Human Mesenchymal Stem/Stromal Cells in Immune Regulation and Therapy

Éva Mezey

Abstract
Studies of mesenchymal stem (or stromal) cells (MSCs) have moved from bedside to bench and back again. The stromal cells or fibroblasts are found in all tissues and participate in building the extracellular matrix (ECM). Bone marrow (BM)-derived MSCs have been studied for more than 50 years and have multiple roles. They function as stem cells and give rise to bone, cartilage, and fat in the BM (these are stem cells); support hematopoiesis (pericytes); and participate in sensing environmental changes and balancing pro- and anti-inflammatory conditions. In disease states, they migrate to sites of injury and release cytokines, hormones, nucleic acids depending on the microenvironment they find. Clinicians have begun to exploit these properties of BM, adipose tissue, and umbilical cord MSCs because they are easy to harvest and expand in culture. In this review, I describe the uses to which MSCs have been put, list ongoing clinical trials by organ system, and outline how MSCs are thought to regulate the innate and adaptive immune systems. I will discuss some of the reasons why clinical applications are still lacking. Much more work will have to be done to find the sources, doses, and culture conditions needed to exploit MSCs optimally and learn their healing potential. They are worth the effort.
**Introduction**

Bone marrow stromal cells (BMSCs; or mesenchymal stem or stromal cells, also called MSCs which is the name I will use in this review) were discovered and first studied in detail by Friedenstein et al. They found that there are cells in the bone marrow that could differentiate into the various mature cells found there and suggested that the marrow space is a unique environment where stem cells might respond to local needs. When MSCs are placed in another site, the bone marrow stroma was thought to be a building block of the bone marrow (BM) environment for many decades producing matrix proteins typical for the BM environment. The heterogeneous population of bone marrow MSCs containing multipotent progenitors is defined by their quick adherence to plastic and the ability to form colonies. In addition, according to the definition by the International Society for Cellular Therapy, they must express CD105, CD73, and CD90 and must be negative for CD45, CD34, CD14, CD11b, CD79a, CD19, and HLA-DR surface molecules. They differentiate into 3 lineages—bone, cartilage, and fat cells. Lazarus suggested that restoring the BM micro-environment using in vivo expansion and co-transfusion of BMSCs with HSCs improved BM reconstitution with hematopoietic cells and showed that infusion of in vitro expanded MSCs was safe in all doses used. DiNicola and coworkers suggested that MSCs may also suppress induced T-cell proliferation, a result of their production of soluble factors. This finding suggested that they might be used to mitigate graft versus host disease (GVHD) following bone marrow transplantation. The idea was especially attractive because there appeared to be no rejection of MSCs even if the cells were allogeneic and not autologous in origin. Given this, Katarina LeBlanc’s group used MSC therapy to treat a patient with severe GVHD after all other treatments had failed. After they transplanted haploidentical MSCs they found that the “clinical response was striking”. They published their paper 1 year after the MSC treatment and the patient was doing well at the time. Similarly, a year later another study of Lazarus showed that co-transplantation of MSCs and HSCs improved the occurrence and reduced severity of GVHD in cancer patients after myeloablation and BM transplantation. This result gave rise to a new and exciting field. Members of many other groups began to look for effects of MSCs hoping to drive inflammatory disorders back to normal, no matter how far or in which direction they had veered out of the normal range. Many reviews of this work have been published and I cannot summarize them all. My colleagues and I have reviewed studies of MSCs in infectious diseases and summarized the interactions between the MSCs and a variety of cells of the immune system. In this paper, I have focused on human MSCs in vitro and ongoing clinical trials. In the Discussion section, I have tried to summarize what is known about the potential mechanisms of actions responsible for immune modulation by MSCs and the questions that we need to answer before we can use the cells optimally. Unless specified differently, MSC below refers to cells derived from bone marrow. Due to the vast amount of data in the literature, I will not attempt to list all clinical trials that have been done or planned to date. An extensive list of these can be found in recent reviews.

**GVHD**

As I mentioned in the Introduction, the first clinical use of systemic human MSCs was in acute GVHD (aGVHD) following bone marrow transplantation in a child. After that study was done, many others established that MSC therapy in acute GVHD is safe, and some showed efficacy. Since the leading cause of death after allogeneic hematopoietic stem cell (HSC) transplantation is a GVHD-induced organ failure, novel treatments are needed. Thus, even though our understanding of their mechanisms of action is incomplete, interest in using MSCs or MSC products to fight steroid-resistant aGVHD has remained high. Steroid therapy is thought to fail in about half of pediatric patients following BM transplant. MSCs have been tested in many trials all over the world as a second line of treatments. A review of these trials has appeared recently. Among 25 patients, 24% had complete remissions and 76% had partial responses. None of the patients who had complete remissions died; 26% of the patients who had partial remissions died. In a summary of 92 refractory GVHD patients in several countries (including pediatric as well as adult patients) MSC infusions (both BM- and umbilical cord (UC)-derived cells) were found safe and efficacious. Ninety-six percent of the steroid-refractory patients responded to the treatments; 72% had complete responses.

The patients in the studies described above received MSC-Frankfurt am Main (MSC–FFM) preparations which are manufactured by pooling mononuclear cells from 8 patients’ bone marrow aspirates. Aliquots of the pooled samples are passaged twice after they are thawed and prepared for administration. The concept behind pooling different donor-derived MSCs is to even out donor variations since there is no good marker to select the donor MSCs that perform best in patients.

