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REVIEW

Mesenchymal Stromal Cells: an Antimicrobial and Host-Directed Therapy for Complex Infectious Diseases

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SUMMARY There is an urgent need for new antimicrobial strategies for treating complex infections and emerging pathogens. Human mesenchymal stromal cells (MSCs) are adult multipotent cells with antimicrobial properties, mediated through direct bactericidal activity and modulation of host innate and adaptive immune cells. More than 30 *in vivo* studies have reported on the use of human MSCs for the treatment of infectious diseases, with many more studies of animal MSCs in same-species models of infection. MSCs demonstrate potent antimicrobial effects against the major classes of human pathogens (bacteria, viruses, fungi, and parasites) across a wide range of infection models. Mechanistic studies have yielded important insight into their immunomodulatory and bactericidal activity, which can be enhanced through various forms of preconditioning. MSCs are being investigated in over 80 clinical trials for difficult-to-treat infectious diseases, including sepsis and pulmonary, intra-abdominal, cutaneous, and viral infections. Completed trials consistently report MSCs to be safe and well tolerated, with signals of efficacy against some infectious diseases. Although significant obstacles must be overcome to produce a standardized, affordable, clinical-grade cell therapy, these studies suggest that MSCs may have particular potential as an adjunct therapy in complex or resistant infections.

KEYWORDS antimicrobial, cell therapy, clinical trials, host-directed therapy, immunomodulation, immunotherapy, infectious diseases, mesenchymal stromal cells, pathogens

INTRODUCTION

There is an urgent need to develop new therapeutic strategies for treating infectious diseases (1, 2). Research approaches include pathogen-directed therapies, comprising innovative antimicrobial compounds and drug combinations, as well as host-directed therapies (HDTs), which enhance the immune response to promote pathogen clearance. A wide variety of candidate HDTs have been proposed, including repurposed drugs, recombinant proteins, monoclonal antibodies, and cellular therapies (3–5).

Mesenchymal stromal cells (MSCs) are adult multipotent cells with immunomodulatory, anti-inflammatory, and antimicrobial properties (6). More than 1,000 clinical trials into MSC therapies have been registered on ClinicalTrials.gov, of which the majority study their potential in promoting tissue repair and regeneration after injury or modulation of dysregulated inflammation (as in the acute respiratory distress syndrome and acute graft rejection) (https://clinicaltrials.gov/). However, MSCs are also being investigated to treat infectious diseases and/or sepsis. These clinical trials (>80 to date [https://clinicaltrials.gov/]) are supported by laboratory studies exploring diverse antimicrobial mechanisms of MSCs in various infection models (7–9).

This review summarizes and critically appraises the preclinical and clinical evidence for MSC efficacy against bacterial, viral, fungal, and parasitic infections. We also give an overview of the current limitations of MSC therapies, the key questions around the source and nature of MSC therapy, and finally the therapeutic potential of MSCs for treating complex human infections for which there are limited treatment options.

MESENCHYMAL STROMAL CELLS

MSCs are nonhematopoietic multipotent adult stromal cells that contribute to tissue repair and regeneration across the body. They were first isolated from bone marrow where they play a supportive role in the hematopoietic stem cell niche (10). They have since been found in the perivascular component of a diverse range of organs, including the lung, umbilical cord (Wharton's jelly), and adipose tissue (11). They have broad *in vitro* differentiation potential, including into cells of the mesenchymal lineage (osteoblasts, adipocytes, and chondrocytes) (12) and also into ecto- and endodermal cells, such as lung epithelium and astrocytes (13). In health, MSCs have important regulatory roles in inflammation and can modulate the activity of immune cells, including dendritic cells (DCs), monocytes/macrophages, neutrophils, and lymphocytes that drive regenerative processes (14). MSCs express a range of Toll-like receptors (TLRs) through which they sense host injury and pathogen activity (15).

MSCs are defined by the International Society for Cellular Therapy (ISCT) (16) as (i) being plastic-adherent under standard culture conditions; (ii) being able to differentiate *in vitro* into osteoblasts, adipocytes, and chondroblasts; and (iii) having a specific surface antigen profile (positive for CD105, CD73, and CD90; negative for CD45, CD34, CD14, CD11b, CD79α, CD19, or human leukocyte antigen [HLA]-DR). The ISCT distinguishes mesenchymal stromal cells from "mesenchymal stem cells," which must have demonstrable self-renewal properties, and they recommend the use of the abbreviation MSCs for mesenchymal stromal cells supplemented by the tissue-source origin of the cells to reflect any tissue-specific properties (17).

Tissue Sources for MSCs

Bone marrow-derived MSCs (BM-MSCs) remain the most extensively studied tissue source, which are employed for the majority of *in vivo* infection studies and clinical trials using human MSCs (Tables 1 to 3). However, a wide range of other tissue sources are increasingly under investigation for infectious diseases, including adipose tissue (AD-MSCs) (18–20), umbilical cord blood or umbilical cord connective tissue (Wharton's jelly) (UC-MSCs) (21, 22), menstrual blood (Men-MSCs) (23), dental pulp (DP-MSCs) (ClinicalTrials registration no. NCT04336254), and olfactory mucosa (OM-MSCs) (ClinicalTrials registration no. NCT04382547).

BM-MSCs are isolated following bone marrow aspiration which is an invasive procedure with associated risks for the donor. In addition, the MSC yield is small (as for dental pulp and olfactory mucosa) and necessitates massive cell expansion to achieve sufficient numbers for therapeutic use. AD-MSCs are isolated from adipose tissue sampling by liposuction, which yields more tissue with less trauma for the donor. UC-MSCs are found in large quantities from Wharton's jelly, which is typically discarded postpartum. Therefore, AD-MSCs and particularly UC-MSCs have practical advantages over BM-MSCs, although the evidence base for their efficacy is not as well-established.

MSCs from different tissue sources are similar morphologically and biologically but have some distinct characteristics (24, 25). They include differences in surface cell markers (such as CD36 which is specific to AD-MSCs [26]) and differentiation capacity (with BM-MSCs demonstrating greater osteogenic potential than AD-MSCs [27]). Differences in potency between MSC tissue source have been reported, although they are better characterized in noninfectious disease models using animal MSCs (28, 29). Only two *in vivo* studies to date have compared BM-MSCs and UC-MSCs in infection models, with both using cecal ligation and puncture. One study found human BM-MSCs and UC-MSCs were comparable in promoting survival in murine peritoneal sepsis through modulating regulatory T cell (Treg) function (30). However, a later study reported human BM-MSCs were more protective than UC-MSCs (31). Although both cell types modulated levels of systemic inflammatory cytokines (including interleukin-6 [IL-6], IL-1β, and tumor necrosis factor alpha [TNF-α]), only human BM-MSCs improved 7-day murine survival and enhanced bacterial clearance in blood, lung, and spleen. The discrepancy between in these two studies may be related to the model severity, with 7-day survival rates of 80% and 30%, respectively, in the placebo-treated groups.

TABLE 1 Human MSCs in preclinical trials of infectious diseases[a]

Reference	Infection model	Intervention	Outcome	Proposed mechanism
Gupta et al. (183)	C57BL/6 mice, i.t. instillation of *E. coli* LPS	0.75×10^6 human BM-MSCs, i.t. administration	↑ survival, ↓ lung proinflammatory cytokines, ↓ histological lung injury, ↓ lung water	N/A
Németh et al. (140)	C57BL/6 mice, cecal ligation and puncture	1×10^6 cells/kg human BM-MSCs, i.v. administration	↑ survival, ↑ renal and hepatic function	PGE2-mediated increase in IL-10
Lee et al. (184)	*Ex vivo* human lungs, i.t. instillation of *E. coli* endotoxin	5×10^6 human BM-MSCs, i.t. administration	↓ lung inflammatory cell infiltrate, ↓ lung water	KGF
Gonzalez et al. (18)	C57BL/6 mice, cecal ligation and puncture	1×10^6 human AD-MSCs, i.p. administration	↑ survival; ↓ CFU in blood, peritoneum, liver, and spleen; ↓ serum proinflammatory cytokines	N/A
Krasnodembskaya et al. (108)	C57BL/6 mice, i.t. instillation of *E. coli*	1×10^6 human BM-MSCs, i.t. administration	↓ CFU in lung, ↓ lung inflammatory cell infiltrate, ↓ lung total protein	LL-37
Danchuk et al. (60)	BALB/c mice, OA aspiration of *E. coli* LPS	5×10^5 human BM-MSCs; i.v., i.p., and OA administration	↓ lung proinflammatory cytokines, ↑ lung IL-10, ↓ lung water, ↓ lung total protein	TSG-6
Kim et al. (22)	ICR mice, i.t. instillation of *E. coli*	1×10^5 human UC-MSCs, i.t. administration; concurrent antibiotic therapy	↑ survival, ↓ CFU in lung ↓ lung proinflammatory cytokines, ↓ histological lung injury, ↓ lung water	N/A
Gupta et al. (126)	C57BL/6 mice, i.t. instillation of *E. coli*	0.75×10^6 human BM-MSCs, i.t. administration	↑ survival, ↓ CFU in lung, ↓ lung proinflammatory cytokines, ↑ lung lipocalin-2, ↓ histological lung injury, ↓ lung water	Lipocalin-2
Krasnodembskaya et al. (113)	C57BL/6 mice, i.p. injection of *Pseudomonas aeruginosa*	1×10^6 human BM-MSCs, i.v. administration	↑ survival, ↓ hypothermia, ↓ CFU in blood, ↑ phagocytosis in mononuclear cells *ex vivo*	Upregulation of C5a activation in monocytes
Martinz-Gonzalez et al. (86)	BALB/c mice, i.n. instillation of *E. coli* LPS	1×10^6 human sST2-overexpressing AD-MSCs, i.v. administration	↓ lung inflammatory cell infiltrate, ↓ lung proinflammatory cytokines, ↓ histological lung injury	↓ IL-33 expression, ↓ macrophage TLR-4 expression
Bustos et al. (68)	C57BL/6 mice, i.p. injection of *E. coli* LPS	0.5×10^6 human BM-MSCs, i.v. administration	↓ lung inflammatory cell infiltrate, ↓ lung proinflammatory cytokines, ↑ lung IL-10 and IL-1RN, ↓ lung water	↑ IL-10 and IL-1RN
Lee et al. (109)	*Ex vivo* human lungs, i.t. instillation of *E. coli*	5×10^6–10×10^6 human BM-MSCs, i.t. administration	↓ CFU in lung, ↓ lung inflammatory cell infiltrate	KGF, GM-CSF
Asmussen et al. (112)	Adult sheep, i.t. instillation of *Pseudomonas aeruginosa*	5×10^6–10×10^6/kg human BM-MSCs, i.v. administration	↓ tachycardia and hypotension, ↑ oxygenation, ↓ lung water, ↓ serum AST	N/A
Zhang et al. (266)	C57BL/6 mice, i.t. instillation of *E. coli* LPS	7.5×10^5 human AD-MSCs, OA administration	↓ histological lung injury	N/A
Chao et al. (30)	Wistar rats, cecal ligation and puncture	5×10^6 human BM-MSCs or UC-MSCs, i.v. administration	↑ survival, ↓ serum proinflammatory cytokines, ↑ circulating Treg cells	↑ Treg cell activity

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TABLE 1 (Continued)

Reference	Infection model	Intervention	Outcome	Proposed mechanism
Alcayaga-Miranda et al. (23)	C57BL/6 mice, cecal ligation and puncture	7.5×10^5 human Men-MSCs ± antibiotics, i.p. administration; MSC-CM ± antibiotics, i.v. administration	↑ survival; ↓ CFU in blood, peritoneal fluid, and spleen; ↓ histological lung injury; ↓ serum AST and ALT; ↓ serum proinflammatory cytokines	Hepcidin
Devaney et al. (61)	Sprague-Dawley rats, i.t. instillation of *E. coli*	2×10^6–10^7/kg human BM-MSCs, i.v. and i.t. administration	↓ CFU in lung, ↓ histological lung injury, ↑ arterial oxygenation, ↑ lung compliance	LL-37, KGF
Zhu et al. (62)	C57BL/6 mice, i.t. instillation of *E. coli* LPS	30 μl of MV from 1.5×10^6 human BM-MSCs over 48 hours, i.t. or i.v. administration	↓ lung inflammatory cell infiltrate, ↓ lung protein, ↓ lung water	Exosome transfer of KGF mRNA to alveolar epithelium
Monsel et al. (63)	C57BL/6 mice, i.t. instillation of *E. coli*	90 μl of MV from human BM-MSCs (9×10^6 over 48 hours), i.t. or i.v. administration	↑ survival, ↓ CFU in blood and lung, ↓ lung inflammatory cell infiltrate, ↓ histological lung injury	KGF
Fang et al. (287)	C57BL/6 mice, i.t. instillation of *E. coli*	0.5×10^6 human BM-MSCs, i.t. administration	↑ survival, ↓ lung inflammatory cell infiltrate, ↓ lung proinflammatory cytokines, ↓ histological lung injury	Lipoxin A4 signaling via ALX/FPR2 receptors
Jackson et al. (141)	C57BL/6 mice, i.n. instillation of *E. coli*	1×10^6 human BM-MSCs, i.v. administration	↓ CFU in lung, ↑ macrophage mitochondrial function (*ex vivo*); ↑ macrophage phagocytosis	Mitochondrial transfer to macrophages via tunneling nanotubes
Sung et al. (129)	ICR mice, i.t. instillation of *E. coli*	Human UC-MSCs (dose not specified), i.t. administration	↓ CFU in lung; ↓ histological lung injury	Beta-defensin-2
Sutton et al. (187); Sutton et al. (188)	*Cftr*^{tm1Kth} mice, t.t. administration of *P. aeruginosa* or *S. aureus*	1×10^6 human BM-MSCs, retro-orbital sinus administration	↓ CFU in lung, ↓ lung inflammatory cell infiltrate	N/A
Morrison et al. (98)	C57BL/6 mice, i.n. instillation of *E. coli* LPS	Adoptive transfer of 2.5×10^5 murine alveolar macrophages treated by human BM-MSC EVs, i.n. administration	↓ lung inflammatory cell infiltrate; ↓ lung proinflammatory cytokines; ↓ lung protein; ↑ macrophage mitochondrial function (*ex vivo*)	Mitochondrial transfer to macrophages via extracellular vesicles
Laroye et al. (21)	Domestic pigs, i.p. instillation of autologous feces	1×10^6 cells/kg human UC-MSCs, i.v. administration	↑ survival, ↑ oxygenation, ↓ tissue hypoxia	N/A
Rabani et al. (20)	Sprague-Dawley rats, i.t. instillation of *E. coli*	1×10^7 cells/kg human AD-MSCs, i.v. administration	↑ macrophage phagocytosis, ↑ macrophage ROS production	PGE2 and PIK3 stimulation of NOX2
Masterson et al. (46)	Adult male Sprague-Dawley rats, i.t. instillation of *E. coli*	1×10^7 cells/kg human BM-MSCs ($CD362^+$, $CD362^-$ or heterogeneous), i.v. administration	↑ oxygenation; ↑ lung compliance; ↓ lung proinflammatory cytokines; ↑ lung IL-10 and KGF; $CD362^+$ and heterogeneous MSCs only: ↓ CFU in lung, ↓ lung inflammatory cell infiltrate	↑ macrophage phagocytosis
Park et al. (186)	*Ex vivo* human lungs, i.t. instillation of *E. coli*	200–400 μl of MV from 1×10^6 human BM-MSCs over 48 hours ± pretreatment with poly(I·C), i.v. administration	↓ lung water; ↓ lung total protein; poly(I·C) pre-treated only: ↓ CFU in lung	N/A

