 2011 (Yang, 2011). Known as Hearticellgram at the time of approval and derived from autologous patient BM-MSCs, the product was developed by FCB-Pharmicell for use within 72 hours after AMI and has been shown to improve LVEF by 6%. A phase III multicentre, open-label, randomized parallel assignment clinical trial (NCT01652209) was led by Prof Jeonghan

Table I: Phase III clinical studies to treat heart diseases (derived from clinicaltrials.gov).

NCT #	Study Title	Brief Summary	Condition	Interventions	Study Type
NCT01759212	Combined With Allogeneic MSCs Implantation in Patients With End-stage HF	To investigate the safety and efficacy of I.M. allogeneic MSCs in patients with end-stage ischemic cardiomyopathy undergoing LVAD implantation.	HF, Ischemic Cardiomyopathy	Allogeneic stem cell implantation	INTER
NCT02672267	A Study of Allogeneic Low Oxygen BM-MSCs in Subjects With MI	To study the safety, tolerability, and efficacy of human allogeneic ischemia tolerant BM-MSCs (aLoOxMBMC) given I.V to AMI (STEMI, non-STEMI) patients.	MI	Stem cells vs. placebo	INTER
NCT01392105	Safety and Efficacy of Intracoronary Adult Human MSCs After AMI	To assess the safety and efficacy of intracoronary autologous BM-MSCs in patients with AMI.	AMI	MSCs vs. control group	INTER
NCT05935423	US-MSC Improves Cardiac Function on STEMI Patients	To study the effectiveness of UC-MSC in patients with STEMI for infarct myocardial size reduction and prevent the incidence of HF in the future.	STEMI	UC-MSCs	INTER
NCT01394432	"ESTIMATION Study" for Endocardial MSCs Implantation in Patients After AMI.	To study endocardial stem cell implantation after PCI could reduce scar formation and increase reverse remodeling in AMI patients.	AMI, HF	PCI and Stem Cells or Placebo	INTER
NCT02032004	Efficacy and Safety of Allogeneic MPCs (Rexlemestrocel-L) for the Treatment of HF.	To determine whether trans-endocardial delivery of allogeneic rexlemestroce effectively treats chronic HF due to LV systolic dysfunction.	CHF	Allogeneic MPCs	INTER
NCT05043610	MSCs for Prevention of MI-induced HF	To determine whether the IC infusion of WJ-MSCs in AMI patients with impaired LVEF would prevent HF and future adverse events.	MI, AMI, STEMI, HF	WJ-MSCs vs. routine Treatment	INTER
NCT01652209	To Evaluate the Efficacy and Safety of Hearticelgram [®] -AMI in Patients With AMI	To compare the efficacy and safety of a single dose of Hearticelgram-AMI injected into AMI patients.	AMI	Hearticelgram-AMI	INTER
NCT03418233	Evaluate the Regenerative Capacity of CardioCell in Patients With CIHF	To compare CardioCell in treating ischemic cardiovascular system damage vs. the control group.	HF	CardioCell vs. Placebos	INTER
NCT03404063	Cardiovascular Clinical Project to Evaluate the Regenerative Capacity of CardioCell in Patients With AMI	To compare CardioCell treating ischemic cardiovascular damage vs. the control group with placebo during the sham procedure.	MI	CardioCell Vs. Placebos	INTER

Abbreviations: AMI: Acute myocardial infarction; BM-MNCs: Bone marrow mononuclear cells; CIHF: Chronic Ischemic Heart Failure; HF: Heart Failure; IC: Intracoronary; Inter: Interventional; I.M: Intramyocardial; LVEF: Left ventricle ejection fraction; LVAD: Left Ventricular Assist Device; MI: Myocardial Infarction; MSCs: Mesenchymal stem cells; MPC: Mesenchymal progenitor cells; PCI: Percutaneous coronary intervention; RCT: Randomized Clinical Trial; STEMI: ST-elevation Myocardial Infarction; UC-MSC: Umbilical cord-derived MSCs; UC-WJ-MSCs: Umbilical cord-derived Wharton's jelly MSCs;

Yoon from Wonju Severance Christian Hospital and sponsored by Pharmicell Co., Ltd., which determined the safety and efficacy of the single dose of the drug product in 90 patients between 20 and 75 years of age. The results of the study have yet to be made available.