At present, there are 40 registered clinical trials testing the efficacy of BM-, UC-, and adipose-derived (ADSC) MSCs (Table 1). The primary goal of MSC therapy in GVHD is the...
| Trial #     | Study title                                                                 | Schedule        | Source | Phase | Patients | Completion     | Country     |
|------------|------------------------------------------------------------------------------|-----------------|--------|-------|----------|----------------|-------------|
| NCT01764100 | Mesenchymal Stromal Cells (MSCs) for the Treatment of Graft Versus Host Disease (GVHD) | Unknown status  | BM I   | I     | 10       | September 2013 | Italy       |
| NCT00827398 | Treatment of Steroid Resistant GVHD by Infusion MSC                           | Completed       | BM     | II/II | 50       | July 2013      | Netherlands |
| NCT02359929 | BMT Autologous MSCs for GvHD                                                  | Completed       | BM     | I     | 11       | January 11, 2021 | US          |
| NCT02291770 | Treatment of Chronic Graft-Versus-Host Disease With Mesenchymal Stromal Cells | Unknown status  | BM     | III   | 130      | December 2019  | China       |
| NCT01754454 | Safety and Efficacy of UC-MSC in Patients With Acute Severe Graft-versus-host Disease | Unknown status  | UC I/II | 30    |          | December 2016  | China       |
| NCT02824653 | Allogenic Bone Marrow Mesenchymal Stem Cells Infusion in Patients With Steroid-refractory GVHD | Completed       | BM I/II | 10    |          | December 2016  | Pakistan    |
| NCT00447460 | Treatment of Refractory (Acute or Chronic) Graft-Versus-Host Disease by the Infusion of Expanded in-Vitro Allogenic Mesenchymal Stem Cell | Unknown status  | BM     | I/II  | 15       | August 2009    | Spain       |
| NCT01549665 | Umbilical Cord Blood-derived Mesenchymal Stem Cells for the Treatment of Steroid-refractory Acute or Chronic Graft-versus-host disease | Unknown status  | UC I/II | 30    |          | December 2012  | Korea       |
| NCT02687646 | Clinical Trial With MSC for Graft Versus Host Disease Treatment               | Active, not recruiting | AT    | I/II  | 16       | June 2022      | Spain       |
| NCT00749164 | Allogeneic Mesenchymal Stem Cell for Graft-Versus-Host Disease Treatment     | Unknown status  | BM I/II | 30    |          | August 2012    | Israel      |
| NCT03847844 | UCMSCs as Front-line Approach of Treatment for Patients With aGVHD            | Recruiting      | UC     | II/III | 100      | December 2021  | Malaysia    |
| NCT02379442 | Early Treatment of Acute Graft Versus Host Disease With Bone Marrow Derived Mesenchymal Stem Cells and Corticosteroids | Terminated      | BM I/II | 1    |          | December 13, 2017 | US         |
| NCT00972660 | Safety and Efficacy Study of Allogeneic Mesenchymal Stem Cells to Treat Extensive Chronic Graft Versus Host Disease | Unknown status  | BM I/II | 52    |          | December 2017  | China       |
| NCT00603330 | Mesenchymal Stem Cell Infusion as Treatment for Steroid-Resistant Acute Graft Versus Host Disease (GVHD) or Poor Graft Function | Recruiting      | BM I/II | 100   |          | November 2021  | Belgium, Netherlands |
| NCT04692376 | MSC for Treatment of cGVHD After Allo- H SCT                                | Recruiting      | BM II   | 152   |          | June 30, 2023  | China       |
| NCT02241018 | MSCs Combined With CD25 Monoclonal Antibody and Calcineurin Inhibitors for Treatment of Steroid-resistant aGVHD | Unknown status  | BM II/III | 200   |          | December 2018  | China       |
| NCT04738981 | Efficacy and Safety of UC-MSCs for the Treatment of Steroid-resistant aGVHD Following Allo-H SCT | Not yet recruiting | UC    | III   | 130      | December 2021  | China       |
| NCT02032446 | Umbilical Cord Derived Mesenchymal Stromal Cells For The Treatment of Severe Steroid-resistant Graft Versus Host Disease | Unknown status  | UC I/II | 47    |          | September 2019 | Italy       |
| NCT01765634 | Mesenchymal Stem Cells for Treatment of Refractory Acute Graft-versus-host Disease | Unknown status  | BM I    | 40    |          | December 2016  | China       |
| NCT01765660 | Mesenchymal Stem Cells for Treatment of Refractory Chronic Graft-versus-host Disease | Unknown status  | BM II   | 60    |          | December 2016  | China       |
| NCT01941394 | Mesenchymal Stem Cells Infusion for aGVHD Prophylaxis Transplantation        | Unknown status  | BM I/II | 70    | October 2014 | Russia       |
| NCT01526850 | Efficacy and Safety Study of Allogenic Mesenchymal Stem Cells for Patients With Chronic Graft Versus Host Disease | Unknown status  | BM II/III | 100   |          | June 2014      | China       |
| Trial #         | Study title                                                                 | Schedule       | Source | Phase | Patients | Completion     | Country       |
|----------------|------------------------------------------------------------------------------|----------------|--------|-------|----------|----------------|---------------|
| NCT01522716    | Mesenchymal Stromal Cells as Treatment of Chronic Graft-versus-host Disease | Terminated     | BM     | I     | 11       | March 2017     | Sweden        |
| NCT04744116    | Addition of Cord Blood Tissue-Derived Mesenchymal Stromal Cells to Ruxolitinib for the Treatment of Steroid-Refractory Acute Graft Versus Host Disease | Not yet recruiting | UC   | I     | 24       | November, 2021 | US            |
| NCT02770430    | Mesenchymal Stem Cells as First Treatment Line for Resistant Acute Graft Versus Host Disease | Unknown status | BM     | II    | 90       | December 2018  | Brazil        |
| NCT01956903    | Treatment of Refractory Acute Graft-Versus-Host Disease by Sequential Infusion of Allogenic Mesenchymal Stem Cell. | Completed      | BM     | I/II  | 15       | September 2013 | Spain         |
| NCT02336230    | A Prospective Study of Remestemcel-L, Ex-vivo Cultured Adult Human Mesenchymal Stromal Cells, for the Treatment of Pediatric Patients Who Have Failed to Respond to Steroid Treatment for Acute GVHD | Completed      | BM     | III   | 55       | April 9, 2018  | US            |
| NCT00314483    | Evaluation of the Role of Mesenchymal Stem Cells in the Treatment of Graft Versus Host Disease | Unknown status | BM     | I/II  | 25       | June 2008      | India         |
| NCT02055625    | Mesenchymal Stem Cells as a Treatment for Oral Complications of Graft-versus-host Disease | Withdrawn      | BM     | I/II  | 0        | August 2019    | Sweden        |
| NCT02270307    | MSC and Cyclophosphamide for Acute Graft-Versus-Host Disease (aGVHD) Prophylaxis | Unknown status | BM     | II/III | 40       | January 2016   | Russia        |
| NCT04629833    | Treatment Of Steroid-Refractory Acute Graft-versus-host Disease With Mesenchymal Stromal Cells Versus Best Available Therapy | Not yet recruiting | BM | III   | 210      | December 2025  | France, Germany |
| NCT01222039    | Multicenter Clinical Trial for the Evaluation of Mesenchymal Stem Cells From Adipose Tissue in Patients With Chronic Graft Versus Host Disease. | Completed      | AT     | I/II  | 19       | June 2014      | Spain         |
| NCT03631589    | MSC for Severe aGVHD                                                        | Recruiting     | BM     | II/III | 50       | December 1, 2021 | China        |
| NCT00504803    | Mesenchymal Stem Cell Infusion as Prevention for Graft Rejection and Graft-versus-host Disease | Completed      | BM     | II    | 30       | December 2010  | Belgium       |
| NCT02923375    | A Study of CYP-001 for the Treatment of Steroid-Resistant Acute Graft Versus Host Disease | Completed      | MSC — mesangioblast | I     | 16       | June 30, 2020  | Australia, UK |
| NCT04328714    | Interferon #-Primed Mesenchymal Stromal Cells as Prophylaxis for Acute Graft v Host Disease | Not yet recruiting | BM | I     | 45       | August 2023    | US            |
| NCT00823316    | Safety and Efficacy Study of Umbilical Cord Blood-Driven Mesenchymal Stem Cells to Promote Engraftment of Unrelated Hematopoietic Stem Cell Transplantation | Completed      | UC     | I/II  | 10       | February 2010  | Korea         |
| NCT01045382    | MSC and HSC Coinfusion in Mismatched Minitransplants                    | Recruiting     | BM     | II    | 120      | July 2023      | Belgium       |
| NCT00361049    | Donor Mesenchymal Stem Cell Infusion in Treating Patients With Acute or Chronic Graft-Versus-Host Disease After Undergoing a Donor Stem Cell Transplant | Completed      | BM     | I     | 49       | November 2010  | US            |
| NCT03106662    | Mesenchymal Stem Cell Infusion in Haploidentical Hematopoietic Stem Cell Transplantation in Patients With Hematological Malignancies | Completed      | BM     | III   | 6        | October 2017   | Turkey        |
suppression of the T-cell response to the host organs after the graft takes hold. There are a few suggested mechanisms underlying the T-cell suppressive behavior of MSCs (see7). In their original report of MSCs’ ability to suppress T-cell proliferation, DiNicola et al suggested that soluble hepatocyte growth factor (HGF) and transforming growth factor-beta (TGF-β) contribute to the development of GVHD.4 In humans, it is generally accepted now that IL-10 and indolamine 2,3 dioxygenase (IDO) are among the several mediators of the immune-suppressive behavior of MSCs. MSCs were shown to make IDO protein and they exhibit increased IDO activity upon stimulation with IFN-γ.18

Monocyte-induced activation appears to be necessary for the MSCs to achieve T-cell suppression and IL1-β may mediate this effect through downregulation of T-cell activation factors.19 Rasmusson et al have reported that IL2, IL10, and possibly prostaglandins may contribute to immune suppression by human MSCs.20 Sato’s group described the role of MSC-derived nitric oxide in mediating T-cell suppression,21 a finding later confirmed by Ren et al22 who added that when MSCs are stimulated by interferon-gamma and an additional pro-inflammatory cytokine (such as TNFα, IL1α, or β) they will produce NO and chemokines that attract T cells bearing the appropriate chemokine receptors. Once the T cells are attracted to the MSCs, MSC-derived NO inhibits their further proliferation. Both Sato and Ren worked with mouse MSCs, and they used knockout animals in their work.

Over time, additional factors have come to light that contribute to the MSC-driven inhibition of T-cell proliferation. Jones et al demonstrated that human MSCs arrest T cells in the G0/G1 cell cycle and decrease their pro-inflammatory environment.23 MSC-derived Galectin-1 (a cell/cell contact modulator) and Sema-3A (a chemo-repellant) were later found to bind to neuropilin 1 (NRP-1).24 Neuropilin-1 is constitutively expressed on the surface of T cells and when it binds to semaphorin, the cells arrest in G0/G1 cell cycle, which was the mechanism suggested also by Jones.21 Another important discovery in mice was described by Choi in 2011, who added another soluble factor to the known and ever-broadening arsenal of MSCs immune suppressive factors, TNF alpha-induced protein 6 (TSG6 or TNFAIP6). TSG6 is a secretory protein that downregulates NF-kB signaling25 and thus decreases cell proliferation. In addition, it was also demonstrated that cell to cell contact with pro-inflammatory macrophages induces TSG6 production and results in more efficient suppression of CD4 T-cell proliferation26 in mice.

Airway and Lung Diseases Including COVID-19 Induced ARDS (Acute Respiratory Distress Syndrome)

One of the first studies using human MSCs in Escherichia coli induced pneumonia in the mouse suggested that MSCs possessed intrinsic antibacterial properties. When the MSCs were applied to the trachea of sick mice they significantly reduced bacterial growth due to their production and secretion of cathelicidin LL-37.27 Preclinical animal models of a variety of lung diseases were reviewed by Cruz and Rocco recently.28

One of the first clinical studies of MSCs in lung disease (NCT00683722) was done in patients with COPD. There was no significant difference in the adverse events in treated (IV infusion of allogeneic MSC once a month for 4 months) versus placebo groups. There was also no significant difference between the 2 groups after 2 years on COPD progression or quality of life. However, in patients who entered the trial with elevated C reactive protein (CRP) levels, a significant decrease in CRP was observed following MSC administration.29

A single-center phase Ib trial was initiated with placenta-derived human MSCs in patients with idiopathic pulmonary fibrosis (IPF). IPF is thought to be due to failed epithelial repair following injuries to the alveolar type II epithelial cells resulting in the over-proliferation of fibroblasts and deposition of collagen.30 As in the COPD trial, the treatment was safe, but no improvement (and no progression) was observed with the doses used in the study.31 In another phase Ib trial, endobronchial infusions of adipose-derived MSCs were given to IPF patients. The MSCs seemed safe, but efficacy was not demonstrated.32

A phase I, dose-escalation study was performed in patients with bronchopulmonary dysplasia or BPD, a chronic lung disease was seen in preterm infants. Umbilical cord MSCs were administered. The treatment proved safe and a significant reduction in inflammatory markers in tracheal aspirates was observed.33 Several trials are being conducted to explore the therapeutic benefit of MSCs in BPD (see34).