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TABLE 1 (Continued)

Reference	Infection model	Intervention	Outcome	Proposed mechanism
Jerkic et al. (82)	Sprague-Dawley rats, i.t. instillation of *E. coli*	1×10^7 cells/kg human UC-MSCs or 1×10^7 cells/kg human IL-10 overexpressing UC-MSCs, i.v. administration	↓ CFU in lung; ↑ macrophage phagocytosis; ↑ macrophage ROS production; IL-10 UC MSCs only: ↓ lung inflammatory cell infiltrate, ↑ heme-oxygenase 1 concentrations in macrophages	IL-10
Liao et al. (191)	C3H/HeN mice, IVag administration of MoPn chlamydial strain	1×10^6 human UC-MSCs, IVag administration	↓ histological FT injury, ↓ FT inflammatory cell infiltrate, ↑ fertility, ↑ serum IL-10	N/A
Kong et al. (185)	New Zealand white outbred rabbits, i.t. instillation of MRSA	i.v. Linezolid ± 4 infusions over 1×10^6 cells/kg human UC-MSCs every 3 days, i.v. administration	↓ cough and rales, ↑ oxygenation, ↓ serum proinflammatory cytokines	N/A
Chow et al. (127)	*Nu/nu* mice, s.c. implantation of *S. aureus* coated mesh	Oral coamoxiclav ± 1×10^6 human BM-MSCs preconditioned in poly(I·C), i.v. administration	↓ CFU in wound, ↓ wound surface	Enhanced neutrophil function
Zhou et al. (227)	C67BL/6 mice, corneal scraping and inoculation with *Fusarium oxysporum*	Natamycin eye drops ± 5×10^4 human UC-MSCs, subconjunctival injection	↓ corneal opacity and scarring, ↓ corneal thickness, ↓ corneal inflammatory cell infiltration on histology, ↓ mRNA expression of fibrosis-related factors	Downregulation of TGFβ1/Smad2 phosphorylation
Li et al. (288)	C57BL/6 mice, i.n. inoculation with *H. influenzae*	Cyclophosphamide or 1×10^6 human UC-MSCs, i.v. administration	↓ CFU in lung, ↑ lung macrophages and Tregs, ↑ macrophage phagocytosis, ↓ lung proinflammatory cytokines	N/A
Varkouhi et al. (31)	C57BL/6 mice, cecal ligation and puncture	2.5×10^5 human BM-MSCs or UC-MSCs, i.v. administration	BM-MSCs: ↓ CFU in blood, lungs and spleen, ↑ survival, ↓ systemic proinflammatory cytokines; UC-MSCs: ↓ systemic proinflammatory cytokines, no effect on survival or bacterial clearance	N/A

[a]AD-MSCs, adipose tissue-derived MSCs; AST, aspartate transaminase; BAL, bronchoalveolar fluid; BM-MSCs, bone marrow-derived MSCs; FT, fallopian tube; ICR, Institute of Cancer Research; i.n., intranasal; i.p., intraperitoneal; i.v., intravenous; IVag, intravaginal; Men-MSCs: menstrual blood-derived MSCs; MSC-CM, MSC-conditioned media; MVs, microvesicles; N/A, not applicable; OA, oropharyngeal; s.c., subcutaneous; TSG-6, TNF-α-induced protein 6; t.t., transtracheal; UC-MSCs, umbilical cord-derived MSCs.

TABLE 2 Completed clinical trials of MSCs in sepsis and infectious diseases[a]

Reference	ClinicalTrials.gov registration no.	Condition	Study design	Intervention	Primary outcome	Main finding
Peng et al. (263)	NCT00956891	Hepatitis B-induced liver failure	Case controlled, open label, observational; $n = 158$	Autologous BM-MSCs, 3.4×10^8 cells; single dose, i.v.	LFTs, incidence of HCC	Short-term improvement in LFTs, no difference to long-term incidence of HCC or mortality
Zhang et al. (261)	NCT01213186	Immune reconstitution inflammatory syndrome	Phase 2, randomized, placebo controlled, double blind; $n = 72$	Allogeneic UC-MSCs, 0.5 or 1.5×10^6 cells/kg; 6 doses over 48 wks, i.v.	$CD4^+$ cell count, HIV load, incidence of opportunistic infections	↑ CD4+ cells in immune nonresponders, ↓ systematic inflammation
Weiss et al. (253)	NCT00683722	Moderate-to-severe COPD	Phase 2, multicenter, randomized, double blind, placebo controlled; $n = 62$	Allogeneic commercial MSCs; single dose, i.v.	COPD exacerbations, CRP	No MSC-related adverse events, ↓ CRP after 1 mo
Skrahin et al. (50)	DRKS00000763	MDR or XDR tuberculosis	Phase 1, nonrandomized, open label, parallel assessment; $n = 30$	Autologous BM-MSCs, 1×10^6 cells/kg; single dose, i.v.	Safety	No serious adverse events, no TB disease progression
Galstyan et al. (249)	NCT01849237	Neutropenic sepsis	Phase 1, randomized, open label, parallel assessment; $n = 27$	Autologous BM-MSCs, 1×10^6 cells/kg; single dose, i.v.	Mortality	↑ 28-day survival, no effect on 90-day survival
Panés et al. (256)	NCT01541579	Perianal fistulizing Crohn's disease	Phase 3, randomized, double blind, placebo controlled; $n = 278$	Allogeneic AD-MSCs, 120×10^6; intralesional injection	Remission of perianal fistulas	↑ fistula closure and resolution of abscess
McIntyre et al. (251)	NCT02421484	Sepsis	Phase 1, single group, open label, dose escalation; $n = 9$	Allogeneic BM-MSCs; 0.3, 1.0, or 3.0×10^6 cells/kg; single dose, i.v.	Safety, tolerability	No MSC-related adverse events
Yue et al. (250)	NCT02247973	Severe aplastic anemia with refractory bacterial or fungal infection	Phase 1, single group, open label; $n = 6$	Allogeneic BM-MSCs; 1×10^6–2×10^6 cells/kg; two doses 14 days apart, i.v.	Safety	No serious MSC-related adverse events
Barnhoorn et al. (257)	NCT01144962	Refractory perianal Crohn's disease	Phase 1/2, randomized, triple blind, placebo controlled; $n = 21$	Allogeneic BM-MSCs, 9×10^7 cells; intralesional injection	Remission of perianal fistulas	↑ fistula closure

[a]BM-MSCs, bone marrow-derived MSCs; HCC, hepatocellular carcinoma; LFTs, liver function tests; MDR/XDR, multidrug resistant/extensively multidrug resistant; TB, tuberculosis; UC-MSCs, umbilical cord-derived MSCs.

TABLE 3 Current clinical trials of MSCs in sepsis and infectious diseases[a]

ClinicalTrials.gov registration no.	Condition	Study design	Intervention	Infection-related outcome
NCT02866721	Cystic fibrosis	Phase 1, open label, dose escalation, single group assignment; $n = 14$	Allogeneic BM-MSCs; 1×10^6, 3×10^6, or 5×10^6 cells/kg; single dose, i.v.	Quantitative sputum microbiology
NCT01872624	Pulmonary emphysema	Phase 1, open label, nonrandomized, placebo controlled; $n = 10$	Allogeneic BM-MSCs, dose not specified; i.t.	ESR, CRP
NCT02625246	Bronchiectasis	Phase 1, open label, single-group assignment; $n = 6$	Allogeneic BM-MSCs, 1×10^8 cells; single dose, i.v.	Quantitative sputum microbiology
NCT01686139	Diabetic neuropathic ulcer	Phase 1, open label, single-group assignment; $n = 12$	Allogeneic BM-MSCs, 1×10^7–2×10^7 cells; single dose, intradermal	Frequency of adverse events
NCT03826433	Decompensated hepatitis B liver cirrhosis	Phase 1, open label, nonrandomized, placebo controlled; $n = 20$	Allogeneic UC-MSCs, 6×10^7 cells; single dose, i.v.	2-yr survival
NCT03158727	Community-acquired pneumonia and sepsis	Phase 1/2, quadruple blind, randomized, placebo controlled; $n = 36$	Allogeneic AD-MSCs, 1.6×10^7 cells; 2 doses over 3 days, i.v.	28-day mortality, time to clinical cure
NCT02645305	Moderate-to-severe COPD	Phase 1/2, open label, single-group assignment; $n = 20$	Autologous AD-MSCs, dose not specified; single dose, i.v.	CRP
NCT03113747	Burn wounds	Phase 1/2 open label, randomized, placebo controlled; $n = 20$	Allogeneic AD- MSCs, dose not specified; 2 doses over 3 days, topical	Neutrophil phagocytic activity
NCT03267784	Diabetic neuropathic ulcer	Phase 1/2 open label, single-group assignment; $n = 37$	Allogeneic commercial MSCs, dose not specified; 2 doses over 6 wks, topical	Occurrence of wound infection
NCT02145923	Neutropenic enterocolitis	Phase 1/2, open label, single-group assignment; $n = 16$	Allogeneic BM-MSCs, 1.5×10^6–2×10^6 cells per kg; single dose, i.v.	Frequency of neutropenic enterocolitis, frequency of infectious complications
NCT02095444	Influenza-induced lung injury	Phase 1/2, open label, single-group assignment; $n = 20$	Allogeneic Men-MSCs, 10^7 cells/kg; 4 doses over 2 wks; i.v.	Severity of lung injury
NCT02290041	HIV immunological discordant response	Phase 1/2 double blind, randomized, placebo controlled; $n = 15$	Allogeneic AD-MSCs, 1×10^6 cells/kg; 4 doses over 20 wks	Incidence of opportunistic infection, $CD4^+$ count
NCT02883803	Sepsis with organ failure	Phase 2, double blind; $n = 65$	Allogeneic heterogeneous MSCs, 1×10^6 cells/kg; single dose, i.v.	SOFA score
NCT02083731	Refractory CMV infection after hematopoietic stem cell transplant	Phase 2, open group, single-group assignment; n = not specified	Allogeneic BM-MSCs, 1×10^6 cells; 1–2 doses over 14 days, i.v.	Remission of CMV infection

[a]AD-MSCs, adipose tissue-derived MSCs; BM-MSCs, bone marrow-derived MSCs; ESR, erythrocyte sedimentation rate; UC-MSCs, umbilical cord-derived MSCs.

In addition, three *in vivo* studies have compared rodent BM-MSCs and AD-MSCs in infection models, reporting that they have similar efficacy in attenuating Crohn's disease colitis (32), endotoxin-induced lung injury (33), and sepsis (34). However, they also reported differential responses in systemic levels of some proinflammatory mediators, with BM-MSCs associated with a greater reduction in vascular endothelial growth factor (VEGF) and transforming growth factor β (TGF-β) (33) and AD-MSCs with reduced IL-8 levels (34). This finding suggests that distinctive immunomodulatory mechanisms may be employed by the two MSC types. More work is under way to explore differences in the efficacy and paracrine effectors secreted by human MSC types in preclinical and clinical settings of infection.

Allogeneic Versus Autologous Sources for MSCs

MSCs constitutively express low levels of human leukocyte antigen (HLA) major histocompatibility class I (MHC-I) and negligible levels of HLA MHC-II molecules (35, 36). They are therefore considered immune privileged (37), although this conclusion has recently become a matter of debate, as several animal studies have reported rejection

of cells from MHC-II mismatched donors (38–41). In human studies, however, allogeneic transplant of MSCs has consistently generated a minimal transfusion reaction (42), and most clinical trials, although not all, utilize allogeneic MSCs that are extracted from well-characterized healthy volunteers.

There are variations between sites and tissue sources in the techniques and protocols available for the isolation of MSCs for allogeneic administration (43). Briefly, healthy volunteers are recruited for donation of tissue (e.g., BM-MSCs from bone marrow aspiration, AD-MSCS from adipose tissue, and UC-MSCs from postpartum umbilical cord). MSCs can be isolated from tissue based on plastic adherence and other physical characteristics, such as cell size and density. The MSC population can be enriched in these preparations by the selection of surface markers, such as CD271 (44), Stro-1 (45), and CD362 (46). MSC identity is then confirmed by surface marker expression according to ISCT criteria (positive for CD105, CD73, and CD90 and negative for CD45, CD34, CD14, CD11b, CD79α, CD19, or HLA-DR). MSCs are then expanded *in vitro* usually in automated, large-scale cell culture systems prior to harvesting. Preservation of the phenotype is confirmed by surface marker expression, and MSCs are typically tested for sterility, mycoplasma contamination, and karyotype stability before their release as a clinical-grade therapy (47, 48).

Autologous MSCs are derived from the patient's own tissues, which further minimizes the risk of rejection. However, the process of acquiring sufficient autologous MSCs for therapy is protracted and challenging. Prospective patients must undergo biopsy for MSC sampling, followed by a labor-intensive and expensive period of cell expansion (49, 50). In human trials, the period between MSC sampling and autologous therapy can be up to 4 weeks (50). While feasible for the treatment of chronic diseases, including some chronic infections, this period is prohibitive in acute illness, such as sepsis or pneumonia. Generating an autologous MSC therapy may also be more expensive and less feasible than off-the-shelf allogeneic products, especially if the patient is acutely unwell. There have been no head-to-head comparison studies in humans between autologous and allogeneic cells, but preclinical and clinical evidence do not support a significant advantage to autologous cells (42, 51).

Safety of MSC Therapies

The safety considerations for a cell therapy must address the theoretical risks of transfusion reaction, cell clumping, and vessel occlusion and engraftment with ectopic or neoplastic tissue formation (52). There are also concerns over possible immunosuppression and susceptibility to infection in light of MSC immunomodulatory properties, particularly in patients with impaired immunity (53).

Most tracking studies in humans suggest that the majority of transfused MSCs are destroyed or escape from circulation within 24 hours of infusion (54). The proportion that migrates into tissue appears to be dependent on the target organ and degree of injury, with a significant number typically captured by the pulmonary microcirculation in the first hours, followed by accumulation in the liver and spleen in the following days. The therapeutic benefit of MSCs is seen in preclinical models within hours or days, suggesting they exert their effects acutely before their destruction by apoptosis or host cell clearance. Reporting of viable MSCs in target organs beyond 10 days is rare (55), although a tiny population of fluorescently labeled rat BM-MSCs were still detectable in rat lung tissue up to 8 weeks after intratracheal (i.t.) administration (56).