Considering the recent progress in cell culture techniques and optimization of cell-harvesting and processing protocols, the future of the global MSC market is promising in terms of medical advancements and economic growth. Projected to achieve a 3.12-billion-dollar target in 2023, it is expected to grow at a CIGAR

rate of nearly 13% between 2024 and 2030. This significant growth presents a wealth of opportunities for those involved in regenerative medicine, particularly MSC users. Some leading companies hold dominant shares in the MSC market, including Thermo Fisher Scientific, Inc., STEMCELL Technologies, Merck KGaA, Lonza, and Promocell GMBH, to name a few.

Conclusion

Unlike the contemporary symptomatic treatment options for cardiovascular pathologies, mainly focusing on

Table II

Product and Manufacturer	Approved in (country)	Cell source	Potential uses
Alofisel® (Tigenix)	European Union	AlloAD-MSCs	Perianal Fistula in patients with Crohn's Disease
Cartistem® (Medipost)	South Korea	AlloUCB-MSCs	Knee cartilage defects, rheumatoid arthritis, degenerative arthritis
Cupistem® (Anterogen)	South Korea	AutoAD-MSCs	Crohn's fistula
CellGram-AMI® (FCB Pharmicell)	South Korea	AutoBM-MSCs	Acute MI
Neuronata® (Corstem)	South Korea	AutoBM-MSCs	Amyotrophic lateral sclerosis
Queen cell® (Anterogen)	South Korea	AutoBM-MSCs	Connective tissue disorders
Stemirac® (Nipro Corp)	Japan	AutoBM-MSCs	Spinal cord injury
Stempeuce®	India	AlloAD-MSCs	Critical limb ischemia
TEMCELL® (JCR Pharma Ltd)	Japan, Canada, and New Zealand	AlloBM-MSCs	COPD, Crohn's Disease, MI, Acute GvHD, Type-I diabetes.
Cymerus™ (Cynata Therapeutics Ltd)	UK, Medicines and Healthcare Products Regulatory Agency (MHRA)	iPSC-MSCs (mesenchymoangioblasts)	GvDH
Maestro Cell (Cell Tech Pharmed Co.)	FDA, Iran (IR-FDA)	BM-MSCs	Knee osteoarthritis
Ryoncil (Parenchymal, Remestemcel-Lrkn; Mesoblast Inc.,)	Canada and the USA FDA	BM-MSCs	Steroid-refractory GvDH

Abbreviations: AD: Adipose tissue; Auto: Autologous; Allo: Allogenic; BM: Bone marrow; COPD: Chronic obstructive pulmonary disease; CD: Crohn's disease; GVDH: Graft vs. host disease; MI: Myocardial Infarction; MSCs: Mesenchymal stem cells; UCB: Umbilical cord blood.

the heart, living biodrug MSC-based therapy is a potential reparative and curative treatment approach. This is even more significant for no-option patients. However, despite all the optimism and even when multiple MSC-based products have been marketed, many unanswered questions exist. Similarly, numerous factors that influence the effectiveness of heart cell therapy need to be addressed for a better prognosis. The available biodrugs may need to be modified, i.e., physically, chemically, or genetically, to address these issues, depending upon their subsequent therapeutic application and given their particular logistic considerations. Together, MSCs have transpired into the mainstay of cell-based therapy ahead of other stem/progenitor cell types. Moreover, their derivative exosomes and secretomes are also moving into the clinical assessment phase (i.e., SECRET-HF, NCT05774509), as Habib et al. described elegantly after extensive characterization in small and large experimental models of myocardial infarction and heart failure (Habib et al., 2025). However, it will need some time to establish optimized protocols to ensure standardization and quality control before these derivatized preparations of MSCs are available as a routine treatment option in clinical settings.

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