Sarcoidosis, a complex autoimmune disorder, frequently presents in the lung and causes airway inflammation and decline in pulmonary function. The disease is treated with steroids which are harmful in the long run. In a recent study, mononuclear cells (70%–95% macrophages) were freshly isolated from bronchoalveolar lavage fluid of sarcoidosis patients and cocultured with allogeneic MSCs from healthy donors. There was a statistically significant decrease in pro-inflammatory TNFα production by the airway macrophages and a significant increase in their production and release of IL-10, an anti-inflammatory cytokine. The authors suggested that MSC treatment in such patients might alleviate their symptoms and decrease their need for steroids.35

When the COVID-19 epidemic started it soon became evident that the virus targets the lungs and can quickly lead to severe pneumonia, ARDS, organ failure, and death. The use of MSC therapy was considered.36 In an earlier study (NCT01775774) 2 different doses of cells were given to ARDS patients found to be safe.37 Cocultures of BMSCs and broncho-alveolar lavage (BAL) derived cells from patients with ARDS confirmed that MSCs respond to the actual inflammatory environment in a disease-specific manner.38 In a phase I clinical trial, UC and placental MSCs were administered intravenously to COVID-19 patients. No serious adverse effects were reported and a reduced dyspnea and a significant decrease of pro-inflammatory biomarkers in the serum of 7 out of 11 patients were found. Patients who developed sepsis before the infusions did not seem to respond to treatment.39 There are over 50 ongoing clinical trials to test various sources and doses of MSCs in COVID patients with ARD. Lists of these trials and summaries of available findings are available in recent reviews.12,40 Since the beginning of MSC research it has been assumed that most intravenously administered MSCs are trapped in lung capillaries. Thus, it was logical to think of the variety of ways they could help fight COVID-19 disease progression. Many studies have shown that the inflammatory cytokine environment will induce the immune-suppressive behavior of MSCs. An excellent recent review41 gives a good overview of possible responses of MSCs to INFγ stimulation in the pro-inflammatory environment associated with viral infections (eg, COVID-19) of the lungs. These MSC effects are thought to be due to released anti-inflammatory
cytokines that can “tame” the proinflammatory cells in the vicinity of the MSCs. Also, in addition to immune regulation, they have been known to help in tissue repair in cellular regeneration. Thus, ideally, when the timing and the dosing are right the MSCs could help to block disease progression and/or to help and speed up healing of COVID-19-induced lung disease at several levels. A summary of ongoing clinical trials for lung disease is listed in Table 2.

Skeletal Diseases: Osteoarthritis
Since MSCs can differentiate into bone, cartilage, and adipose tissue, MSCs were tested as treatments for skeletal diseases such as bone defects soon after their discovery. Cellular replacement therapy was attempted after differentiating them into bone or cartilage at the site of pathology. Although this use of MSCs is not the focus of my review, it seems relevant to talk about osteoarthritis, a disease associated with both tissue degeneration and chronic inflammation. In this disorder, the anti-inflammatory, immune regulatory effects of MSCs could be beneficial and the cells could potentially regenerate cartilage as well. In fact, the anti-inflammatory effect might be required for regeneration to occur.

Osteoarthritis is a very common debilitating disease that affects approximately 30 million people in the US. The disease occurs when the cartilage at the end of the bones gradually wears down and an inflammatory reaction - because of bone-on-bone contact - develops. The lubricating synovial fluid becomes thick and inflammatory cells are invade the joint. Bone spurs also develop and increase the pain and inflammation (see 42). The disease can occur in any joint, but the most common and functionally devastating is in the knee or hip joint which affects mobility in addition to having to live with chronic pain. There is no cure, but maintenance of mobility is achieved by rest, physiotherapy, support (ie, use of walker or cane; weight loss) and NSAIDs to fight the inflammation and pain. Eventually, surgery is the only final solution, but even artificial joints have a life span and a limitation of who can tolerate the long procedure of surgery and recovery. This is, why the disease was one of the first targets of possible MSC therapy. Good reviews are available that summarized MSC trials regarding OA up to 2020. While at the beginning most studies used autologous cells, as the knowledge and the now-how developed, the more convenient and consistent use of allogeneic cells became more popular. Unfortunately, like in most of the cases when MSCs were used in clinical trials, there are not enough large-scale, double-blind studies that used the same cells in similar patient populations that a result of effectiveness could be determined. Most trials (summarized in 43,44) confirmed though that the treatment is safe and results in a significant decrease in pain (without NSAIDs) and improvement of function. Continuing the testing of MSC as cellular therapy in OA are 14 ongoing clinical trials (see Table 3). Among these, the largest trial is in the US (with the goal of recruiting 480 patients) is a randomized multicenter single-blind trial comparing a variety of sources for stem cells (NCT03818737). Unfortunately, the COVID-19 epidemic significantly delayed recruitment, so the original completion date of December 31, 2021, will be delayed.

Gastrointestinal System
The gastrointestinal (GI) tract is a major target of the immune system in GVHD. In addition to GVHD, there are several other chronic immune-related diseases of the GI system with no known cure. Most of these can be controlled but the quality of patients' lives is not ideal. These diseases include several GI inflammatory (autoimmune) diseases as well as liver and gall bladder problems (inflammatory bowel disease such as Crohn's disease and ulcerative colitis and autoimmune hepatitis and cholangitis). Currently, inflammatory bowel diseases are treated with steroids and anti-TNF agents that must be given for life and have side effects in a significant fraction of patients. Better treatments are needed. Although little is known about the development of these diseases it is generally accepted that dysregulation of the immune system drives their pathology. Diet, toxins, and genetic factors probably contribute to them as well.

Intravenous allogeneic MSCs were given to 16 patients suffering from active luminal Crohn's disease (CD). Eleven patients had clinical improvement in their disease and 7 of these patients had an adverse effect, but it was not thought to be related to the MSC infusion. Adipose-derived MSCs have been given locally to several hundred patients with refractory peri-anal CD and they appeared to be safe. The trials have been summarized in a review written in 2017. The phase III clinical trial by Panes et al described in Lancet in 2016 is an MSC success story. The trial included over 100 patients with Crohn's disease derived peri-anal fistulas in each (placebo and treatment) of 2 arms. The double-blind, placebo-controlled study recruited people in 49 countries. Those in the active arm had single doses of allogeneic, adipose-derived, expanded cells injected into their lesions and based on the results of the trial, the European Medicines Agency (EMA) approved the use of the MSC preparation tested (named Alofisel) as a treatment for peri-anal fistulas. Although the exact mechanism of the effect of MSCs is not clear, it has been reported that there is a change in the ratio of the different T-cell subsets in CD and it pushes the balance toward pro-inflammatory activity. MSCs are likely to tip the balance back toward normal function as reported in other diseases. While CD is localized in the small intestine, ulcerative colitis (UC) is the equivalent IBD of the large intestine and the efficacy of MSCs has been tested in this disorder as well. Seven human studies have been summarized in a 2019 review that includes a description of animal data as well. The authors concluded that the therapy is safe and promising. Both innate and adaptive immunity are thought to participate in the pathogenesis of UC. Based on studies of patient biopsies, IL-13 has been suggested to play a key role in the deficiency of the epithelial barrier function in UC. Interleukin-5 produced by natural killer cells was also found to contribute to barrier dysfunction.

Acute pancreatitis is a dangerous and hard to treat disease. To date, the use of MSCs in this condition has only been studied in animals. A novel mechanism of action of MSCs in acute pancreatitis in rats has been suggested by Tu et al. They found that MSCs affect AQP-1 aquaporin production decreasing intestinal edema associated with pancreatitis. Thus, the MSCs that travel to sites of injury may reduce local inflammation. These trials are summarized in Table 4.

Cardiovascular System
Over the last decade, a few trials were initiated to test the potential of using MSCs in patients with heart failure. There are 4 clinical trials with published results and 3 going on at