The 2011 SafeCell study (53) was a systematic review and meta-analysis which included 36 studies, representing 1,012 patients, in which MSCs had been administered by intravenous (i.v.) infusion. It concluded that overall MSCs were safe, with no significant associated cardiovascular, pulmonary, gastrointestinal, or renal adverse effects. There was no increase in infection rates, malignancy, or death in the MSC treatment groups. Transient fever was associated with MSC therapy.

A 2019 updated systematic review and meta-analysis capturing 47 randomized controlled trials (RCTs) and representing 2,696 patients (42) had similar findings. Transient fever that did not proceed to acute infusional toxicity was the only adverse effect

significantly associated with MSC administration. Indeed, a pooled analysis on mortality found that the risk of death was reduced in the MSC group (relative risk [RR], 0.78; 95% confidence interval [CI], 0.65 to 0.94). Although there was no evidence from this meta-analysis for MSC engraftment and malignancy, long-term follow-up has become a secondary safety measure for many current trials.

Dosing is a further safety consideration, with no consensus on the optimal dosage and frequency of MSC therapies (57). Phase 1 safety testing is important each time a MSC therapy is tested for a new clinical indication, but few studies address a substantial dose range. Trial dosages are often based arbitrarily on prior tolerated regimens in other indications or those given in preclinical models. Many trials now employ a dose-escalation element in phase 1 to determine a "maximum tolerated dose" across a prespecified dose range. Doses employed for systemic use in clinical trials range from of 0.5×10^6 to 10×10^6 cells/kg (57), although some trials that employ fixed dosing have given up to 900 million cells per patient (ClinicalTrials registration no. NCT02611609). A review of dose-response data from available trials suggested an optimal dosage in the range of 100 to 150 million MSCs per patient with efficacy falling with higher and lower dosages (58). However, these trials tested MSCs in the settings of diabetes (glycemic control and diabetic nephropathy) or rehabilitation medicine (physical recovery from hip arthroplasty and age-related frailty). No dose-response data have yet been reported in MSC trials of infectious diseases. A further concern is the frequency of dosing, with many studies now testing multiple (typically two to four) doses at regular intervals (examples in Table 3). However, there is still a paucity of evidence to guide decisions over the dosage frequency and interval of MSCs in clinical trials for a given indication.

Routes of Administration

Optimizing MSC administration strategies is important for maximizing their delivery to the site of disease. Intravenous (i.v.) administration has been studied most extensively but is limited by a pulmonary "first-pass" effect whereby the lung microcirculation traps a large proportion of the MSCs (59). Although this effect appears beneficial for the treatment of some pulmonary conditions, it is still reliant on successful migration of MSCs to focal sites of injury within the lung. A number of preclinical studies have used intratracheal (i.t.) instillation, intranasal (i.n.) instillation, and oropharyngeal aspiration (OA) for pulmonary infections with similar clinical benefits to i.v. administration (see examples in Table 1). Intraperitoneal (i.p.) injection is practically easier to administer than i.v. and has been reported efficacious in models of pulmonary and intra-abdominal infection (18, 23, 60).

Four studies have compared the efficacy of MSCs in the setting of pneumonia given by different routes (i.v. versus i.p., i.t., and/or OA) (60–63). There was no difference in efficacy between routes for most outcomes, including survival, histological lung changes, and levels of proinflammatory cytokines. In one study, i.v. was superior to i.t. administration in reducing bacterial CFU in lung (63), whereas others reported MSCs given i.t. resulted in higher lung concentrations of the antimicrobial peptide LL-37 (61). Most clinical studies in infection have used i.v. administration for systemic illness, although topical application is being trialed for treating cutaneous infections. However, more comparison studies are needed as much remains unknown about the pharmacokinetics of MSCs after administration, particularly via routes other than i.v.

"Licensing" of MSCs

MSCs exhibit modulatory activity in their resting state, although some functions require activation by a stimulus (64). Preconditioning of MSCs can enhance their desired therapeutic effect in a process is known as licensing (65, 66). The main licensing methods investigated for MSCs in infections are discussed below.

Culture conditions. Incubation of MSCs in an inflammatory milieu activates NF-κB transcription, enhances their migration to sites of injury, and stimulates expression of immunomodulatory mediators, such as IL-10 and prostaglandin E2 (PGE2) (67, 68). One study has reported that human MSCs with strong bactericidal activity *in vitro* did not have the same effect *in vivo* unless preactivated by the TLR3 ligand poly(I·C) (69). Similarly,

interferon gamma (IFN-γ)-pretreated human BM-MSCs were more effective than unstimulated MSCs in improving survival and attenuating systemic inflammation in a mouse model of experimental colitis (70). Pretreatment with TNF-α had a similar but less pronounced effect, whereas incubation in a proinflammatory cytokine mixture of IFN-γ, TNF-α, and IL-1β (known as "cytomix") potently enhanced human BM-MSC and AD-MSC protection of lipopolysaccharide (LPS)-stimulated mononuclear cells (67). However, more studies are needed to test inflammation-stimulated human MSCs in preclinical and clinical studies of infection.

Carbon monoxide-preconditioned murine BM-MSCs were more effective than naive MSCs in improving bacterial clearance and attenuating liver and kidney injury in a mouse model of polymicrobial sepsis (71). Mechanistic studies highlighted the role of CO-mediated release of specialized proresolving lipid mediators, such as lipoxin A4, from mouse MSCs, which were important particularly for enhancing neutrophil phagocytosis. Hypoxic preconditioning ($<$1% environmental O_2) stabilizes MSC levels of hypoxia-inducible factor 1α, which controls metabolism, reduces reactive oxygen species (ROS) production, and protects against oxidative stress (72). Oxygen starvation both mimics the conditions in MSC source tissues (1% to 7% O_2 in bone marrow [73], 2% to 8% in adipose tissue [74], and 2% to 5% in the gravid uterus [75]) and prepares the MSC for survival in ischemic microenvironments that accompany inflammation (76). Hypoxic preconditioned animal and human MSCs have been reported beneficial in *in vivo* studies of noninfectious diseases (including hind limb ischemia and myocardial infarction [72, 77–79]), but they are less well described in infection models. Indeed, hypoxic-preconditioning of Men-MSCs abrogated their *in vitro* antimicrobial activity in association with reduced secretion of the antimicrobial peptide hepcidin (23).

Other cellular stress preconditions have generated MSCs *in vitro* with improved survival and enhanced function. They include serum deprivation which induces autophagy in human BM-MSCs through mTOR inhibition (80) and heat shock treatment which reduces rat BM-MSC susceptibility to apoptosis (81).

Genetic modification. Upregulation of specific genes in MSCs is associated with improved survival and increased potency *in vitro* and *in vivo*. For instance, IL-10-overexpressing human UC-MSCs given to rats with *Escherichia coli* pneumonia, resulting in improved survival, reduced lung CFU and increased the bactericidal activity of alveolar macrophages (82).

A number of other protective gene candidates have been identified, including hepatocyte growth factor (HGF), Ang1, and soluble ST2 which were upregulated in human MSCs and resulted in attenuated lung injury in treated rodents (83–86). Overexpression of other mediators, such as keratinocyte growth factor (KGF) (87), ACE2 (88), and Miro1 (89) in animal MSCs has proven beneficial in some models of infection, but the efficacy of their upregulation in human MSCs has yet to be seen.

Pharmacological augmentation. MSCs are able to take up and release pharmacological compounds, raising their potential as drug delivery vehicles (90). Human BM-derived MSCs preconditioned in 100-mg/liter ciprofloxacin were able to internalize approximately 0.7 pg/cell, of which more than 90% was released into the surrounding media within 24 hours (91). If extrapolated to a typical trial dose of 1 million cells/kg, this would equate to approximately 0.7-mg/kg ciprofloxacin. Although dose is around 10-fold less than the adult i.v. dose given commonly to treat sepsis, the homing ability of MSCs to sites of injury may still deliver high concentrations to infected tissue (92, 93). The ciprofloxacin released by MSCs retained bactericidal efficacy against *E. coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* at the expected MIC. Ciprofloxacin-primed MSCs were more than 90% viable, as well as having significantly enhanced direct antimicrobial activity against *E. coli*. There is exciting an potential for MSC loading with other antimicrobials for direct delivery to infected tissue, but further work is needed to understand the *in vivo* pharmacodynamics of drug-primed MSCs.

MSC-drug combinations may also enhance their secretion of soluble mediators. A high-throughput strategy has screened over 1,000 compounds for enhanced MSC

PGE2 secretion and detected 5 candidates, including the calcium channel blocker tetrandrine (94). Tetrandrine increased baseline PGE2 secretion by 30%, which is sustained for 48 hours after removal from human BM-MSC culture without causing cytotoxicity. In a limited *in vivo* study, the tetrandrine-primed human BM-MSCs reduced local levels of TNF-α in a mouse ear skin inflammation model generated by intradermal LPS injection, but levels were unchanged by unprimed MSCs or a phosphate-buffered saline (PBS) placebo (94).

MSC Secretome-Based Therapies

The MSC secretome comprises a large number of soluble factors and extracellular vesicles (EVs), which mediate paracrine signaling. EVs are categorized by diameter into "exosomes" (50 to 100 nm) or "microvesicles" (0.1 to 1 μm) and contain a diverse range of cargo, including organelles, proteins, DNA, and RNA (95, 96). The secretome has been shown in preclinical studies of bacterial pneumonia to confer comparable benefits as a whole-cell therapy (63, 98, 186). These benefits included promoting animal survival, enhancing bacterial clearance, reducing inflammatory cell infiltrate, and ameliorating histological evidence of lung injury.

MSC EVs have pragmatic advantages, remaining viable through the freeze-thaw process, and they do not require the addition of toxic preservatives for cold storage (99). They may be less costly to manufacture, as EVs are more resilient than cells and are less likely to shear during purification. They also do not self-replicate and so carry less theoretical risk of engraftment and ectopic tissue formation, although toxicology studies do not suggest that engraftment and replication are common features.

However, EV-based products have some important limitations also. The number of MSCs required to generate a volume of EVs with equivalent biological activity to cell-based therapy is currently prohibitively high (186). Also, some mechanisms of MSCs are dependent on the microenvironment and may require activation at the site of injury, which is an advantage of whole-cell therapy.

Mobilization of Endogenous MSCs

In normal health, MSCs have important regulatory roles in the induction and resolution of physiological inflammation (100). MSCs express a range of Toll-like receptors (TLRs) through which they sense host injury and pathogen activity (15). MSCs are present constitutively in circulation in low numbers which are increased in response to injury, such as trauma, burns, and ischemia (101–103). During acute inflammation, MSCs are mobilized from bone marrow in response to T cell-derived IFN-γ (104). They migrate to sites of injury and can modulate the activity of principal immune cells, including dendritic cells, monocytes/macrophages, neutrophils, and T and B lymphocytes that drive regenerative processes (14).

These observations have raised the potential of *in situ* strategies to enhance the host's own MSC regenerative capacity in a range of conditions. Mobilization of endogenous MSCs with granulocyte colony-stimulating factor (G-CSF) has been trialed in a mouse study of traumatic brain injury with an enhanced resolution of hemorrhage (105). It has also been observed in patients with acute respiratory distress syndrome (ARDS) undergoing extracorporeal membrane oxygenation, although its role is unclear (106). However, the utility of endogenous MSC mobilization in the treatment of infectious diseases has not yet been investigated.

DIRECT ANTIMICROBIAL ACTIVITY OF MSCs

MSCs express a range of TLRs through which they sense and become activated by microbial antigens, such as flagellin, peptidoglycan, and lipopolysaccharide (LPS) (15). Early studies demonstrated that human BM-MSCs had broad-spectrum, direct antimicrobial activity, inhibiting the growth of important Gram-positive bacterial pathogens, including *Staphylococcus aureus*, *Staphylococcus epidermidis*, group B streptococci, and *Enterococcus faecium* (107). MSCs also have direct bactericidal activity against pathogenic Gram-negative bacteria, including *Escherichia coli* (61, 108, 109), *Klebsiella*

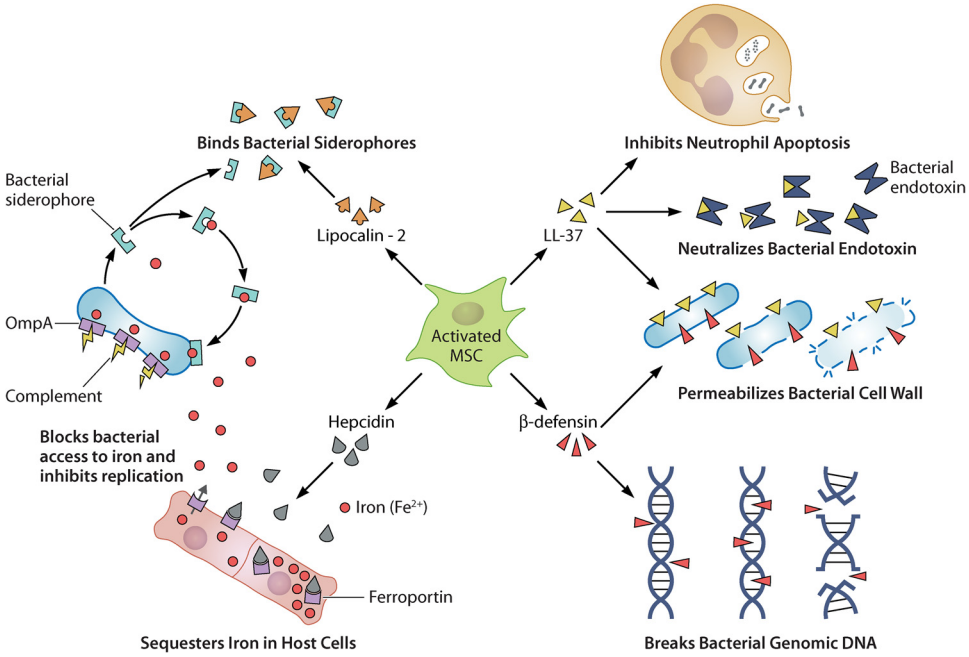

FIG 1 Direct antimicrobial activity of MSCs through secretion of antimicrobial peptides. Activated MSCs secrete antimicrobial peptides which have a range of bactericidal and bacteriostatic effects. LL-37 permeabilizes the bacterial cell walls and neutralizes endotoxins. β-Defensin also targets the bacterial cell wall, as well as genomic DNA. Hepcidin binds the iron transporter ferroportin and sequesters iron inside host cells. Lipocalin-2 binds to bacterial siderophores to reduce their access to iron.

pneumoniae (110), *Pseudomonas aeruginosa* (108, 111–113), *Acinetobacter baumannii* (114), and *Vibrio cholerae* (115), as well as mycobacteria (116, 117), viruses (107, 118), and parasites (107).