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|------------|------------------------------------------------------------------------------|----------|--------|-------|----------|----------------------------|-------------|
| NCT01902082 | Adipose-derived Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome | Unknown  | AT     | 1     | 20       | June 1, 2014               | China       |
| NCT04289194 | Clinical Study to Assess the Safety and Preliminary Efficacy of HCR040 in Acute Respiratory Distress Syndrome | Recruiting | AT     | 1/2   | 26       | July 20, 2022              | Spain       |
| NCT04362189 | Efficacy and Safety Study of Allogeneic HB-adMSCs for the Treatment of COVID-19 | Active, not recruiting | AT     | 2     | 100      | October 31, 2021           | USA         |
| NCT04366323 | Clinical Trial to Assess the Safety and Efficacy of Intravenous Administration of Allogeneic Adult Mesenchymal Stem Cells of Expanded Adipose Tissue in Patients With Severe Pneumonia Due to COVID-19 | Active, not recruiting | AT     | 1/2   | 24       | October 1, 2021            | Spain       |
| NCT04611256 | Mesenchymal Stem Cells in Patients Diagnosed With COVID-19                   | Recruiting | AT     | 1     | 20       | December 30, 2020          | Mexico      |
| NCT02112500 | Mesenchymal Stem Cell in Patients With Acute Severe Respiratory Failure      | Unknown  | BM     | 2     | 10       | December 1, 2016           | S.Korea     |
| NCT04377334 | Mesenchymal Stem Cells (MSCs) in Inflammation-Resolution Programs of Coronavirus Disease 2019 (COVID-19) Induced Acute Respiratory Distress Syndrome (ARDS) | Not yet recruiting | BM     | 2     | 40       | July 1, 2021               | Germany     |
| NCT04397796 | Study of the Safety of Therapeutic Tx With Immunomodulatory MSC in Adults With COVID-19 Infection Requiring Mechanical Ventilation | Recruiting | BM     | 1     | 45       | June 1, 2021               | USA         |
| NCT04444271 | Mesenchymal Stem Cell Infusion for COVID-19 Infection                       | Recruiting | BM     | 2     | 20       | September 30, 2020         | Pakistan    |
| NCT04447833 | Mesenchymal Stromal Cell Therapy For The Treatment Of Acute Respiratory Distress Syndrome | Active, not recruiting | BM     | 1     | 9        | June 30, 2025              | Sweden      |
| NCT04629105 | Regenerative Medicine for COVID-19 and Flu-Elicited ARDS Using Longeveron Mesenchymal Stem Cells (LMSCs) (RECOVER) | Recruiting | BM     | 1     | 70       | July 1, 2025               | USA         |
| NCT04366063 | Mesenchymal Stem Cell Therapy for SARS-CoV-2-related Acute Respiratory Distress Syndrome | Recruiting | BM/UC/AT | 2/3 | 60       | December 10, 2020          | Iran        |
| NCT04336254 | Safety and Efficacy Study of Allogeneic Human Dental Pulp Mesenchymal Stem Cells to Treat Severe COVID-19 Patients | Recruiting | DP     | 1/2   | 20       | December 31, 2021          | China       |
| NCT04315987 | NestaCell® Mesenchymal Stem Cell to Treat Patients With Severe COVID-19 Pneumonia | Not yet recruiting | n/a | 2     | 90       | August 1, 2020             | Brazil      |
| NCT04371393 | MSCs in COVID-19 ARDS                                                         | Active, not recruiting | n/a | 3     | 300      | February 1, 2022           | USA         |
| NCT04466098 | Multiple Dosing of Mesenchymal Stromal Cells in Patients With ARDS (COVID-19) | Active, not recruiting | n/a | 2     | 30       | December 1, 2021           | USA         |
| NCT04537351 | The Mesenchymal covid-19 Trial: a Pilot Study to Investigate Early Efficacy of MSCs in Adults With COVID-19 | Recruiting | n/a | 1/2   | 24       | March 31, 2021             | Australia   |
| NCT04382547 | Treatment of Covid-19 Associated Pneumonia With Allogeneic Pooled Olfactory Mucosa-derived Mesenchymal Stem Cells | Enrolling by invitation | OM | 1/2   | 40       | June 30, 2021              | Belarus     |
| NCT02444455 | Cord Blood-Derived Mesenchymal Stem Cells for the Treatment of COVID-19 Related Acute Respiratory Distress Syndrome | Recruiting | UC     | 1/2   | 20       | April 30 2021              | China       |
| NCT03042143 | Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration (REALIST) (COVID-19) | Recruiting | UC     | 1/2   | 75       | October 1, 2022            | UK          |
| NCT04252118 | Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With COVID-19 | Recruiting | UC     | 1     | 20       | December 1, 2021           | China       |
| NCT04269525 | Umbilical Cord(UC)-Derived Mesenchymal Stem Cells(MSCs) Treatment for the 2019-novel Coronavirus(nCOV) Pneumonia | Recruiting | UC     | 2     | 16       | December 1, 2020           | China       |
present. These studies originally focused on the ability of MSCs to stimulate tissue regeneration versus regulating immune function. The first results (NCT00768066) came from a small number of patients who received trans-endocardial injections of MSCs, bone marrow cells (BMCs), or a placebo. Only the MSC injected patients showed functional improvement and the treatment seemed safe.\(^{57}\) Butler et al injected ischemia tolerant MSCs (iTMSCs) which had been cultured in hypoxic conditions (NCT02467387).\(^{58}\) This was reported in an earlier study to increase the migration of the cells toward damaged tissue.\(^{59}\) In subjects given MSCs intravenously, there was a decrease in the number of natural killer (NK) cells and an increase in left ventricular ejection fraction.\(^{60}\) These observations were interesting since most workers in the field thought that iv. MSCs would not be useful in heart failure and opted for local treatments instead.

In another study patients with non-ischemic dilated cardiomyopathy (DCM) were given MSCs percutaneously (NCT01392625). The results suggested that stromal-derived factor 1 (SDF-1) secreted by the cells might modulate inflammatory cytokine concentrations\(^{60}\) and vascular endothelial progenitors and showed that allogeneic MSCs can do this twice as efficiently as autologous cells. In an earlier clinical study, the same group reported that a decrease in circulating

**Table 2.** Continued

| Trial #       | Study title                                                                 | Schedule       | Source | Phase | Patients | Completion       | Country   |
|---------------|------------------------------------------------------------------------------|----------------|--------|-------|----------|------------------|-----------|
| NCT04273646   | Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Severe COVID-19 | Not yet recruiting | UC     | n/a   | 48       | February 1, 2022 | China     |
| NCT04288102   | Treatment With Human Umbilical Cord-derived Mesenchymal Stem Cells for Severe Coronavirus Disease 2019 (COVID-19) | Completed       | UC     | 2     | 100      | July 9, 2020       | China     |
| NCT04339660   | Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia | Recruiting     | UC     | 1/2   | 30       | June 30,2020 | China     |
| NCT04347967   | Mesenchymal Stem Cells For The Treatment of Acute Respiratory Distress Syndrome (ARDS) | Not yet recruiting | UC     | 1     | 18       | December 1, 2022 | Taiwan    |
| NCT04355728   | Use of UC-MSCs for COVID-19 Patients                                          | Completed       | UC     | 1/2   | 24       | October 31,2020 | USA       |
| NCT04366271   | Clinical Trial of Allogeneic Mesenchymal Cells From Umbilical Cord Tissue in Patients With COVID-19 | Recruiting     | UC     | 2     | 102      | May 31,2021      | Spain     |
| NCT04392778   | Clinical Use of Stem Cells for the Treatment of Covid-19                     | Recruiting     | UC     | 1/2   | 30       | September 1, 2020 | Turkey    |
| NCT04416139   | Mesenchymal Stem Cell for Acute Respiratory Distress Syndrome Due for COVID-19 | Recruiting     | UC     | 1     | 10       | May 1, 2021       | Mexico    |
| NCT04457609   | Administration of Allogenic UC-MSCs as Adjuvant Therapy for Critically-Ill COVID-19 Patients | Recruiting     | UC     | 1     | 40       | September 30,2020 | Indonesia |
| NCT04565665   | Cord Blood-Derived Mesenchymal Stem Cells for the Treatment of COVID-19 Related Acute Respiratory Distress Syndrome | Recruiting     | UC     | 1     | 70       | April 30, 2021   | USA       |
| NCT04573270   | Mesenchymal Stem Cells for the Treatment of COVID-19                         | Completed       | UC     | 1     | 40       | September 1,2020 | USA       |
| NCT04461925   | Treatment of Coronavirus COVID-19 Pneumonia (Pathogen SARS-CoV-2) With Cryopreserved Allogeneic P_MMSCs and UC-MMSCs | Recruiting | UC/P | 1/2   | 30       | December 1, 2021 | Ukraine   |
| NCT04313322   | Treatment of COVID-19 Patients Using Wharton’s Jelly-Mesenchymal Stem Cells | Recruiting     | WJ     | 1     | 5        | September 30,2020 | Jordan    |
| NCT04390139   | Efficacy and Safety Evaluation of Mesenchymal Stem Cells for the Treatment of Patients With Respiratory Distress Due to COVID-19 | Recruiting     | WJ     | 1/2   | 30       | December 1, 2021 | Spain     |
| NCT04390152   | Safety and Efficacy of Intravenous Wharton’s Jelly Derived Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Due to COVID 19 | Recruiting     | WJ     | 1     | 40       | April 1, 2022    | Colombia  |
| NCT04456361   | Use of Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Caused by COVID-19 | Active, not recruiting | WJ     | 1     | 9        | December 15, 2020 | Mexico    |
inflammatory cytokine concentrations results in an improved quality of life and performance measures in an elderly frail population with DCM.61

Finally, a combination of MSCs and cardiac c-kit positive stem cells were administered together to patients with ischemic heart failure in a multi-center trial (NCT02501811). The combination of the 2 cell types seemed to result in clinical improvement without affecting the structure and function of the left ventricle, indicating a possibly paracrine, systemic mechanism. The authors suggest further studies on how the combination of these 2 different cell types might improve function through secretion of beneficial immunomodulatory, anti-inflammatory, antiapoptotic, or other factors.62

The 2 presently ongoing phase I clinical trials (NCT02408432, NCT02962661) both focus on the treatment of cardiomyopathy due to damage caused by a chemotherapeutic agent (anthracycline).

Dermatological Diseases
The first short review summarizing the potential of MSCs in treating dermatological diseases was published in 2015.63 Since then, numerous clinical trials were initiated, and some have been completed already. Fifteen trials are under way (Table 5). A number of diseases have been targeted including psoriasis, scleroderma, epidermolysis bullosa (EB), atopic dermatitis, and diabetic skin ulcers; (see64). While these problems are relatively common, there are other, rarer serious diseases without treatment that should also be examined in the future.

Psoriasis, one of the most common skin diseases has been characterized by increased angiogenesis in hyperplastic epidermal lesions which are sites of infiltrating immune cells. The pathophysiology of psoriasis is very complex, but the involvement of a variety of inflammatory cytokines and the role of immune cells (T cells, dendritic cells, neutrophils) have been well established; (see65). Case reports of 2 patients treated with UC MSCs were published in 2016. Successful treatment was followed by long (5 and 4 years thus far) relapse-free periods.66 In the same year another description of 2 patients was published, who were treated with autologous adipose tissue-derived MSCs. They had psoriasis vulgaris and psoriatic arthritis, respectively. No adverse effects were observed. The patient with psoriasis vulgaris improved and no longer required methotrexate. The one with psoriatic arthritis also responded to the MSCs but needed a combination of MSCs and monoclonal antibodies to drive TNFα levels down.67

### Table 3. Osteoarthritis.

| Trial # | Study Title                                                                 | Schedule           | Source | Phase | Patients | Completion            | Country    |
|---------|------------------------------------------------------------------------------|--------------------|--------|-------|----------|-----------------------|------------|
| NCT04675359 | Adipose-derived MSCs After Enzymatic Digestion vs. Mechanically Fragmented Fat Transfer in Knee Osteoarthritis Treatment | Not yet recruiting | AT     | IV    | 100      | December 1, 2023       | Poland     |
| NCT04314661 | Comparative Effectiveness of Arthroscopy and Non-Arthroscopy Using Mesenchymal Stem Cell Therapy (MSCs) and Conditioned Medium for Osteoarthritis | Recruiting          | BM     | I/II  | 15       | December 8, 2020       | Indonesia  |
| NCT05060107 | Intra-articular Injection of MSC-derived Exosomes in Knee Osteoarthritis (ExoOA-1) | Not yet recruiting | BM     | I     | 10       | October 5, 2023        | Chile      |
| NCT05027581 | Chondrochymal® for Subjects With Knee Osteoarthritis (Knee OA) | Recruiting          | BM     | II    | 70       | September 10, 2024     | Taiwan     |
| NCT04750252 | Safety and Tolerability of StroMel™ in Subjects With Moderate to Severe Osteoarthritis of the Knee Joint | Not yet recruiting | BM     | I/II  | 20       | December 31, 2021      | US         |
| NCT05016011 | Efficacy of Allogeneic UCMSCs for Treating Large Defects Knee Injury | Recruiting          | UC     | II    | 50       | June 1, 2023           | Malaysia   |
| NCT03608579 | Autologous Culture Expanded Adipose DerivedMSCs for Treatment of Painful Hip OA | Recruiting          | AT     | I     | 24       | December 31, 2021      | US         |
| NCT03477942 | Impact of Mesenchymal Stem Cells in Knee Osteoarthritis | Recruiting          | BM     | I     | 16       | July 2022              | US         |
| NCT03818737 | Multicenter Trial of Stem Cell Therapy for Osteoarthritis (MILES) | Active, not recruiting | BM, AT, UC | III | 480 | December 31, 2021 | US |
| NCT04427930 | Follow-up Study for Participants of Jointstem Phase 3 Clinical Trial | Enrolling by invitation | AT | III | 260 | December 30, 2027 | Republic of Korea |
| NCT04043819 | Evaluation of Safety and Exploratory Efficacy of an Autologous Adipose-derived Cell Therapy Product for Treatment of Single Knee Osteoarthritis | Active, not recruiting | AT | I | 125 | January 2021 | US |
| NCT04321629 | Knee Arthritis Treatment With Autologous Fragmented Adipose Tissue and PRP - Comparison of Two Treatment Methods | Recruiting          | AT     | II    | 60       | December 31, 2022      | Poland     |
### Table 4. Gastrointestinal diseases.

| Trial #    | Study title                                                                 | Schedule          | Source   | Phase | Patients | Completion        | Country    |
|------------|------------------------------------------------------------------------------|-------------------|----------|-------|----------|-------------------|------------|
| NCT03115749 | Intestinal Mesenchymal Stem Cells and Inflammatory Bowel Diseases            | Unknown           | GI MSC   | N/A   | 60       | February 2021     | France     |
| NCT03299413 | Use of Mesenchymal Stem Cells in Inflammatory Bowel Disease                  | Unknown           | UC-MSC   | I/I   | 20       | January 2020      | Jordan     |
| NCT01540292 | Mesenchymal Stem Cell Therapy for the Treatment of Severe or Refractory Inflammatory and/or Autoimmune Disorders | Unknown           | BM-MSC   | I/I   | 20       | June 2017         | Belgium    |
| NCT04073472 | Mesenchymal Stem Cells for the Treatment of Pouch Fistulas in Crohn’s       | Not yet recruiting | BM-MSC   | I     | 15       | June 1, 2023      | US         |
| NCT02445547 | Umbilical Cord Mesenchymal Stem Cell Treatment for Crohn’s Disease          | Completed         | UC-MSC   | I/I   | 82       |                   | China      |
| NCT04312113 | Angiographic Delivery of AD-MSC for Ulcerative Colitis                     | Recruiting        | AT-MSC   | I     | 20       | December 31, 2022 | US         |
| NCT04519671 | Mesenchymal Stem Cells for the Treatment of Perianal Fistulizing Crohn’s Disease | Recruiting        | BM-MSC   | I/I   | 40       | November 2022     | US         |
| NCT01144962 | Dose-escalating Therapeutic Study of Allogeneic Bone Marrow Derived Mesenchymal Stem Cells for the Treatment of Fistulas in Patients With Refractory Perianal Crohn’s Disease | Completed         | BM-MSC   | I/I   | 21       | December 2014     | Netherlands |
| NCT03901235 | MSC Intratissular Injection in Crohn Disease Patients                       | Recruiting        | BM-MSC   | I/I   | 60       | December 31, 2022 | Belgium    |
| NCT03609905 | Adipose Mesenchymal Stem Cells (AMSC) for Treatment of Ulcerative Colitis  | Recruiting        | AT-MSC   | I/I   | 50       | December 1, 2021  | China      |
| NCT00294112 | Prochymal™ Adult Human Mesenchymal Stem Cells for Treatment of Moderate-to-severe Crohn’s Disease | Completed         | BM-MSC   | II    | 10       | July 21, 2006     | US         |
| NCT01874015 | Transplantation of Bone Marrow Mesenchymal Stem Cell in Crohn’s Disease   | Unknown           | BM-MSC   | I     | 10       | February 2018     | IRAN       |
| NCT04519679 | Mesenchymal Stem Cells for the Treatment of Rectovaginal Fistulas in Participants With Crohn’s Disease | Recruiting        | BM-MSC   | I/I   | 40       | October 2022      | US         |
| NCT02442037 | Human Umbilical-Cord-Derived Mesenchymal Stem Cell Therapy in Active Ulcerative Colitis | Unknown           | UC-MSC   | I/I   | 30       | December 2017     | China      |
| NCT04519684 | Study of Mesenchymal Stem Cells for the Treatment of IlealPouch Fistula’s in Participants With Crohn’s Disease | Recruiting        | BM-MSC   | I/I   | 40       | October 2022      | US         |
| NCT04545853 | Study of Mesenchymal Stem Cells for the Treatment of Medically Refractory Crohn’s Colitis | Recruiting        | BM-MSC   | I/I   | 24       | October 2023      | US         |
| NCT04543994 | Study of Mesenchymal Stem Cells for the Treatment of Medically Refractory Ulcerative Colitis (UC) | Recruiting        | BM-MSC   | I/I   | 24       | November 2023     | US         |
| NCT02677350 | AlloGeneic Human Mesenchymal Stem Cells (hMSC) in Patients With Fistulaizing Crohn’s Disease Via Perifistula iNjections (GALENE) | Withdrawn         | BM-MSC   | I     | 0        | December 2026     | US         |
| NCT04791878 | Study of Mesenchymal Stem Cells for Pediatric Perianal Fistulizing Crohn’s Disease | Recruiting        | BM-MSC   | I     | 10       | April 1, 2023     | US         |
| NCT03220243 | Stem Cell Coated Fistula Plug in Patients With Crohn’s RVF                | Completed         | BM-MSC*  | I     | 5        | September 20, 2020 | US         |
| NCT01915927 | Stem Cell Fistula Plug in Perianal Crohn’s Disease                        | Completed         | BM-MSC*  | I     | 20       | December 2019     | US         |
| NCT02403232 | Autologous Adipose-precursor Stem Cells (ASCs) for the Treatment of Perianal Fistula in Crohn Disease: A Pilot Study | Unknown           | AT-MSC*  | II    | 10       | December 2018     | Italy      |
| NCT03449069 | Pediatric MSC-AFP Sub-study for Crohn’s Fistula                          | Recruiting        | BM-MSC*  | I     | 5        | February 28, 2022 | US         |
| NCT03945487 | Mesenchymal Stem Cells Treatment for Decompensated Liver Cirrhosis       | Recruiting        | UC       | II    | 200      | December 30, 2023 | China      |
and macrophages, resulting in unbalanced cytokine and chemokine levels. The high pro-inflammatory cytokine concentrations drive fibrosis. Two cases of refractory scleroderma were treated with intravenous UC MSC infusions. The treatment was safe and there appeared to be a clinical improvement. A recent review by Escobar-Soto summarized the results of studies of 100 patients with scleroderma (systemic sclerosis) who were treated with MSCs and concluded that no definite conclusion can be reached without better-designed, larger studies. However, there were no significant adverse events reported, supporting the belief that MSC infusions are safe.