MSCs secrete various soluble factors that mediate some of these direct antimicrobial effects, including cathelicidin LL-37, lipocalin-2, beta-defensin-2, and hepcidin (Fig. 1) (8).

LL-37

The human cathelicidin LL-37 is secreted by many cell types, including epithelial cells and immune cells (119), and was the first AMP recognized to mediate MSC antimicrobial activity (108). LL-37 neutralizes bacterial endotoxins and forms pores in the membranes and cell walls of Gram-positive and -negative bacteria (120). It also orchestrates variable host-protective effectors, dependent on the stage of inflammatory induction and resolution, by modulating master regulators, such as NF-kβ inhibitor-α, mitogen-activated protein kinases, and phosphoinositide 3 kinases (121). LL-37 inhibits apoptosis of neutrophils, activates monocyte differentiation into macrophages, and promotes wound healing through angiogenesis.

In vivo, mice treated with i.t. human BM-MSCs for *E. coli* pneumonia had reduced CFU, inflammatory cell count, and total protein in bronchoalveolar lavage (BAL) fluid, but this infection was abrogated largely with the coadministration of the LL-37 neutralizing antibody (108). Similarly, human BM-MSCs given i.t. and i.v. promoted the survival and lung CFU clearance in a rat model of *E. coli* pneumonia (61). Interestingly, i.t. administration was associated with higher plasma and alveolar levels of LL-37.

Lipocalin-2

Lipocalin-2 (Lcn2) is a widely distributed protein that can bind iron and small organic molecules (122). Bacterial metabolism and replication are dependent on retrieving extracellular iron through siderophores. Iron availability also controls the expression of bacterial virulence, such as the outer membrane protein A (OmpA) which protects bacteria from host attack by binding and degrading complement (123). Lcn2

sequesters bacterial siderophores to restrict the access of bacteria to essential iron, inhibiting replication and exposing them to complement (Fig. 1). Its importance in infection control has been shown in Lcn2-deficient mice, which appear to be phenotypically normal in a pathogen-free setting but succumb easily to sepsis (122).

Lcn2 is a key antimicrobial mediator of MSCs in animals, including mice and horses (124, 125). Murine BM-MSCs given i.t. to mice in an *E. coli* pneumonia model increased survival and reduced BAL fluid CFU in association with a higher BAL fluid concentration of Lcn2 (126). This effect was abrogated when mice were given MSCs premixed with the Lcn2-blocking antibody, indicating that the antimicrobial effect of MSCs was mediated partly by Lcn2. Interestingly, parallel *in vitro* tests showed that bacterial endotoxin and cytomix increased murine MSC Lcn2 production 10-fold and also stimulated its expression in activated alveolar macrophages, suggesting that the local inflammatory microenvironment could modulate the MSC antimicrobial potential.

Human MSCs secrete Lcn2 constitutively, and it can be further increased by IFN-γ and poly(I·C) stimulation (127). However, the definitive role for Lcn2 in mediating human MSC antimicrobial activity in infection models has yet to be reported in mechanistic studies.

β-Defensin-2

Human defensins are short, cationic peptides with direct and broad antimicrobial activity against Gram-positive and -negative bacteria (128). Their bactericidal mechanisms include permeabilization of cell membranes to induce lysis and binding to genomic DNA to cause breaks. Human α-defensins are produced mostly by monocytes, lymphocytes, and natural killer (NK) cells, whereas β-defensins are produced by epithelial cells as well as innate immune cells (121). They also have an important role in immune cell chemotaxis, particularly in the recruitment of macrophages, dendritic cells, and immature memory T cells to sites of infection.

One study has suggested a key antimicrobial role for β-defensin-2 (BD2) in human UC-MSCs (129). Human UC-MSCs given to mice with *E. coli* pneumonia resulted in reduced BAL fluid CFU, neutrophil infiltration, and histological evidence of lung injury. However, BD-2 concentrations in BAL fluid and the associated benefits of MSC treatment were both abrogated when MSCs were pretreated with small interfering RNA (siRNA) targeting TLR4. Similarly, when TLR4 was inhibited by siRNA in MSCs *in vitro*, BD2 secretion was lost and MSCs failed to inhibit the growth of *E. coli*. This failure was rescued by supplementation of exogenous BD2. The authors concluded that activation of TLR4 by *E. coli* induced BD2 production, which inhibited bacterial growth, but additional downstream mediators not identified in the study are likely to be involved.

Hepcidin

Hepcidin plays an essential role in human iron homeostasis (130) and is secreted in two forms of MSCs in response to IL-6, as follows: hep-25 which partly mediates its antimicrobial effect through limiting iron availability and hep-20 which acts through an unknown antimicrobial mechanism (23, 131). Hep-25 binds the host iron transporter ferroportin and sequesters it inside cells (132), preventing iron from being exported to extracellular bacteria, which is essential for their replication. This iron restriction causes a broad-spectrum antimicrobial effect against extracellular Gram-negative and -positive bacteria, as well as pathogenic fungi and mycobacteria (132, 133). However, manipulation of intracellular iron sequestering has been described by intracellular pathogens, such as *Mycobacterium tuberculosis* and *Listeria monocytogenes*, including through the induction of hepcidin secretion (134, 135). MSCs appear to employ other mechanisms to enhance intracellular clearance of these pathogens (117, 136).

Hepcidin has been reported in small concentrations in the secretome of human BM-MSCs and UC-MSCs (137), but to date, its antimicrobial activity has been reported only for Men-MSCs where its secretion appears to be oxygen dependent (23). Men-MSCs and their secretome inhibited the growth of commensal gut bacteria cultured from mouse feces, but this effect was lost when Men-MSCs were cultured in hypoxia. Hypoxia also abrogated Men-MSC expression of hepcidin, whereas bacterial stimulation (like the

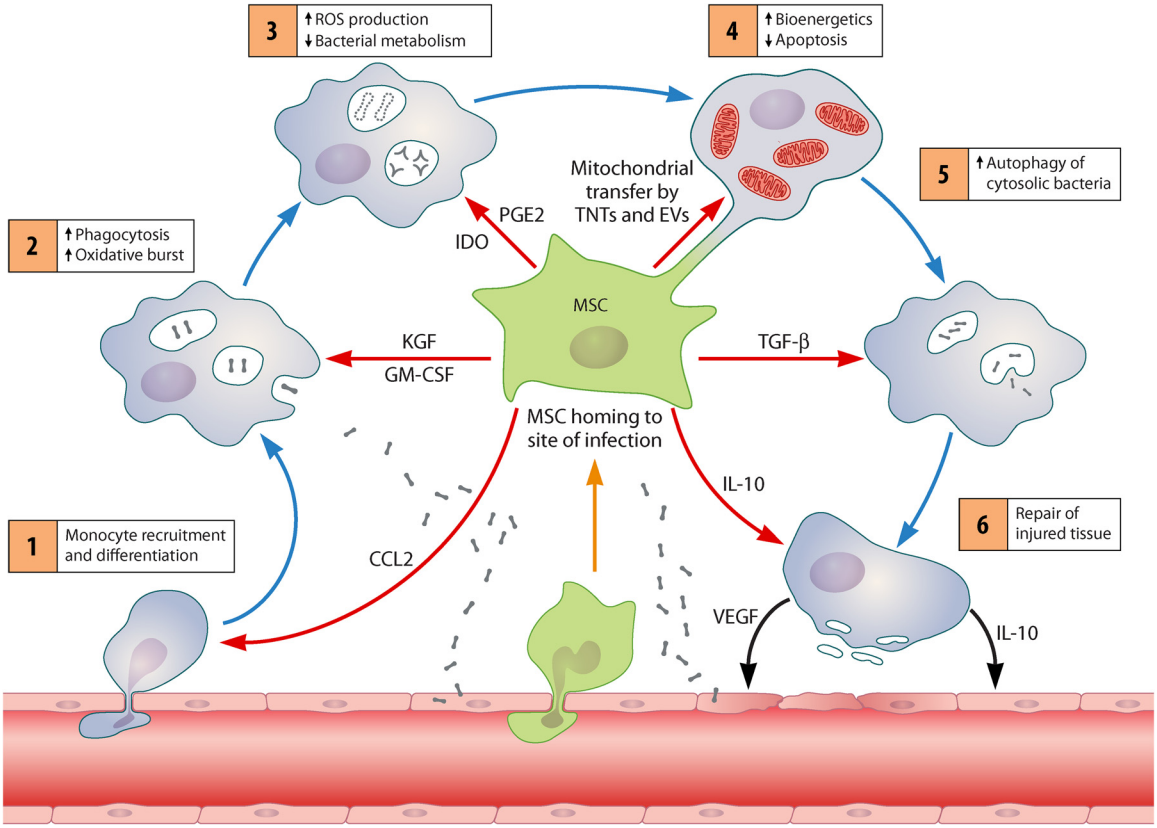

FIG 2 MSC modulation of monocytes and macrophages. MSCs home to the site of infection and exert a range of immunomodulatory effects on macrophages to enhance their function, including (i) promoting monocyte recruitment and differentiation into macrophages via CCL2 secretion, (ii) increasing phagocytosis and oxidative burst via KGF and GM-CSF, (iii) enhancing macrophage degradation of bacteria via PGE2 and IDO signaling, (iv) promoting macrophage bioenergetics and inhibition of apoptosis by transfer of mitochondria, (v) enhancing autophagy of cytosolic bacteria by TGF-β, and (vi) supporting macrophage repair of injured tissue via IL-10.

response of lipocalin to endotoxin) increased basal levels of hepcidin expression by 50-fold. The correlation between Men-MSC antimicrobial activity and hepcidin levels suggests that the hepcidin activity contributes to the antimicrobial effect, although this was not investigated by inhibition studies. Also, the impairment of Men-MSC activity through hypoxic preconditioning is inconsistent with findings of other studies in which hypoxia augmented MSC function (72, 138). These results support the need for better understanding optimal tissue source and licensing strategies for MSC activity in any given model or disease.

IMMUNOMODULATORY ACTIVITY OF MSCs

Monocytes and Macrophages

Modulation of monocytic phagocytes in infection is the most extensively characterized immunomodulatory activity of MSCs (139). Preclinical models of sepsis have shown that the beneficial effects of MSCs are monocyte/macrophage dependent (140, 141). This distinct relationship between MSCs and macrophages has been linked to their shared origin and close proximity in the hemopoietic stem cell niche (95, 142). MSCs can modulate macrophage function and behavior in a number of ways (Fig. 2).

First, MSCs recruit monocytes to sites of infection. MSCs are potent producers of CCL2 (MCP-1), the primary recruiting cytokine for inflammatory monocytes, and its expression is enhanced by inflammatory activation (69). MSCs home to sites of inflammation (23, 93) where they release CCL2 and other chemokines to attract circulating monocytes (69, 92, 95).

Second, MSCs enhance the clearance of intracellular bacteria in infected macrophages through the secretion of paracrine mediators, including granulocyte-macrophage

colony-stimulating factor (GM-CSF) (112), keratinocyte growth factor (KGF) (62, 143), and TGF-β (144).

GM-CSF stimulates the expression of IFN-γ which induces type 1 T helper (Th1) cells to activate intracellular pathogen killing in macrophages (145). It also activates phosphorylation of macrophage STAT5 which leads to increased phagocytosis (146). GM-CSF regulates zinc homeostasis, restricting access during infection, which inhibits bacterial replication (147). Sequestering zinc in phagocytes also increases oxidative burst and enhances intracellular killing of bacteria by ROS (147).

KGF is an epithelial mitogen and differentiation factor produced by cells of the mesenchymal lineage (148). KGF may contribute to infection clearance by driving secretion of opsonins and macrophage phagocytosis of bacteria (143, 148). TGF-β is secreted by activated MSCs and can induce autophagy in macrophages (144). MSC-induced autophagy has been effective in reducing high-glucose injury to pancreatic cells and in theory could be helpful for targeting intracellular bacteria that escape to the cytosol, such as *M. tuberculosis* and *L. monocytogenes* (149).

Third, MSCs improve the bioenergetics of infected macrophages. Under oxidative stress, MSCs transfer partially depolarized mitochondria to neighboring macrophages where they fuse with the macrophage mitochondria (95). Mitochondrial fusion occurs physiologically between cells and provides genetic complementation for mitochondrial DNA (150). In the inflammatory microenvironment, this has the benefit of reducing mitochondrial ROS levels in MSCs and promoting their survival in oxidative stress while improving the bioenergetics of macrophages, enhancing phagocytosis, and driving inflammatory resolution (95).

Mitochondria are channeled between MSCs and macrophages, as well as other cell types, by direct cell contact through cytoplasmic bridges known as tunneling nanotubes (TNTs) (141) and Connexin 43-containing gap junctional channels (151). Mitochondria can also be transferred in extracellular vesicles in a cell contact-independent mechanism (98). This process is facilitated by MSC microRNAs that tolerize the macrophage to the incoming mitochondria through inhibition of TLR signaling (95).

Fourth, MSCs promote host-protective differentiation of macrophages. Early reports described *in vitro* and *in vivo* MSC induction of an atypical M2-like macrophage phenotype with enhanced phagocytic and bacterial killing properties (69, 98). Later studies showed that MSCs can promote a heterogeneous population of host-protective macrophages *in vitro* and *in vivo* that also included M1-like macrophages (20, 152). These M1-like macrophages killed bacteria more effectively through enhanced production of phagosomal ROS while protecting epithelial cells through the secretion of the vascular endothelial growth factor (VEGF).

This process of macrophage differentiation is dependent primarily on the paracrine activity of MSC-produced indolamine 2,3-dioxygenase (IDO) and PGE2 (20, 152). IDO catalyzes the conversion of tryptophan to kynurenine and is released by activated MSCs to deplete macrophage stores of tryptophan (152, 153). Tryptophan is an essential factor for bacterial replication as well as for T cell activation and macrophage M1 polarization (153). IDO secretion therefore promotes a host-protective M2-like phenotype while displaying broad-spectrum activity against a range of pathogens, including staphylococci, enterococci, human herpesviruses, and *Toxoplasma gondii* (107, 153).

MSC-derived PGE2 induces several changes in macrophages, including upregulation of scavenger receptor expression, increased phagocytic activity, increased IL-10 production, and activation of NAPDH oxidase (NOX2) to produce phagosomal ROS (20, 154). This PGE2 signaling promotes the development of coexisting and complementary M1-like and M2-like macrophages, partly explaining their ability to suppress excessive inflammation while enhancing microbial killing. However, the protective effect of MSC-secreted PGE2 may be pathogen specific or host immune status dependent. For instance, PGE2 has correlated with an increased susceptibility to organisms, such as *P. aeruginosa*, *Paracoccidioides brasiliensis*, and some herpesviruses in preclinical and clinical settings (111, 155–157). Further work is needed to dissect the different effects of MSC-derived PGE2 on macrophage function in specific host-pathogen settings.