Atopic dermatitis (AD) is a complex inflammatory skin disease with no known cure. MSCs were tested in AD patients and found useful. Intravenous infusions of umbilical cord MSCs resulted in a dose-dependent improvement of symptoms in a group of 34 patients. A decrease in serum IgE and eosinophilic cells were documented, and no adverse effects were reported following the treatments.

Epidermolysis bullosa is a genetic disease in which the molecules that anchor the epidermis and dermis to one another are inefficient. Even small traumatic events cause the skin layers to separate, and painful blisters form that can then be infected. The disease ranges from mild to fatal and can be caused by mutations in one or more genes. Gene therapies are being explored. Meanwhile, MSC treatments have been tested and found beneficial. How the cells act in epidermolysis bullosa is unknown; (see).

Deficient wound healing is another common problem in dermatology and is especially troublesome in diabetes (due to circulatory problems) and in geriatric patients. Wound healing starts with cytokines and chemokines release. This attracts neutrophils and macrophages to initiate debridement of the injured area. MSCs limit inflammation and tissue damage at sites of injury by decreasing IL-1 and TNFα production and T-cell proliferation. They also stimulate the proliferation of fibroblasts to promote healing. Several trials of BM-MSCs and UC-MSCs are ongoing for wound healing in diabetic patients. An agent that could help heal chronic wounds is much needed and there have been many animal studies and clinical trials of MSCs as cellular therapy. The fact that MSCs are present in the skin and participate in wound healing normally was an argument in favor of their use. A recent excellent review summarizes the animal data as well as the past and present clinical trials to test this idea and analyzes the challenges of such treatments. Most of these challenges are like in other MSC disease treatments (I will mention these in the Discussion) but using MSCs in wound healing might have some special requirements. The variety of sources of MSCs should be screened to find which would be optimal for use in wounds. Possibly find a specific subpopulation that has the best efficacy in this application. To adjust treatments (dose and timing) to the known phases of wound healing and to find the best scaffold to graft MSCs in chronic wounds is needed.

Finally, the BMSCs have been shown to affect mast cell function which suggests that urticaria might be a target of MSC therapy.

### Neurological Diseases

There are many neurodegenerative diseases. Basic and clinical scientists have hoped for decades that stem cells could be used to replace losses of cells in the nervous system because neurons cannot divide. Fetal stem cells were the first ones tried, but ethical issues surrounding their use led clinicians to study adult stem cells from bone marrow, adipose tissue, and umbilical cord instead. Giving the cells intravenously or intrathecaly has been safe, but it has been hard to show efficacy consistently. It is likely that some of the beneficial effects seen from reduced inflammation as opposed to the replacement of dying cells with new ones.

There is not enough space to list the hundreds of clinical trials that have focused on treating neurological diseases with MSCs. Instead, I will give some examples and in Table 6 list ongoing trials in a few diseases to show the approaches and sources of cells in use. Given their immune suppressive effects, the most logical targets for MSCs are neurodegenerative diseases like multiple sclerosis (MS) in which the immune system attacks myelin proteins or strokes in which tissue damage causes local inflammation. There are 2 new (2021) phase I and phase I/II studies registered to explore regeneration and explore the safety and tolerability of MSC infusion into patients with MS, respectively in a small number of patients. One of these (NCT04749667) uses intrathecally applied autologous cells, while the other (NCT04956744) uses IMS001, a human embryonic cell-derived MSC, given intravenously.

The other potentially promising neurological target I would like to mention here is stroke, where the rescue of neurons at the border of the lesion (penumbra) is the primary goal and seems more likely to be successful than hoping for stem cell-derived replacement of neurons. These studies were triggered by a variety of earlier basic science experiments suggesting that through paracrine effects MSCs might significantly improve recovery from stroke. This inference has led to studies using the secretomes of MSCs. The mixture of hormones/ cytokines/ chemokines and even mRNA species might have beneficial effects. In fact, secretome therapy is now seen as a potential alternative to MSC treatment. How best to do this is a work in progress. A nice overview of how a potential stroke treatment evolved from searching for
cell replacement to utilizing the anti-inflammatory effects of MSCs can be found in a comprehensive review by Stonesifer et al. A recent study by the same authors described how intracarotid infusions of BM-derived cultured NCS-01 cells protected rat cortical cells from oxygen deprivation-induced injury in vitro. Furthermore, in vivo experiments in rats revealed significant reductions of the infarct area accompanied by improvements in motor function when the cells were given as long as 3 days after the stroke. This could be very important in a clinical setting. The injected stem cells reached out with filopodia toward the damaged neurons and produced large amounts of bFGF and IL-6 that might be responsible for the observed changes. Based on the preclinical data outlined above, the FDA approved a trial of intra-carotid injections of NCS-01 cells in patients with ischemic strokes (NCT03915431).

### MSC and Cancer

The role of fibroblasts/cancer stroma in tumors and the immunological effects of these cells have been studied extensively. I cannot describe these studies in detail but will refer to appropriate recent reviews on the subject. Fibroblasts are building blocks of all tissues, and cancer in any tissue is associated with fibroblasts. As described above in detail, MSCs can affect both innate and adaptive immune functions. Cancer is always surrounded by inflammatory cells, the extracellular matrix (ECM) is rebuilt, cell migration, cell proliferation is all altered affecting metastasis forming. For about 2 decades researchers wondered what the role of cancer stroma (fibroblasts) in cancer might be. Thinking of MSCs’ ability to reduce T-cell proliferation, one role might be to help the cancer cells by reducing the immune response and eliminating the attack by cytotoxic T cells. The idea that

| Trial #        | Study title                                                                 | Source    | Phase | Patients | Completion   | Country |
|---------------|-----------------------------------------------------------------------------|-----------|-------|----------|-------------|---------|
| NCT01771679   | Safety Study of Bone Marrow Derived Stem Cells on Patients With Cutaneous Photoaging | Suspended | I/II  | 29       | December 2022 | US      |
| NCT02213705   | Treatment of Refractory Sever Systemic Scleroderma by Injection of Allogeneic Mesenchymal Stem Cells | Active, not recruiting | BM    | I/II     | 20          | January 27, 2022 | France |
| NCT04785027   | Comparison of PSORI-CM01 Formula vs Gu Ben Hua Yu Formula Combined With AD-MSCs in Psoriasis | Recruiting | AT    | I/II     | 16          | September 30, 2022 | China |
| NCT03265613   | Safety and Efficacy of Expanded Allogeneic AD-MSCs in Patients With Moderate to Severe Psoriasis | Active, not recruiting | AT    | I/II     | 7           | December 28, 2021 | China |
| NCT03392311   | Efficacy and Safety of AD-MSCs Plus Calpocitroil Ointment in Patients With Moderate to Severe Psoriasis | Enrolling by invitation | AT    | I/II     | 8           | April 30, 2021 | China |
| NCT03765957   | Clinical Research on Treatment of Psoriasis by Human Umbilical Cord-derived Mesenchymal Stem Cells | Recruiting | UC    | I        | 12          | June 1, 2021 | China |
| NCT04275024   | Efficacy and Safety of AD-MSCs Plus Calpocitroil Ointment and PSORI-CM01 Granule in Psoriasis Patients | Enrolling by invitation | AT    | N/A      | 8           | December 24, 2021 | China |
| NCT02685722   | UC-MSCs Gel Treatment Difficult Healing of Skin Ulcers                      | Completed  | UC    | I        | 20          | December 2015 | China |
| NCT02582775   | MT2015-20: Biochemical Correction of Severe EB by Allo HSCT and Serial Donor MSCs  | Recruiting | BM    | II       | 84          | September 2022 | US      |
| NCT04173650   | MSC EVs in Dystrophic Epidermolysis Bullosa                                  | Not yet recruiting | BM-EV | I/II     | 10          | July 2022 | US      |
| NCT01033552   | Biochemical Correction of Severe EB by Allo HSCT and “Off-the-shelf” MSCs    | Recruiting | BM, UC | II       | 75          | October 2021 | US      |
| NCT04356287   | Treatment With Human Umbilical Cord-derived Mesenchymal Stromal Cells in Systemic Sclerosis | Not yet recruiting | UC    | I/II     | 18          | December 2022 | US      |
| NCT02918123   | Safety of FURESTEM-CD Inj. in Patients With Moderate to Severe Plaque-type Psoriasis | Recruiting | UC    | I        | 9           | December 2021 | Korea |
| NCT04723303   | Phase 1 Study of ULSC in Patients With Polymyositis (PM) and Dermatomyositis (DM) | Recruiting | BM    | I        | 9           | February 2022 | US      |
| NCT04104451   | Phase1, open label safety study of umbilical cord lining mesenchymal stem cells (Corlycite®) to heal chronic diabetic foot ulcers | Recruiting | BM    | I        | 20          | August 28, 2021 | US      |
Table 6. Neurological diseases.

| NCT Number   | Title                                                                 | Status        | Conditions                  | Source | Phase | Patients | Completion         | Country     |
|--------------|------------------------------------------------------------------------|---------------|-----------------------------|--------|-------|----------|--------------------|-------------|
| NCT03505034  | Intrathecal Transplantation of UC-MSC in Patients With Late Stage of Chronic Spinal Cord Injury | Recruiting    | Spinal cord injuries         | UC     | II    | 43        | December 31, 2021  | China       |
| NCT03521336  | Intrathecal Transplantation of UC-MSC in Patients With Sub-Acute Spinal Cord Injury | Recruiting    | Spinal cord injury           | UC     | II    | 84        | December 31, 2021  | China       |
| NCT03521323  | Intrathecal Transplantation of UC-MSC in Patients With Early Stage of Chronic Spinal Cord Injury | Recruiting    | Spinal cord injuries         | UC     | II    | 66        | December 31, 2021  | China       |
| NCT04288934  | Treatment of Spinal Cord Injuries With (AutoBM-MSCs) vs (WJ- MSCs)    | Recruiting    | Spinal cord injuries         | BM     | I     | 20        | September 2020     | Jordan      |
| NCT04385056  | Evaluate Umbilical Cord-derived Allogeneic Mesenchymal Stem Cells for the Treatment of Bradykinesia | Recruiting    | Bradykinesia                 | UC     | I     | 15        | July 1, 2022       | US          |
| NCT03684122  | Use of Mesenchymal Stem Cells (MSCs) Differentiated Into Neural Stem Cells (NSCs) in People With Parkinson's (PD). | Recruiting    | Parkinson disease            | UC     | I     | 10        | September 2020     | Jordan      |
| NCT03356821  | Perinatal Arterial Stroke Treated With Stromal Cells Intranasally     | Recruiting    | Perinatal arterial ischemic stroke neonatal stroke | BM     | I/II  | 10        | December 2021     | Netherlands |
| NCT04506073  | IIa Randomized Placebo Controlled Trial: Mesenchymal Stem Cells as a Disease-modifying Therapy for iPD | Recruiting    | Parkinson's disease          | UC     | II    | 45        | May 1, 2023        | US          |
| NCT03384433  | Allogeneic Mesenchymal Stem Cell Derived Exosome in Patients With Acute Ischemic Stroke | Recruiting    | Cerebrovascular disorders    | BM-EV  | I/II  | 5         | December 17, 2021  | Iran        |
| NCT04388982  | the Safety and the Efficacy Evaluation of Allogeneic Adipose MSC-Exos in Patients With Acute Ischemic Stroke | Recruiting    | Alzheimer disease            | AT-EV  | I/II  | 9         | April 2022        | China       |
| NCT04749667  | Study of Mesenchymal Autologous Stem Cells as Regenerative Treatment for Multiple Sclerosis | Not yet recruiting | MS                      | BM     | I/II  | 18        | January 4, 2025    | US          |
| NCT03069170  | Study of Mesenchymal Autologous Stem Cells as Regenerative Treatment for Multiple Sclerosis | Recruiting    | MS                          | BM     | I     | 50        | January 1, 2021    | US          |
| NCT03356821  | Perinatal Arterial Stroke Treated With Stromal Cells Intranasally     | Recruiting    | Mesenchymal stem cells       | BM     | I     | 10        | December 1, 2021   | Netherlands |
| NCT03356821  | Perinatal Arterial Stroke Treated With Stromal Cells Intranasally     | Recruiting    | Stroke neonatal              | BM     | I     | 10        | December 1, 2021   | Netherlands |
| NCT03384433  | Perinatal Arterial Stroke Treated With Stromal Cells Intranasally     | Recruiting    | Stroke                       | BM     | I/II  | 5         | December 17, 2021  | Iran        |
| NCT04956744  | Allogeneic Mesenchymal Stem Cell Derived Exosome in Patients With Acute Ischemic Stroke | Recruiting    | MS                          | hESC-MSC | I  | 30        | December 2027     | US          |
| NCT03915431  | A Study to Evaluate the Safety, Tolerability, and Exploratory Efficacy of IMS001 in Subjects With Multiple Sclerosis | Recruiting    | Ischemic stroke              |        | II    | 16        | October, 2021      | US          |
cancer might recruit stromal cells for that very reason seemed logical and has been studied broadly. The origin of tumor stroma is still not clear. Cancer-associated fibroblasts (CAF) can help cancer in many ways: suppressing immune response, inducing new vessel formation, changing the ECM to help migration/metastasis, and changing the microenvironment to benefit the cancer cells' needs. The mechanisms of how MSCs can promote the growth of tumors are numerous.79 Cancer stroma can originate from local fibroblasts, circulating bone marrow-derived MSCs, pericytes around local vasculature, or vascular and lymphatic endothelium. The process is regulated by signals from the chemokines and cytokines around cancer, and since this environment changes constantly, the behavior and recruitment of fibroblasts do the same. If one tries to imagine this interaction it is almost impossible to do due to the differences between different kinds and stages of all cancers in addition to the differences between the immune system of the individual hosts. Another interesting question in cancer biology has been the role of senescent cells in cancer and the importance of the senescence-associated secretory phenotype (SASP) of the stroma. Ozcan et al demonstrated that the secretome of senescent stromal cells can suppress the proliferation of myeloma cells in vitro but only if they have not been in the company of the cancer cells previously. Once they are thus conditioned, the cancer cells seem to be able to eliminate or significantly decrease their anti-tumor activity.80,81 All the above makes it very complicated to understand the best ways to try to utilize the immune-modifying activity of the tumor stroma (MSC) for cancer treatment. I want to refer the reader to excellent recent reviews on the topic that focus on the role of fibroblasts MSCs in human cancer82,83 and lists ongoing clinical trials.84,85

MSC-Derived Microvesicles/Exosomes in Clinical Trials

It has been known for some time that most mammalian cells release vesicles into their environment. These extracellular vesicles (EVs) contain proteins, lipids, and RNA and are divided into 2 major classes depending on their cellular origin and size: microvesicles that are shed off of the plasma membrane and smaller exosomes.86 Instead of using MSCs to treat patients, clinical investigators have begun to use MSC-derived EVs. I will discuss the pros and cons of doing this in the Discussion. Table 7 lists some of the applications of EVs in clinical trials to date.

Discussion

Originally described as stromal cells in bone marrow Friedenstein,1 fibroblasts are found in most tissues11,12 including the BM where several subpopulations of fibroblasts were found to have different roles in producing collagen, supporting hematopoiesis, giving rise to bone, cartilage, and fat. A recent article gives a very detailed comparison of fibroblast populations in a variety of different tissues in mice based on their expression profile87 suggesting a lot of common and many unique features depending on the organ of origin. Bone marrow, adipose tissue, and umbilical cord-derived MSCs are easy to collect and expand in culture; thus, these sources of cells became the favorites for clinical use. Many excellent reviews have been published in the last decade on interactions between MSCs and immune cells. Below we give some examples and refer readers to more detailed specific accounts.

MSC’s Response to Cytokines and Chemokines

One important feature of MSCs is that they sense hypoxic and injured tissues and are attracted to them.88-90 Once the MSCs reach such tissues, they seem to sense the cellular and cytokine composition of the environment there and respond accordingly by regulating and coordinating the functions of the immune cells in the area.

The MSCs are equipped with a variety of receptors to be able to synthesize the appropriate response to the surrounding tissue (Fig. 1). They express many chemokine receptors, such as CCR1, CCR7, CCR9, CXCR4-6 all of which respond to their distinct ligands (many of which are also produced by MSCs (for details see81,93). Most of the chemokines will induce/ affect the migration ofMSCs to injury sites. Once they arrive, their large array of receptors will respond to the actual cytokine environment through specific receptors (among these the TNFRI1/2, IFN, TGFB1R1, and 2 are the most studied).94,95 Since the MSCs used in most studies and trials are a mixed population of cells, researchers have long wondered if there is a subpopulation of MSCs that are immune-modulatory in nature or whether all MSCs are capable of this depending on the environment they are in. It has been suggested that a small percentage of MSCs—ones that are similar to pluripotent stem cells (called multilineage differentiating stress enduring (MUSE) cells) are the ones that recognize damage signals and migrate to sites of trouble.96,97 However, based on many studies, it does not seem likely that these MUSE cells could be responsible for all the immune-modulatory effects of MSCs, since these effects have been reported with non-selected, cultured cells from a variety of sources and MUSE cells are less than 1% of the MSC population. All MSCs seem to express a variety of pattern recognition receptors (TLRs) to respond to potentially harmful stimuli98 including TLR3 that responds to foreign double-stranded RNA.99 After migrating to the injury/attack site and receiving the input signal through one of its receptors, the MSC prepares the optimal “brew” of agents to bring the site back to homeostasis by regulating functions of the immune cells recruited by the injury (Fig. 1). What do we know about these interactions?