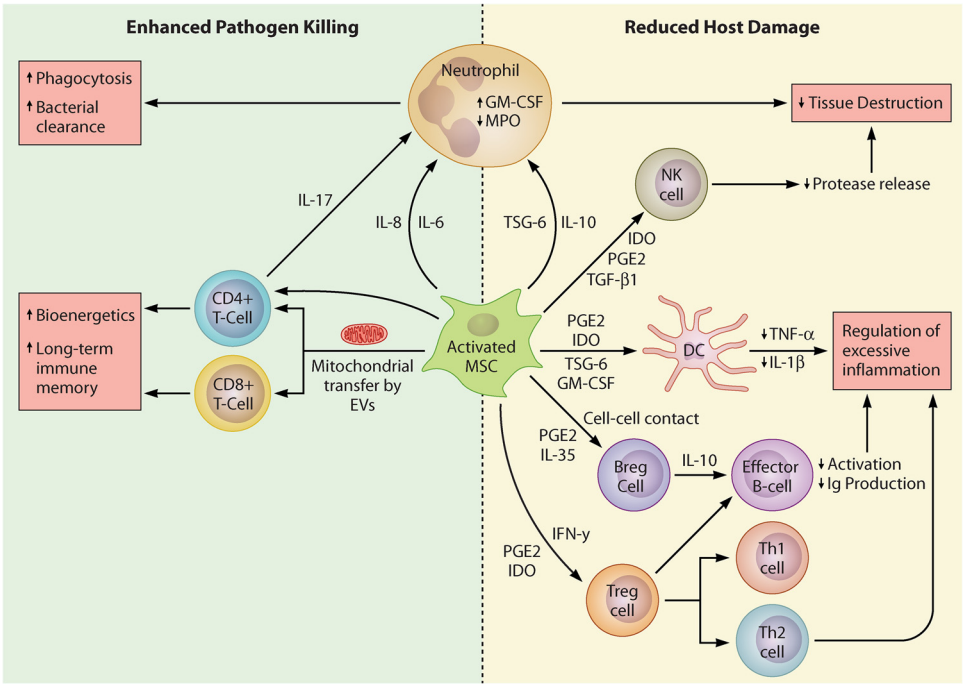

FIG 3 MSC modulation of other immune cells. MSCs modulate innate and adaptive immune cells to enhance pathogen clearance and reduce host tissue damage. MSCs increase levels of GM-CSF in neutrophils via IL-6 and IL-17 signaling, which enhances phagocytosis and bacterial clearance. MSCs transfer mitochondria to $CD4^+$ and $CD8^+$ lymphocytes which augments their bioenergetics and improves long-term immune memory. MSCs protect host tissue by inhibiting release of MPO from neutrophils and proteases from NK cells. MSCs suppress excessive inflammation by modulating DCs and regulatory lymphocytes via numerous soluble mediators, including IDO, PGE2, and TSG-6.

Neutrophils

Neutrophils are typically recruited to injured tissues within minutes and drive the early inflammatory response (158). Activated neutrophils release proteolytic enzymes, such as myeloperoxidase (MPO) which have bactericidal activity but can also cause oxidative damage to host tissues (159). In early lung infection, MSCs promote neutrophil recruitment to the site of injury through expression of IL-6, IL-8, and GM-CSF (160). However, MSCs also prevent excessive neutrophil infiltration through secretion of IL-10 and tumor necrosis factor α-induced protein (TSG-6), which inhibits their transepithelial migration and secretion of MPO (60) (Fig. 3). This migratory inhibition also maintains a larger proportion of neutrophils in circulation, which is associated with elimination of bacteremia (140).

MSCs also promote neutrophil survival in an inflamed environment and inhibit their apoptosis through secretion of IL-6, IFN-β, and GM-CSF. MSCs enhance neutrophil function by activating and improving phagocytosis through cell contact (161) and direct paracrine mechanisms (69), although the precise mediators are less well described. MSCs also act indirectly through upregulating IL-17 expression in $CD4^+$ memory T cells which promotes neutrophil phagocytic activity (162). Despite these beneficial effects, MSC-neutrophil modulation may be auxiliary rather than critical for mediating their antimicrobial potential of MSCs in some settings. For example, in a murine model of *E. coli* pneumonia, MSC treatment of mice in which neutrophils had been depleted was still effective at reducing lung tissue damage and bacterial counts in BAL fluid (141). Nevertheless, MSCs may mediate a careful balance between recruiting sufficient phagocytes for microbial killing and limiting damage caused by excessive inflammation (140).

Dendritic and Natural Killer Cells

MSC modulation of dendritic cells results in host protection from excessive inflammation during infection (Fig. 3). MSCs inhibit the maturation of dendritic cell precursors in

acute inflammation and suppress the adaptive immune response through secretion of PGE2, TSG-6, and GM-CSF (163) (Fig. 3). They can also downregulate DC expression of antigen-presenting molecules to reduce lymphocyte activation and induce their apoptosis (164). Activated DCs in coculture with $CD4^+$ T cells typically stimulate the expression of proinflammatory cytokines, such as TNF-α and IL-1β; yet, in the presence of human MSCs, they are suppressed partially through MSC production of IL-10 (164).

Similarly, MSC modulation of NK cells is largely host protective and characterized by reduced cytotoxicity, cytokine production, and protease release. This process is mediated by MSC direct cell contact (which modulates NK cell surface expression) as well as secretion of IDO, PGE2, and TGF-β1 (165, 166) (Fig. 3). However, these modulations depend on the maturity and microenvironment of the NK cells, as MSCs have also been reported as stimulating NK cytotoxic function at low MSC:NK cell ratios (167).

Lymphocytes

MSC modulation of lymphocytes has been observed on all T cell subpopulations through the expression of several mediators, including IDO and PGE2 (14) (Fig. 3). Most evidence comes from *in vitro* and *in vivo* models of noninfective inflammatory disease. However, these findings remain relevant for informing how MSCs may protect host tissue from excessive inflammation during the infection immune response. MSC coculture inhibits the activation of $CD4^+$ T helper cells, increases the proportion of regulatory T cells by inducing FoxP3 expression and CD25 expression (168), and promotes polarization of Th1 cells to Th2 cells (14, 169). The overall effect is the suppression of proinflammatory T cell activity in the hyperinflamed state. This effect concurs with a report of MSC therapy in rats with polymicrobial sepsis, whereby human BM-MSCs and UC-MSCs improved survival in association with increased numbers of circulating Treg cells (30).

MSCs can also reduce the proliferation, differentiation, and immunoglobulin production of stimulated B cells via a number of mechanisms (170) (Fig. 3). MSC-produced PGE2 and IL-35 promote the development of IL-10-producing regulatory B (Breg) cells in the setting of *in vivo* noninfective systemic inflammation (171, 172). A similar population of Breg cells were generated from quiescent tonsillar B cells following cellular contact with human AD-MSCs, although the precise molecules involved are unknown (173). Indirectly, MSC-produced IFN-γ acts on Treg cells to suppress effector B cell activity and immunoglobulin production, which aids in the resolution of the inflammatory response (14).

MSCs can also rescue lymphocyte exhaustion in a prolonged infection through mitochondrial donation (174). This has been observed in the antiviral response of T cells, particularly for $CD8^+$ and less so for $CD4^+$ cells (175). Such chronically stimulated T cells are not able to metabolize glucose sufficiently and exhibit smaller, fragmented mitochondria, which correlate with poorer long-term immune cell memory and effective antipathogen responses in the setting of chronic lymphocytic choriomeningitis virus infection (176, 177). MSC mitochondrial transfer may remedy "unfit" T-cells and therefore aid in rebuilding long-term immune memory, as well as strong, immediate, immune effector functions in acute infections (178).

MSCs IN PRECLINICAL MODELS OF INFECTIOUS DISEASES

There have been more than 30 published *in vivo* bacterial infection models investigating human MSCs and their secretome (Table 1), with many more animal models trialing same-species MSCs (179). Although a small number of these studies have reported mixed or negative effects with animal MSCs (180–182), human MSCs have been associated invariably with clinically relevant benefits in preclinical models. MSCs exhibit species-specific antimicrobial mechanisms, with human MSCs showing greater preclinical efficacy than animal MSCs in comparative studies (107). However, the paucity of negative and neutral studies reported on human MSCs warrants caution over the risk of publication bias. Here, we summarize the evidence for human MSC therapeutic potential from the most relevant preclinical models of infection:

Preclinical Models of Bacterial Infections

Pneumonia. The most common *in vivo* pneumonia models in rodents use bacterial endotoxin (60, 183, 184) or live bacteria (61, 109–111). Human MSC therapy has been associated consistently with benefits such as increased survival, enhanced bacterial clearance, attenuated histological lung injury, and reduced levels of proinflammatory cytokines (Table 1). In larger animal models of pneumonia, including rabbits (185), sheep (112), and pigs (21), MSC treatment also resulted in increased arterial oxygenation and lung compliance. *Ex vivo* human lung models have helped determine the importance of MSCs in promoting lung epithelial repair and reducing pulmonary edema (109, 186). MSCs have been administered by various routes, including i.v., i.t., i.n., i.p. and OA, with favorable outcomes reported across different approaches (Table 1) and similar benefits reported within studies that compared different routes (60–63).

Human BM-MSCs and AD-MSCs have also been tested for cystic fibrosis-associated bacterial pneumonia using cystic fibrosis transmembrane conductance regulator-deficient ($Cftr^{tm1Kth}$) mice (187). There are important limitations to this model, as $Cftr^{tm1Kth}$ mice do not spontaneously develop either pulmonary inflammation or chronic bacterial infection and are not more susceptible to *P. aeruginosa* than wild-type mice. Nevertheless, $Cftr^{tm1Kth}$ mice challenged with bacteria followed by a single dose of 1 million human MSCs had 100-fold and 10-fold reduced bacterial counts in BAL fluid for *P. aeruginosa* or *S. aureus*, respectively, after 10 days. In a subsequent study using the same model, total BAL fluid inflammatory cell infiltrate was reduced in MSC-treated mice, with a shift in the differential count toward reduced neutrophil and higher macrophage numbers (188).

A number of important mechanisms of the effect of MSCs have been revealed using pneumonia models. They include modulation of host immune cells by MSC mitochondrial donation (98, 141) and secretion of KGF, GM-CSF, TSG-6, and PGE2 (20, 61–63, 189), as well as pathogen-directed mechanisms like secretion of antimicrobial peptides LL-37, Lcn-2, and BD-2 (108, 126, 129).

Intra-abdominal infection. Preclinical models of intra-abdominal sepsis are generated typically by cecal ligation and puncture (23) or by i.p. injection of bacteria (113) or feces (21). In these settings of polymicrobial sepsis, i.v. or i.p. administration of human MSCs has been associated with increased survival, improved renal and liver function, and normothermia, as well as reduced bacteremia and circulating levels of proinflammatory cytokines (23, 140, 190).

The mechanisms of MSC activity in abdominal sepsis are not as well characterized as in pneumonia but bear some similarities. For instance, mononuclear cells isolated from the blood of MSC-treated mice with *P. aeruginosa* peritonitis had improved phagocytic capacity (32% compared with $<$20% in the control groups) via upregulation of C5a activation, suggesting that MSC modulation of monocytes and macrophages remains important (113). Likewise, MSC control of inflammation has been credited with improving organ function and survival via Treg cell modulation, as well as direct secretion of anti-inflammatory cytokines, such as IL-10 and IL-1Ra (30, 68, 140). One study suggested a distinctive mechanism for Men-MSCs in polymicrobial sepsis, where the activity of the antimicrobial peptide hepcidin correlated with survival, liver protection, and systemic bacterial clearance with an association not yet observed with other tissue sources of MSCs (23).

Human UC-MSCs have also been reported as protective in a preclinical model of chronic salpingitis (191). C3H/HeN mice were infected intravaginally with *Chlamydia trachomatis* before intravaginal administration of 1 million human UC-MSCs or placebo. MSC-treated mice had complete amelioration of histological evidence of fallopian tube injury and improved fertility (5/5 mice pregnant within 8 weeks, compared with 1/5 in the control group).

Skin and soft tissue infections. MSCs have been tested in a small number of preclinical studies of infected skin and soft tissue. Rodent MSCs administered to same-species models of *S. aureus* pouch or surgical mesh infections have demonstrated

bactericidal activity, enhanced neutrophil phagocytosis, and promotion of wound healing (69, 192). Human BM-MSCs have yielded similar results in rats with *S. aureus* pouch infections, with additional evidence from *in vitro* studies demonstrating antibiofilm activity against developing and established methicillin-resistant *Staphylococcus aureus* (MRSA) biofilms (192). Mechanistic studies from equine BM-MSCs suggest that direct secretion of cystine proteases, including cathepsins B and V, may contribute to MSC antibiofilm activity (114, 193).

Canine MSCs have been reported useful in the management of soft tissue infections in pet dogs (69). This study included five dogs with joint or soft tissue infections caused by multidrug-resistant (MDR) staphylococci, *E. coli*, and/or *P. aeruginosa*. All animals were enrolled after treatment failure with antimicrobial therapy and received 3 doses of allogeneic canine AD-MSCs, preactivated with poly(I·C), over 3 weeks with continuation of antibiotics. After 8 weeks, the clinical evidence of infection had resolved, and viable bacteria had been eliminated in dogs with native tissue infections. These findings were limited by the absence of a control group and heterogeneity of infectious presentations but support further investigation of human MSCs in cutaneous and musculoskeletal infections.

Preclinical Models of Mycobacterial Infection

Mycobacteria are characterized by their ability to infect macrophages and other host cells, evade degradation, and form an intracellular replicative niche (194, 195). Given their phagocyte-enhancing properties, MSCs have gained interest as a potential adjunct therapy for mycobacterial infections, particularly those caused by MDR/extensively drug-resistant (XDR) *Mycobacterium tuberculosis* and pathogenic nontuberculous mycobacteria (NTM) like *Mycobacterium abscessus* (3, 116).

Concerns about MSC susceptibility to intracellular mycobacterial infection were important to address before determining their therapeutic potential. Early reports suggested *Mycobacterium tuberculosis* can establish latent infection in the hypoxic niche of endogenous murine BM-MSCs, even after antimycobacterial treatment. MSCs from mice with latent *M. tuberculosis* infection could also generate infection in other mice by transplantation (196, 197). *M. tuberculosis* DNA could also be detected from BM-MSCs extracted from patients after treatment for pulmonary tuberculosis, although viable *M. tuberculosis* was not isolated (197). However, MSCs have since demonstrated direct antimycobacterial properties which may be species and setting specific. Human BM-MSCs and UC-MSCs phagocytosed *M. tuberculosis* via scavenger receptors at a similar efficacy as mouse and human macrophages and degrade bacilli through autophagy and nitric oxide (NO)-mediated killing (136). *M. tuberculosis* did not multiply in human MSCs but rather decreased in number over 7 days without inducing cell death. Similarly, murine BM-MSCs internalized and restricted intracellular growth of *M. bovis* BCG and *M. smegmatis* through the antimicrobial peptide cathelicidin but required inflammatory stimulation to control the intracellular growth of *M. tuberculosis* (198).

Most *in vivo* studies of mycobacterial infection have employed animal MSCs, with mixed results. Mice with disseminated *Mycobacterium bovis* BCG infection were given murine BM-MSCS $\pm$ preactivation of TLR3 receptors (182). Naïve MSC treatment resulted in a greater rise in splenomegaly and splenic mycobacterial counts than those of control mice, whereas preconditioned MSCs saw a fall in both outcomes. However, this model failed to generate sufficient counts of *M. bovis* in liver and lung tissue to determine an antimicrobial MSC effect, and human MSCs may have been more efficacious.

A separate study investigated MSCs in murine *M. abscessus* pulmonary infection (116). Mice treated with murine BM-MSCs had improved survival and around 50% reduction in lung and splenic CFU after 10 days. Parallel mechanistic studies found MSCs suppressed intracellular *M. abscessus* growth in macrophages by secreting PGE2 which upregulated nitric oxide production by macrophage inducible nitric oxide synthase (iNOS). A more recent study tested human BM-MSCs in murine models of *Mycobacterium avium* and/or *Mycobacterium intercellulare* cystic fibrosis pulmonary infection and reported a significant reduction in lung homogenate CFU after 7 days

compared with that of the control group (199). These reports warrant further research into human MSCs therapies for chronic NTM pulmonary infections.

Current antimicrobial therapies for NTM pulmonary infections are prolonged, poorly tolerated, and frequently ineffective so there is an urgent drive to develop new treatment strategies (100). NTM are variably susceptible to some antimicrobial peptides secreted by MSCs, such as lipocalin-2, hepcidin, and defensins (200), although some species are intrinsically resistant to LL-37 (201). However, the immunomodulatory ability of MSCs on macrophages may disrupt their intracellular mycobacterial niche and assist in bacterial killing, which may have particular application in patients with impaired immunity.

Preclinical Models of Viral Infection

Viral pneumonia. Four preclinical studies have tested human MSCs in viral pneumonia and all employed influenza virus (118, 202–204). Two studies found no beneficial effect for pulmonary edema or inflammatory cell infiltrate when human BM-MSCs were administered to C57BL/6 mice with mouse-adapted H1N1 pulmonary infection (202, 203). There was also no survival benefit, although in one of the studies, the influenza infection did not cause any mortality (203). However, a later study, in which BALB/c mice were infected with H5N1 influenza virus, a single dose of human BM-MSCs was associated with increased survival, reduced proinflammatory cytokines, and increased numbers of M2-like macrophages in the BAL fluid (118). The protective effect was attributable partly to MSC secretion of KGF and Ang-1 which promotes repair of the vascular endothelium (205). Most recently, human UC-MSCs were compared against human BM-MSCs in H5N1-infected BALB/c mice (204). MSCs did not reduce lung viral titers, nor did they confer a significant survival benefit, although MSC-treated mice did have reduced BAL fluid inflammatory cytokines and pulmonary edema. UC-MSCs were more protective than BM-MSCs and secreted larger amounts of Ang-1 and HGF.

The inconsistencies between these studies may be due to discrepancies in the models. The negative studies both tested a mouse-adapted strain of H1N1 virus in C56BL/6 mice, whereas the positive studies infected BALB/c mice with the more virulent H5N1 strain (206, 207). Inbred mouse strains also have differential responses to viral influenza, with BALB/c mice demonstrating higher lung viral titers in early infection and C56BL/6 mice having slower viral clearance (208). Although MSCs have already progressed to clinical trials for influenza-related ARDS, improving these preclinical models will be important for mechanistic and optimization studies.

Preclinical testing of human MSCs for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has also been hindered by the lack of a clinically relevant model (209). The technical challenges in establishing a model include the requirements of adequate containment facilities, specialist researcher training, and a reliable supply chain of resources amid the global economic pandemic. A murine model would be most desirable, but mice do not typically express compatible receptors for SARS-COV-2. The recently reported human ACE2 transgenic mouse did contract SARS-CoV-2 infection, with viral replication and infiltration of inflammatory cells into the alveolar tissue (210). However, the resultant pneumonia was mild, and clinically relevant results from interventional studies will be limited. The same investigators infected rhesus macaques with SARS-CoV-2 and observed interstitial pneumonia with viral replication and weight loss (211). Others have successfully modeled viral replication in hamsters, ferrets, and cats, although transmission between individuals is limited, disease severity is low, and there is no associated mortality (212). To date, these models have not been used to trial human MSCs and the urgency of developing interventions for COVID-19 has accelerated their progress into clinical trials, as described below.

Herpesvirus infections. Herpesviruses are capable of infecting human MSCs *in vitro*, with some members (herpes simplex virus 1 [HSV-1], HSV-2, varicella-zoster virus [VZV], and cytomegalovirus [CMV]) capable of persistent intracellular replication (213, 214). However, BM-MSCs and placenta-derived MSCs isolated from seropositive donors have undetectable levels of the herpesvirus genome, suggesting that viral persistence may

not occur *in vivo*. Human BM-MSCs appear to be resistant to Epstein-Barr virus (EBV) infection and have some direct antiviral activity against CMV and HSV-1, mediated through an increased expression of IDO (107, 214).

HIV infection. Early studies indicated that MSCs were susceptible to HIV infection with subsequent suppression of their immunomodulatory properties (215). Specific HIV proteins, such as p55-gag, can also suppress MSC cytokine expression and drive cellular senescence *in vitro* (216). However, MSCs may still be beneficial against latent HIV infection. MSCs can reactivate latent HIV in infected macrophages and T-helper lymphocytes, removing them as reservoirs and enhancing HIV eradication (217). MSC conditioned media also significantly enhanced the latency-reversing effect of panobinostat, suggesting the presence of MSC soluble mediators that may enhance host response in latent HIV.

Viral hepatitis. There are conflicting reports on the susceptibility of MSCs to infection with hepatitis B virus (HBV) (218, 219), but there is no evidence to date that hepatitis C virus (HCV) can replicate inside human MSCs. However, MSCs can enhance host cellular response against both HBV and HCV *in vitro*. Human MSCs suppressed HBV replication in hepatoblastoma cells when cocultured with splenic lymphocytes and reduced HCV replication in epithelial cells (220, 221).

Preclinical Models of Fungal Infections

Invasive candidiasis. The first evidence of MSC fungicidal activity was reported in a subset (~3%) of isolated human BM-MSCs that expressed IL-17 and exhibited anti-*Candida* activity (222). These IL-17+ BM-MSCs were superior to unselected BM-MSCs in reducing *Candida albicans* CFU *in vitro* and promoting fungal clearance in a mouse model of invasive candidiasis. However, unselected MSCs performed better than IL-17+ BM-MSCs in treatment of polymicrobial sepsis caused by chemically induced acute colitis, particularly in reducing colonic transmural inflammation and restoring normal intestinal structure. The antifungal mechanisms of IL-17 are not well understood but may be related to the recruitment of neutrophils, which are important for controlling mucosal *Candida* infection, or induction of fungicidal antimicrobial peptides calprotectin, β-defensin-3, and lipocalin-2 (223, 224). This hypothesis raises the interesting prospect that MSCs could be selected and enriched where subphenotypes have demonstrated enhanced efficacy in particular indications.

Aspergillosis and mold infections. Human BM-MSCs can directly phagocytose *Aspergillus* conidia and reduce viable CFU by around 20% after 4 hours (225). This process did not appear to elicit any significant inflammatory response in MSCs, which was measured by mRNA and protein levels of IL-6, GM-CSF, and RANTES. However, MSCs may themselves be susceptible to *Aspergillus* virulence factors, such as gliotoxin which induces mitochondrial dysfunction (226).

MSCs also did not significantly modulate *in vitro* innate or adaptive immune response activity against *Aspergillus* sp. (225). Human MSCs have yet to be tested in *in vivo* models of invasive aspergillosis.

Human UC-MSCs were protective in a mouse model of fungal corneal keratitis generated by the mold *Fusarium oxysporum* (227). MSC-treated mice had reduced corneal opacity, corneal thickness, and inflammatory cell infiltration. MSC treatment also had reparative benefits, restoring collagen removal and reducing mRNA expression of fibrosis-related factors (such as α-SMA [smooth muscle actin] and TGF-β1) in the cornea. However, the study did not report on whether human MSCs had any effect on *Fusarium* viability.

Dimorphic fungi. *Paracoccidioides brasiliensis* is the causative agent of paracoccidioidomycosis, an endemic mycosis in Latin America (228). Murine BM-MSCs can directly phagocytose *P. brasiliensis*, although this did not significantly change the viable CFUs (229). However, CFUs in coculture with MSCs did not differ from those cultured without, suggesting that MSCs had no direct fungicidal effect. In an *in vivo* pulmonary infection, mice treated with murine BM-MSCs had a significantly higher *Paracoccidioides* burden in lung and spleen, as well as increased lung infiltrate of neutrophils, eosinophils, and M2-type macrophages (180). The negative effect of MSCs in

this study might be related to the host and MSC species or to the complex pathogenesis of dimorphic fungi which transform from mold to yeast form during infection of mammalian hosts (230). These findings warrant further characterization of the interaction between MSCs and dimorphic yeasts, especially to establish whether human MSCs are similarly detrimental in preclinical models of paracoccidioidomycosis.

Preclinical models of Parasitic Infection

Malaria. Malarial parasites replicate intracellularly inside susceptible hosts and induce regulatory T cells to evade the immune response (231). MSCs extracted from the spleens of mice with malaria were administered by adoptive transfer to naive mice prior to infection with *Plasmodium bergei* (232). MSC-treated mice arrested parasite replication by day 9, cleared parasitemia by day 19, and survived the study, in contrast to control mice which had uncontrolled parasitemia and 100% mortality by day 14. Treated mice also had fewer circulating regulatory T cells and higher serum levels of proinflammatory cytokines, including IL-12, IFN-γ, TNF-α, IL-1β, and IL-6. In dysregulated overexpression, these cytokines can cause the hyperinflammatory response seen in sepsis, but at controlled levels, they are instrumental in generating the type 1 immune response required to eradicate intracellular pathogens (233). The effect of human MSCs in preclinical models of malaria has yet to be determined.

Trypanosomiasis. Chagas disease is a common cause of cardiomyopathy and heart failure in Latin America, which is caused by the parasite *Trypanosoma cruzi* (234). The myocardial injury is characterized by inflammatory, structural, and ischemic changes, leading to interest among cell therapy investigators over potential disease modulation by MSCs (235).

Murine BM-MSCs given i.v. migrate to damaged cardiac tissue in chagastic mice and are associated with reduced right ventricular dilatation (236). Rats with chronic trypanosomiasis and established cardiac injury had improved ventricular function and reduced histological evidence of myocardial fibrosis after treatment with a combination of autologous BM-MSCs and skeletal myoblasts (237). Therapies consisting of bone marrow mononuclear cells, a heterogeneous population, including MSCs, resulted in fewer histological counts of parasites in myocardial tissue of the treated mice. (235, 238). Together, these data suggest the potential for MSC-based therapy in Chagas disease treatment.

Schistosomiasis. Schistosomiasis remains endemic in many parts of world, with an estimated global prevalence of over 230 million cases (239). The infectious agents are trematode *Schistosoma* parasites, of which *Schistosoma haematobium*, *Schistosoma mansoni*, and *Schistosoma japonicum* are the three main species that cause human infection. Praziquantel is the current first-line therapy, although it is less active against larval forms of *Schistosoma* spp., and treatment failure is common in children (240). In a rat model of chronic schistosomiasis, rat BM-MSC therapy improved survival and reduced histological evidence of injury on the liver and spleen (241). A similar attenuation of liver injury on histological examination has been observed in mice infected with *S. mansoni* or *S. japonicum* and treated with murine BM-MSCs (242, 243), human UC-MSCs (244), and human UC-MSC EVs (245).

Toxoplasmosis. Human BM-MSCs can directly inhibit growth of *Toxoplasma gondii* by IDO-induced tryptophan starvation (107). Human BM-MSCs are more efficacious against *T. gondii* than mouse BM-MSCs, which require prestimulation with IFN-γ, TNF-α, and IL-1β to have any antitoxoplasma effect. Later studies also showed that activated murine MSCs were active against the low virulent type II ME49 strain but not the more virulent type I RH strain of *T. gondii* (246). Human MSCs have yet to be tested in *in vivo* models of toxoplasmosis.

Leishmaniasis. MSCs appear to be susceptible to leishmania infection and induce a pathogen-permissive Treg cells response in preclinical models. Several *Leishmania* species can infect human AD-MSCs, with some species viable up to 28 days after infection (247). Disseminated *Leishmania* parasites can reside in a latent form in murine MSCs extracted *in vivo* from bone marrow and spleen, persisting up to 60 days after infection

(248). Murine BM-MSC therapy given to mice with cutaneous footpad leishmaniasis resulted in a higher parasitic load and concentration of IL-10 in the footpad lesion, as well as increased numbers of IL-10-secreting splenic T cells (181). Confirming if murine MSCs are detrimental in other models of leishmaniasis and whether this is reproducible with human MSC therapy will be key for determining if MSCs will be a viable treatment option for this disease.

CLINICAL DATA FOR MSC THERAPY IN INFECTIOUS DISEASES

Clinical trials focused specifically on MSCs in the management of complex and resistant infections remain underrepresented among cell therapy trials. In this section, we highlight those infectious disease trials that are completed (Table 2) or ongoing (Table 3) that measure outcomes relating to pathogen elimination and/or improving host immunity.

MSC Trials in Sepsis

The Russian RUMCESS open-label phase 1 trial investigated MSC potential in neutropenic sepsis treatment and reported improved short-term survival (249). Thirty patients were recruited and randomized to receive conventional therapy with or without a single dose of 1 million per kg allogeneic BM-MSCs. MSC therapy was well tolerated and conferred a significant reduction in 28-day mortality compared with conventional therapy (3 of 15 patients, versus 12 of 15, $P = 0.05$), although there was no difference in subsequent death within 90 days from sepsis-related organ failure. However, this study had important limitations, including a small sample size, no placebo in the control arm, and an absence of clear power calculations for mortality.

MSCs have been trialed in a small group of patients with neutropenic sepsis related to acquired severe aplastic anemia (SAA) and treatment-refractory infections (250).

In this phase 2 study, six SAA patients were recruited with refractory bacterial and/or fungal infections, defined as no response or recurrence of new signs of infection to appropriate antibiotic or antifungal therapy. Participants received concurrent allogeneic hematopoietic stem-cell transplantation (HSCT) with 2 doses of 2 to 4 million allogeneic BM-MSCs at day 0 and day 14. Infusions of MSCs were well tolerated with no adverse effects reported. There were no further episodes of bacteremia or sepsis in any patient following HSCT nor intensive care unit (ICU) admission for organ support requirement. Five of six patients were still alive at the time of reporting (range of 17- to 40.5-month follow up), and one patient died after 3 months from acute graft-versus-host disease. Two patients had complete resolution of pulmonary infections 1 month post-HSCT with resolution in all other surviving patients by 6 months. Although this study was limited by the small participant number and lack of a placebo control, the findings support further testing of human MSCs in refractory neutropenic sepsis and invasive fungal infections.

The Canadian CISS trial was a phase 1 clinical trial of safety of allogeneic BM-MSC therapy for septic shock treatment (251). Escalating doses of 0.3, 1.0, and 3.0 million cells per kg were given to nine patients in a 3 + 3 + 3 design study, with 21 participants in an observational arm. There were no differences in temperature, physiological or pulmonary parameters, or mortality or plasma cytokine levels between the MSC-treated and observational subjects. The study was not powered to measure efficacy, but it reported that the therapy was well tolerated with no adverse MSC-related events.

There are two trials in progress for MSC therapy in sepsis, namely, SEPCELL and CHOCMSC. The SEPCELL study is a phase 1/2 double-blind study testing allogeneic AD-MSCs in two doses over 3 days in patients with community-acquired pneumonia and sepsis (ClinicalTrials.gov under registration no. NCT03158727). This study aims to recruit 36 patients and measure safety as the primary outcome, based on adverse effects and plasma cytokine levels in the 90 days following the first MSC infusion. The CHOCMSC study is a phase 2 double-blind study in community-acquired sepsis with organ failure (ClinicalTrials.gov under registration no. NCT02883803). Sixty-six participants will be recruited, with parallel assignment to interventional and placebo arms.

Treated participants will receive a single dose of 10 million/kg heterologous MSCs with sequential organ failure assessment (SOFA) score measured as the primary outcome.

MSC Trials in Pulmonary Infection

Pulmonary tuberculosis is characterized by a failure of the type 1 immune response to contain and clear *Mycobacterium tuberculosis*. Antimicrobial therapy is prolonged (at least 6 months) and often poorly tolerated, leading to drug resistance and poor patient outcomes. The combination of host- and pathogen-directed activities of MSCs in preclinical studies highlighted their potential as an adjunct therapy for tuberculosis (4, 252).

MSCs have been trialed in a phase 1 study for multidrug resistant (MDR) or extensively drug resistant (XDR) tuberculosis (50). Thirty patients with smear-positive MDR or XDR tuberculosis were recruited to this open-label trial to commence a new course of personalized second-line antitubercular therapy based on antimicrobial-susceptibility results. Bone marrow aspiration was performed within 1 month of the new antibiotic regimen to prepare autologous BM-MSCs, which were administered as a single dose of 1 million cells per kg. Thirty time-matched control patients were recruited consecutively to receive no MSC intervention. All patients received concurrent antitubercular medication and were followed up for 6 months.

The safety record of MSCs from this phase 1 trial was reassuring. There were no severe adverse effects associated with MSC infusion, nor in the 6-month observation period afterward. There was no deterioration in radiological changes, sputum culture rates, or hematological or biochemical parameters compared with the control population. There was a fall in C-reactive protein (CRP) at 1 month after MSC treatment, but the study was underpowered to assess for significance. There was also no impairment to IFN-γ production by peripheral blood mononuclear cells after MSC infusion. This was to investigate the risk of MSC suppression of type 1 immune responses, which are essential for mycobacterial eradication.

Fourteen phase 1 or 2 trials into MSC safety and/or efficacy in chronic obstructive pulmonary disease (COPD) have commenced since 2010 (253). Of these trials, three have been reported (49, 253, 254) and one has completed, for which we await results (ClinicalTrials.gov under registration no. NCT02216630). All reported trials have verified the safety of MSC infusions in COPD patients with two studies confirming this with multiple (i.e., two to four) doses. In two of the reported trials, CRP levels were significantly reduced at least 1 month after MSC infusion, although more research is required to determine the clinical significance of this finding (255).

The CEASE cystic fibrosis (CF) trial was the first to test MSCs in adults with CF and has recently finished recruitment (ClinicalTrials.gov under registration no. NCT02866721). Fourteen participants were recruited to this open label, single-group phase 1 study and received up to 5 million allogeneic BM-derived MSCs as a single infusion. There are 10 primary outcome measures that cover safety but also include change in sputum quantitative microbiology and number of pulmonary exacerbations.

A phase 1 trial into non-CF bronchiectasis has recently completed with results awaited (ClinicalTrials.gov under registration no. NCT02625246). Six participants were recruited into a single-group, open-label study to determine MSC safety in this patient population. Secondary outcome measures include difference in bacterial CFUs in sputum culture and frequency of acute exacerbations.

MSC Trials in Cutaneous Infections

In burn injury, the success of skin grafting and wound recovery relies on effective neutrophil activity at the injured site. MSC promotion of neutrophil migration to infected tissue have been described in preclinical models of skin infection (160, 192). A phase 1/2 trial is currently testing a tissue-engineered biological construct using allogeneic AD-MSCs in burn wounds (ClinicalTrials.gov under registration no. NCT03113747). The primary outcome will be the degree of wound healing. Neutrophil phagocytosis at skin flaps following MSC administration will be an important secondary outcome measure.

Diabetic foot ulcers (DFUs) are characterized by poor wound healing and susceptibility to chronic infection. A single-arm phase 1/2 study recruited patients with

neuropathic DFU to assess the safety and efficacy of topical application of MSCs to the wound matrix (ClinicalTrials.gov under registration no. NCT03267784). A number of outcome measures are planned, including reduction of wound area and the presence of infection, and the trial has completed with a report awaited.

The ACellDREAM2 phase 2 study is currently open to recruitment and will look into MSC efficacy in critical limb ischemia (ClinicalTrials.gov under registration no. NCT03968198). Forty-three participants will be enrolled into this single-group, open-label study where autologous adipose tissue-derived MSCs will be given by intramuscular injection. The primary outcome measures will be survival without amputation or limb ischemia, but wound healing and infection rates will be measured as secondary outcomes.

MSC Trials in Intra-abdominal Infections

Inflammatory bowel disease (IBD) is characterized by episodes of inflammatory colitis, frequently exacerbated by bacterial translocation and intra-abdominal infection. There are currently more than 30 registered clinical trials investigating MSC therapy for various complications of ulcerative colitis and Crohn's disease (https://clinicaltrials.gov/). A large multicenter, randomized double-blind phase 3 study reported on the benefits of allogeneic AD-MSCs in refractory perianal fistulas in patients with Crohn's disease (256). A total of 212 patients were recruited and randomized 1:1 to receive 120 million MSCs or a placebo by local injection to the fistula site. In the treatment arm, 50% of patients had achieved the primary endpoint of fistula closure and resolution of collections after 24 weeks, compared with 34% who received placebo ($P = 0.024$). A phase 1 trial with a 4-year follow-up period recently reported on using allogeneic BM-derived MSCs for the same indication (257). Doses of 10, 30, and 90 million cells were administered by local injection to cohorts of 5 patients each. Fistula closure was reported in these cohorts of 67%, 86%, and 29%, respectively, after 24 weeks and 63%, 100%, and 43% after 4 years. This finding compared favorably against the placebo group ($n = 6$) which saw fistula closure of 33% and 0% at the same time points, although the study did not appear to be powered to determine significance.

Typhlitis, or neutropenic colitis, is a common complication of chemotherapy for hematological malignancy. A phase 1/2 trial is planned to test allogeneic bone marrow-derived MSC efficacy for preventing neutropenic colitis and enhancing hemopoietic recovery following chemotherapy for Hodgkin's lymphoma (ClinicalTrials.gov under registration no. NCT02145923). Sixteen patients will receive 1.5 to 2 million cells per kg, with no comparator group. The study will measure serious adverse events and reactions as the primary outcome measure, with frequencies of neutropenic enterocolitis and other infectious complications among the secondary outcomes.

MSC Trials in Viral Infections

MSCs were first trialed for COVID-19 treatment in a small case series of 7 Chinese patients in Beijing, China (258). MSCs were well tolerated even in severe ARDS and associated with increased oxygenation, reduced infiltration on computed tomography (CT) imaging, and decreased serum inflammatory markers. Over 80 trials have since been registered to test human MSCs in COVID-19 respiratory disease treatment . The majority of them are phase 1 safety trials with a focus on MSC potential in the amelioration of COVID-19-related ARDS. One of these trials has already reported (ClinicalTrials.gov under registration no. NCT04457609) (259). Forty patients were recruited to receive 1 million UC-MSCs per kg or placebo. Survival rates in the MSC-treated group were 2.5 times higher, rising to 4.5 times in patients with comorbidities (diabetes mellitus, hypertension, chronic kidney disease, or cardiovascular disease). These results are encouraging, although the study sample was relatively small and survival rates will be assessed more reliably in a phase 2/3 trial.

Among phase 2 trials, 1 study of 101 participants has already reported (ClinicalTrials.gov under registration no. NCT04288102) (260). Patients with severe COVID-related ARDS received 3 doses of 40 million human UC-MSCs or placebo. Treated patients tolerated MSC therapy well and had significantly reduced radiological evidence of lung injury after 28 days. Mortality and markers of viral response were not reported. However, there are 31 active or

recruiting trials in phases 2 or 3 trials focused on MSC impact on of mortality, systemic inflammation markers, organ dysfunction, duration of symptoms, and long-term complications, such as pulmonary fibrosis (Table 4).

Among the phase 3 trials for COVID-19, 1 study is testing 2 infusions of 2 million MSCs per kg or placebo plus standard care in 300 participants (ClinicalTrials.gov under registration no. NCT04371393). The primary outcome measure is 30-day mortality, with numerous secondary outcomes, including timing of ARDS resolution and change in inflammatory. The multicenter phase 2 REALIST COVID-19 trial has completed recruitment and results are awaited. In this study, 60 COVID-19 patients were randomized to receive standard care plus UC-MSCs or placebo (ClinicalTrials.gov under registration no. NCT03042143). Patients in the treatment arm received a single dose of 400 million MSCs, which was well tolerated in critical care patients with ARDS in the phase 1 REALIST trial. It will report on oxygenation index and incidence of serious adverse events as primary outcomes, with relevant secondary outcomes, including SOFA score, ventilator dependence, and length of hospital stay and mortality.

The preventative potential of MSCs against COVID-19 is being investigated by two parallel phase 2 trials, looking at allogeneic (ClinicalTrials.gov under registration no. NCT04348435) and autologous (ClinicalTrials.gov under registration no. NCT04349631) AD-MSCs. Participants from "high-risk exposure" occupations, such as front-line health care workers, are being invited to receive five infusions of human AD-MSCs over 14 weeks and observed for incidence of COVID-19 symptoms and hospitalization.

In contrast to the large trial numbers for SARS-CoV-2 and ARDS, only two clinical trials have been registered to test MSCs specifically in viral influenza. The first is a phase 1/2 study planned to test allogeneic menstrual blood stem cells on 20 participants and measure the severity of H7N9 influenza-induced lung injury, although its recruitment status is unknown (ClinicalTrials.gov under registration no. NCT02095444). The second is the RECOVER trial, a phase 1, double-blind, placebo-controlled RCT that will test up to 3 doses of 100 million allogeneic BM-MSCs in subjects with ARDS caused by influenza or SARS-CoV-2 (ClinicalTrials.gov under registration no. NCT04629105). The study outcomes revolve around safety measures, although virus-specific antibody titers are included as a secondary measure.

CMV reactivation is a common complication following allogeneic HSCT. Ganciclovir is the current first-line therapy, but its use is limited due to associated bone marrow suppression and rising CMV resistance. An open-label phase 2 trial testing allogeneic BM-derived MSC treatment potential for refractory CMV infection following HSCT has completed and results are awaited (ClinicalTrials.gov under registration no. NCT02083731). Participants received 1 million cells per kg as a single dose, with a second dose given after 14 days if they had not entered remission. The study will measure the percentage of patients achieving CMV remission for 1 year as the primary outcome.

In HIV infection, MSCs are currently being trialed for two complications, as follows: discordant immune response (DIR) and immune reconstitution inflammatory syndrome (IRIS). In DIR, there is successful virological control but a failure to recover satisfactory counts of $CD4^+$ T cells. There is no specific therapy for DIR, and it is associated with up to a 3-fold rise in mortality risk from opportunistic infections. Although MSCs are generally associated with suppression of $CD4^+$ T-cell activity, in HIV infection, they suppress their by cytotoxic $CD8^+$ T cells and allow their recovery (261). A single-center phase 1/2 trial is currently investigating the effect of a 4-dose regimen of MSCs over 20 weeks versus placebo on $CD4^+$ T cell count and rate of opportunistic infection (ClinicalTrials.gov under registration no. NCT02290041).

In IRIS, recovery of $CD4^+$ T cells with antiretroviral therapy is associated with a hyperinflammatory response to the antigenic burden accumulated during the period of immunosuppression (262). A small phase 2 trial investigated systemic inflammation and opportunistic infection in seven patients who received UC-MSCs, given in three doses at 1-month intervals, compared with placebo. MSC-treated patients had increased $CD4^+$ T cell numbers and function after 6 months, as well reduced levels of

TABLE 4 Current recruiting and/or active clinical trials of MSCs in COVID-19 and related conditions in phases 2 and 3[a]

Phase	ClinicalTrials.gov registration no.	Study design	Stage	Intervention	Infection-related outcome
1/2	NCT04336254	Phase 1/2, single center, triple blind, randomized, placebo controlled; $n = 20$	Recruiting	Allogeneic human dental pulp MSCs, 3×10^7 cells; 3 doses over 7 days	Viral load, plasma cytokine profile, CRP, radiological improvement
	NCT04366323	Phase 1/2, multicenter, open label, randomized, placebo controlled; $n = 26$	Recruiting	Allogeneic AD-MSCs, 8×10^7 cells; 2 doses	28-day mortality
	NCT04339660	Phase 1/2, single center triple blind, randomized, placebo controlled; $n = 30$	Recruiting	Allogeneic UC-MSCs, 1×10^6 cells/kg; single dose	28-day mortality, viral load, plasma cytokine profile, radiological improvement
	NCT04355728	Phase 1/2, single center, single-blind, randomized, placebo controlled; $n = 24$	Completed, not yet reported	Allogeneic UC-MSCs, 10×10^7 cells; single dose	90-day mortality; WCC, CRP, and D-dimer
	NCT04333368	Phase 1/2, multicenter, triple blind, randomized, placebo controlled; $n = 60$	Active, not recruiting	Allogeneic UC-MSCs, 1×10^6 cells/kg; 3 doses over 5 days	28-day mortality, plasma cytokine profile
	NCT04382547	Phase 1/2, single center, open label, nonrandomized, parallel assignment; $n = 40$	Enrolling by invitation	Allogenic pooled olfactory mucosa-derived mesenchymal stem cells, dose not specified	Viral load, radiological improvement
	NCT04461925	Phase 1/2, single center, open label, nonrandomized, parallel assignment; $n = 30$	Recruiting	Allogeneic placenta-derived MSCs, 1×10^6 cells/kg; 3 doses over 7 days	28-day mortality
	NCT04390152	Phase 1/2, multicenter, quadruple blind, randomized, placebo controlled; $n = 40$	Recruiting	Allogeneic UC-MSCs, 5×10^7 cells; 2 doses	28-day mortality
	NCT04390139	Phase 1/2, multicenter, quadruple blind, randomized, placebo controlled; $n = 30$	Recruiting	Allogeneic UC-MSCs, 1×10^6 cells/kg; 2 doses over 3 days	28-day mortality, plasma cytokine profile, WCC
	NCT04494386	Phase 1/2, multicenter, triple blind, randomized, placebo controlled; $n = 60$	Recruiting	Allogeneic UC-MSCs, 1×10^8 cells; up to two doses over 2 days	WCC
	NCT04392778	Phase 1/2, multicenter, quadruple blind, randomized, placebo controlled; $n = 30$	Recruiting	Allogenic MSCs, source not specified; 3×10^6 cells, 3 doses over 6 days	Symptomatic improvement, viral load
	NCT04537351	Phase 1/2, multicenter, open label, randomized, parallel assignment; $n = 24$	Recruiting	Commercial MSCs, 2×10^6 cells/kg; single dose	Clinical improvement scale, CRP
	NCT04399889	Phase 1/2, single center, quadruple blinded, randomized, single-group assignment; $n = 30$	Recruiting	Allogeneic UC-MSCs, 1×10^6 cells/kg; up to 3 doses over 3 days	28-day survival, viral load
	NCT04445454	Phase 1/2, single center, open label, single-group assignment; $n = 20$	Recruiting	Allogeneic BM-MSCs, 3×10^6 cells/kg; up to 3 doses over 4 days	Viral load, regulatory T cell profile
	NCT04614025	Phase 1/2, multicenter, open label, parallel assignment; $n = 40$	Recruiting	Commercial placental-derived MSCs, 3×10^8 cells; single dose	28-day mortality
	NCT03042143	Phase 2, single center, triple blind, randomized, placebo controlled; $n = 75$	Recruiting	Allogeneic UC-derived CD362-enriched MSCs, 400×10^6 cells; single dose	28-day and 90-day mortality, SOFA score

(Continued on next page)

TABLE 4 (Continued)

Phase	ClinicalTrials.gov registration no.	Study design	Stage	Intervention	Infection-related outcome
2	NCT04288102[b]	Phase 2, multicenter, double blind, randomized, placebo controlled; $n = 90$	Completed	Allogeneic UC-MSCs, 3×10^7 cells; 3 doses over 6 days	90-day mortality, plasma cytokine profile, radiological improvement
	NCT04362189	Phase 2, multicenter, quadruple blind, randomized, placebo controlled; $n = 110$	Active, not recruiting	Allogeneic AD-MSCs, 100×10^6 cells; 4 doses over 10 days	28-day mortality, plasma cytokine profile, WCC and CRP
	NCT04361942	Phase 2, single center, triple blind, randomized, placebo controlled; $n = 24$	Recruiting	Allogeneic BM-MSCs, 1×10^6 cells/kg; single dose	28-day mortality, plasma cytokine profile, WCC, radiological improvement
	NCT04269525	Phase 2, single center, open label, single-group assignment; $n = 10$	Recruiting	Allogeneic UC-MSCs, 1×10^8 cells; 4 doses over 7 days	28-day mortality, plasma cytokine profile, WCC and CRP
	NCT04366271	Phase 2, multicenter, open label, randomized, parallel assignment; $n = 106$	Recruiting	Allogeneic UC-MSCs, dose not specified; single dose	28-day mortality
	NCT04349631	Phase 2, single center, open label, single-group assessment; $n = 56$	Enrolling by invitation	Allogeneic AD-MSCs, prophylactic use, 50×10^6–200×10^6 cells; 5 doses over 26 wks	Hospitalization for COVID-19, onset of COVID-19 symptoms, plasma cytokine profile, WCC and CRP
	NCT04348435	Phase 2, single center, quadruple blind, randomized, placebo controlled; $n = 100$	Enrolling by invitation	Allogeneic AD-MSCs, prophylactic use, 50×10^6–200×10^6 cells, 5 doses over 14 wks	Hospitalization for COVID-19, onset of COVID-19 symptoms, plasma cytokine profile, WCC and CRP
	NCT04444271	Phase 2, single center, open label, randomized, placebo controlled	Recruiting	Allogeneic BM-MSCs, 2×10^6 cells/kg; up to 2 doses, 7 days apart	30-day survival, viral load
	NCT04615429	Phase 2, single center, double blind, randomized, placebo controlled; $n = 20$	Active, not recruiting	Allogeneic MSCs, source not specified; 1×10^6 cells/kg, single dose	28-day mortality
	NCT04437823	Phase 2, single center, open label, randomized, parallel assignment; $n = 20$	Recruiting	Allogeneic UC-MSCs, 5×10^5 cells/kg; 3 doses over 5 days	30-day mortality, viral load
	NCT04466098	Phase 2, multicenter, triple blind, randomized, placebo controlled; $n = 30$	Recruiting	Allogeneic MSCs, source not specified; 300×10^6 cells, 3 doses over 7 days	28-day mortality
2/3	NCT04366063	Phase 2/3, single center, open label, randomized, parallel assignment; $n = 60$	Recruiting	Allogeneic MSCs, 100×10^6 cells, 2 doses over 2 days ± MSC EVs, 2 doses over 2 days	Symptomatic improvement, plasma biochemical profile
	NCT04367077	Phase 2/3, multicenter, quadruple blind, randomized, placebo controlled; $n = 400$	Recruiting	Commercial BM-MSCs, dose not specified; single dose	28-day mortality
3	NCT04371393	Phase 3, multicenter, triple blind, randomized, placebo controlled; $n = 300$	Active, not recruiting	Commercial BM-MSCs, 2×10^6 cells/kg; 2 doses over 4 days	30-day mortality, plasma cytokine profile, CRP

[a]AD-MSCs, adipose tissue-derived MSCs; BM-MSCs, bone marrow-derived MSCs; CRP, C-reactive protein; EVs, extracellular vesicles; UC-MSCs, umbilical cord-derived MSCs; WCC, white cell count.
[b]Reference is 260.

inflammatory markers, including CRP, D-dimer, and total IgG (ClinicalTrials.gov under registration no. NCT01213186) (261).

MSCs have also been investigated for their potential in the management of viral hepatitis. One trial recruited 527 patients with hepatitis B virus-induced liver failure in a 4-year study, giving a single dose of autologous BM-derived MSCs (ClinicalTrials.gov under registration no. NCT00956891). Although the primary outcome of short-term improvements were met (measured by levels of total bilirubin, albumin, and prothrombin time after 4 weeks), there was no significant difference in the secondary outcome of incidence of hepatocellular carcinoma or mortality after 3 years (263). A current phase 1 study is looking at MSC safety and effectiveness in decompensated hepatitis B cirrhosis (ClinicalTrials.gov under registration no. NCT03826433). Twenty participants are being recruited to this nonrandomized, open-label study that will test the MSC effect versus placebo on mortality and liver function tests.

In HCV-related liver cirrhosis, autologous BM-MSCs were administered to the liver parenchyma of six patients in a nonrandomized, noncontrolled phase 1 trial (264). MSCs were well tolerated, with jaundice resolving in four of six patients after 6 months and a reduction of transaminitis, although this reduction did not reach statistical significance. Histological examination showed evidence of fibrolysis and regeneration of hepatocytes, although the significance of this is uncertain without a control group.

CHALLENGES FOR DEVELOPING MSC THERAPIES

Standardization of Cell Products

The heterogeneity of MSCs between donors and tissue sources leads to potential difficulty in standardizing candidate cell therapies (265, 266). Potency assays are proposed tools to verify that an MSC product has the expected and a consistent effect at a specified dose. These tools should characterize MSC phenotype as well as function (267, 268). The phenotype can be determined on the basis of cluster of differentiation (CD) expression, which differs between MSC tissue sources. An assay for functionality should be specific to the intended effect, and several assays have been suggested, including expression of soluble mediators (such as IDO, PGE2, and TGF-β) and modulation of T cell surface activity (268).

An alternative approach to cellular profiling is based on measuring levels of key MSC transcription factors, known as the Clinical Indications Prediction (CLIP) scale (269). For example, Twist1 is a master regulator of multiple pathways related to MSC functionality, such as cell cycle and growth, differentiation, angiogenic ability, and expression of cytokines and immunomodulatory mediators (270). Higher Twist1 expression in MSC donors was associated with proangiogenetic ability, whereas a lower expression correlated with enhanced immunomodulatory ability. Thus, expression or genetic manipulation of Twist1 could help direct MSC subtypes toward applications in clinical settings that require immunomodulation (such as infection) or angiogenesis (such as stroke or myocardial infarction).

Detailed profiling of candidate MSC therapies remains research priority, as both the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recommend that a satisfactory potency assay should be a prerequisite for approving their clinical use (271, 272).

Manufacturing Standards, Resources, and Costs

The production of a clinical-grade cell therapy requires a scalable and affordable culture system that meets good manufacturing practices (GMPs). This production involves a complex series of upstream processing (isolation from donor, culturing, and expansion), downstream processing (harvesting, concentration, and medium exchange) before formulation, packaging and storage, then final distribution, and administration to patients (273, 274).

Initial efforts to culture the high numbers of cells required focused on planar cultivation systems for monolayer cell growth. The introduction of roller bottles, where cells are cultured in hundreds of rotating cylinders, improved the consistency of pH, oxygen,

and metabolites through the system but still could not deliver sufficient cells for clinical therapy (275). An alternative to conventional culture involves the use of bioreactors, for which there are a number of models (274). The "stirred tank" model uses beads as surface contacts for cell attachment and growth. In the "hollow fibre" model, cells attach during passage through porous capillaries and are fed by media passed through the extracapillary spaces.

During harvesting, cells are detached from the culture scaffold using proteolytic enzymes, collected, washed, and concentrated in cryopreservation buffer. MSCs must then pass quality-control process to check cell identity, purity, characteristics, and efficacy (276). The MSCs undergo formulation which may involve the generation of a cell suspension for systemic administration, encapsulation into beads, or grafting onto a 3D matrix (such as alginate beads or graphene scaffold) for topical therapy (273, 274, 277). The need for substantial and simultaneous investments to generate MSC therapies for infectious diseases to GMP standards remains the greatest challenge for bringing them to the patient bedside (278).

NEXT STEPS AND OUTLOOK

The antimicrobial activities of MSCs have been well established against a broad range of human pathogens, highlighting a potential new strategy in the management of complex infections. Here, we outline the most pressing indications for which MSCs should be further investigated.

The pathogen-directed activity of MSCs offers therapeutic potential in the global fight against MDR infections, in particular chronic disease. MSCs retain activity against multidrug-resistant bacteria, representing a possible new strategy against resistant Gram-positive and -negative organisms (9, 114). The number of effective and tolerable antimycobacterial drugs is already limited, making MSCs an attractive prospect for MDR/XDR tuberculosis and nontuberculous mycobacterial pulmonary disease (50, 199). Complex fungal infections are increasing in incidence globally and are driven partly by the emergence of resistant species, such as *Candida auris* and azole-resistant aspergilli (279, 280). The fungicidal properties of MSCs make them an attractive potential alternative to the limited range of antifungal chemotherapies.

MSCs may have a role in treating drug-resistant environmental commensals that cause pulmonary infections in patients with pre-existing lung disease (187). *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, and *Achromobacter* species cause particularly difficult infections in the setting of cystic fibrosis and bronchiectasis (281). Although MSCs have not yet been tested directly against these pathogens, MSC-related mechanisms, such as antimicrobial peptide expression (282) and macrophage enhancement (283), are important in their clearance.

MSCs may also help meet the growing demand for host-directed therapies in impaired immunity. Infections in the immunocompromised host are rising in incidence and complexity, which is attributable in part to the increased use of immunosuppressant drugs and improved life expectancy for transplant recipients (284). MSCs have activity against opportunistic pathogens (including herpesviruses, *Candida* species, and *Toxoplasma gondii*) that cause severe morbidity among immunocompromised patients and have already shown some clinical benefits in small phase 1 trials of neutropenic infection (107, 222).

Similarly, sepsis is caused by a dysregulated immune response to infection and still has no specific therapy (285). MSCs can modulate innate and adaptive immune cells to protect the host from excessive inflammation while enhancing microbial clearance. Clinical trials have shown that MSCs are safe to administer in sepsis and other infectious diseases, although the process of establishing their efficacy will be more difficult.

Therefore, we propose two priorities to determine the full therapeutic potential of MSCs and facilitate their development as adjunct therapies for infectious diseases:

Enhanced Profiling of MSC Therapies

MSCs are a heterogeneous population of cells, with some subsets already identified that confer advantages for treating infection (46, 222). There are also variable mechanisms

and degrees of potency between MSCs from different tissue sources. In addition, MSCs can activated through a range of preconditioning strategies to produce cell phenotypes that are primed for specific indications. Thus, a considerable amount of effort lies ahead to determine the optimal tissue source, subtype, and preconditions for generating the best MSC therapy for specific infectious diseases. This effort will require international collaboration and investment in cell therapy research and development.

Improved Clinical Trial Design for MSC Therapies

The efficacy of MSCs in graft-versus-host disease generated much excitement over their potential in a wide range of inflammatory and degenerative conditions (286). As a result, MSCs progressed rapidly to clinical trials for some diseases for which their putative therapeutic mechanism and optimal dosage regimen had not been elucidated. Parallel laboratory studies, whereby the mechanism of action can be investigated alongside clinical efficacy, is one addition to clinical trials that will help build confidence in the plausibility and reliability their findings. Another important element will be more comprehensive dose-finding studies, in which participants receive escalating numbers of MSCs in phase 1 to determine the maximum tolerable doses. This element would be followed by subsequent studies to determine the optimal dosing frequency and interval for the indication, which may differ between acute and chronic infections.

With these approaches, we encourage the prioritization of MSCs in clinical trials for the most difficult and complex infections.

CONCLUSIONS

The preclinical and clinical data support the further testing of MSCs for therapy against infectious diseases. Their combined immunomodulatory and direct antimicrobial properties place them uniquely at the interface of host- and pathogen-directed therapies. Their low immunogenicity and accumulating safety record will be important for their progress through medicine licensing. More work is needed to understand their mechanism of action, demonstrate their safety, and produce a standardized cell therapy. Yet, MSCs represent an exciting new avenue for the management of difficult-to-treat infectious diseases.

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