T Cells

Nearly 20 years ago MSCs were shown to suppress the proliferation of CD4 and CD8 T cells in a mixed lymphocyte reaction (MLR). The T cells did not become apoptotic; in fact, they proliferated. The same effect was observed when instead of co-culturing them, the bone marrow MSCs and T cells were separated in a transwell. This suggested that soluble factors such as hepatocyte growth factor (HGF) and transforming growth factor-beta (TGF-β) released by the MSCs were responsible for the effects seen. In the same year, another study showed that MSCs not only block proliferation but also inhibit T-cell responses to their cognate antigens.100 Later several subsets of CD4 and CD8 cells were found to interact with BMSCs. IL-17 produced by Th17 cells stimulates IL-17 receptors on the mouse and human BMSCs.101 In their in vitro work another group reported that MSCs can recruit, regulate, and help maintain the identity of Treg102 a feature that is the focus of a variety of clinical trials listed in a recent review.103 Our group showed that, in a Th2 driven allergic (asthmatic) environment, BMSCs produce TGF-β that likely in concert with recruited Treg drives down eosinophil infiltration, Th2 cytokines, and allergy specific IgGs.104 Leukemia inhibitory factor (LIF) — described as an important player in transplantation
tolerance — is also made by human MSCs and suppresses the proliferation of T cells in an MLR reaction.\textsuperscript{105} There are a few suggested mechanisms underlying the T-cell suppressive behavior of MSCs (see\textsuperscript{17}). In humans, it is generally accepted now that IL-10 and indolamine 2,3 dioxygenase (IDO) are among the several mediators of the immune-suppressive behavior of MSCs. MSCs were shown to make IDO protein and they exhibit increased IDO activity upon stimulation with IFN-γ.\textsuperscript{18} Monocyte-induced activation appears to be necessary for the MSCs to achieve T-cell suppression and IL1-β may mediate this effect through downregulation of T-cell activation factors.\textsuperscript{19} Rasmusson et al have reported that IL2, IL10, and possibly prostaglandins may contribute to immune

| Trial #       | Study title                                                                 | Schedule          | Source          | Phase | Patients | Completion       | Country   |
|--------------|----------------------------------------------------------------------------|-------------------|-----------------|-------|----------|------------------|-----------|
| COVID related|                                                                           |                   |                 |       |          |                  |           |
| NCT04366063  | Mesenchymal Stem Cell Therapy for SARS-CoV-2-related Acute Respiratory Distress Syndrome | Recruiting        | BM MSC or MSC-EV | II/III | 60       | June 6, 2020     | Iran      |
| NCT04276987  | A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia | Completed         | BM-MSC-Exo      | I     | 24       | May 31, 2020     | China     |
| NCT04491240  | Evaluation of Safety and Efficiency of Method of Exosome Inhalation in SARS-CoV-2 Associated Pneumonia | Completed         | BM-MSC-Exo      | I/II  | 30       | October 1, 2020  | Russia    |
| NCT04602442  | Safety and Efficiency of Method of Exosome Inhalation in COVID-19 Associated Pneumonia | Enrolling by invitation | BM-MSC-Exo | II    | 90       | August 1, 2021   | Russia    |
| NCT04753476  | Treatment of Severe COVID-19 Patients Using Secretome of Hypoxia-Mesenchymal Stem Cells in Indonesia | Recruiting        | BM              | II    | 48       | June 8, 2021     | Indonesia |
| NCT04798716  | The Use of Exosomes for the Treatment of Acute Respiratory Distress Syndrome or Novel Coronavirus Pneumonia Caused by COVID-19 | Not yet recruiting | BM              | I/II  | 55       | September, 2021  | US        |
| NCT04747574  | Evaluation of the Safety of CD24-Exosomes in Patients With COVID-19 Infection | Recruiting        | EXO-CD24        | I     | 35       | September 20, 2025 | Israel    |
| Non COVID related |                                                                           |                   |                 |       |          |                  |           |
| NCT02138331  | Effect of Microvesicles and Exosomes Therapy on #-cell Mass in Type 1 Diabetes Mellitus (T1DM) | Unknown status    | BM-MSC-Exo      | II/III | 20       | September 2014   | Egypt     |
| NCT03437759  | MSC-Exos Promote Healing of MHs                                           | Active, not recruiting | BM-MSC-Exo | I     | 44       | December 30, 2021 | China     |
| NCT04356300  | Exosome of Mesenchymal Stem Cells for Multiple Organ Dysfunction Syndrome after surgical aortic dissection | Not yet recruiting | BM-MSC-Exo      | N/A   | 60       | September 1, 2030 | China     |
| NCT04388982  | the Safety and the Efficacy Evaluation of Allogenic Adipose MSC-Exos in Patients With Alzheimer’s Disease | Recruiting        | BM-MSC-Exo      | I/II  | 9        | April 2022       | China     |
| NCT03384433  | Allogenic Mesenchymal Stem Cell Derived Exosome in Patients With Acute Ischemic Stroke | Recruiting        | BM-MSC-Exo      | I/II  | 5        | December 17, 2021 | Iran      |
| NCT04313647  | A Tolerance Clinical Study on Aerosol Inhalation of Mesenchymal Stem Cells Exosomes In Healthy Volunteers | Recruiting        | BM-MSC-Exo      | I     | 27       | May 31, 2020     | China     |
| NCT04173650  | MSC EVs in Dystrophic Epidermolysis Bullosa                               | Not yet recruiting | BM-MSC-Exo      | I/II  | 10       | July 2022        | US        |
| NCT04850469  | Study of MSC-Exo on the Therapy for Intensively Ill Children              | Not yet recruiting | BM-MSC-Exo      | I     | 200      | December 31, 2024 | China     |
| NCT03608631  | iExosomes in Treating Participants With Metastatic Pancreas Cancer With KrasG12D Mutation | Recruiting        | BM-MSC-Exo      | I     | 28       | March 31, 2022   | US        |
suppression by human MSCs. Sato’s group described the role of MSC-derived nitric oxide in mediating T-cell suppression, a finding later confirmed by Ren et al who added that when MSCs are stimulated by interferon-gamma and an additional pro-inflammatory cytokine (such as TNF-α, IL1α, or β) they will produce NO and chemokines that attract T cells bearing the appropriate chemokine receptors. Once the T cells are attracted to the MSCs, MSC-derived NO inhibits their further proliferation. Both Sato and Ren worked with mouse MSCs, and they used knockout animals in their work.

Over time, additional factors have come to light that contribute to the MSC-driven inhibition of T-cell proliferation. Jones et al demonstrated that human MSCs arrest T cells in the G0/G1 cell cycle and decrease their pro-inflammatory environment. MSC-derived Galectin-1 (a cell/cell contact modulator) and Sema-3A (a chemo-repellant) were later found to bind to neuropilin 1 (NRP-1). Neuropilin-1 is constitutively expressed on the surface of T cells and when it binds to semaphorin, the cells arrest in G0/G1 cell cycle, which was the mechanism suggested also by Jones. Another important discovery in mice was described by Choi in 2011, who added another soluble factor to the known and ever-broadening arsenal of MSCs immune suppressive factors, TNF- alpha-induced protein 6 (TSG6 or TNFAIP6). TSG6 is a secretory protein that downregulates NF-κB signaling and thus decreases cell proliferation. In addition, it was also demonstrated that cell to cell contact with pro-inflammatory macrophages induces MSCs’ TSG6 production and results in more efficient suppression of CD4 T-cell proliferation in mice. Another interesting observation by Davies et al showed that MSCs can also secrete PD-L1 and PD-L2, ligands that modulate programmed cell death protein 1 (PD-1) on the surface of T cells involved in T-cell activation.

**B Cells**

MSCs have a variety of pattern recognition receptors allowing them to respond to local signals and interact with lymphocytes. MSCs were reported to induce both regulatory
and naïve B-cells while suppress activated and memory B-cells. This effect is mediated at least partially by soluble secreted factors.\textsuperscript{107,108} Co-culturing BMSCs and B-cells will lead to a suppression of B-cell response by arresting the cell cycle, thus blocking differentiation and reducing Ig production.\textsuperscript{109-111}

**NK Cells**

Natural killer cells are the body’s first line of defense against viral attack and the interaction between BMSCs and NK cells depends on environmental factors. MSCs evade being destroyed by NK cells by upregulation of PGE2 and IDO as well as upregulation of their HLA I antigen that inhibits recognition by NK cells. Resting or activated NK cells interact with BMSCs in different ways. At first, BMSCs inhibit the proliferation of NK cells induced by local IL2 and IL5 but they don’t affect the cytotoxic function of the NK cells already present. But when NK cells are already activated by IL-2 and IL-5 and are cocultured with BMSCs, the latter is able to also affect cytokine production, cytotoxicity, and the release of granzyme B containing vesicles from NK cells — which is another good example of how BMSCs sensor the environment and respond accordingly.\textsuperscript{99,112}

**Macrophages/Monocytes/Dendritic Cells**

In addition to lymphocytes, the phagocytic myeloid cells are also affected by MSCs. MSCs change the character of macrophages from TNFα producing pro-inflammatory M1 to anti-inflammatory IL-10 producing M2. In septic mice, this seems to result from the release of PGE2 induced by activation of TLR4 in the MSCs. Stimulation of macrophage E2 and E4 receptors by the released PGE2\textsuperscript{63} drives the change in the cells. A similar effect was recently seen when human bone marrow stem cells were incubated with pro-inflammatory airway macrophages in broncho-alveolar lavage fluid from sarcoidosis patients.\textsuperscript{35} In addition to PGE2, hepatocyte growth factor (HGF) also appears to play a role in modifying the function of macrophages by activating the ERK1/2 pathway.\textsuperscript{113} An MSC secreted antagonist to the interleukin-1 receptor (IL1RA)\textsuperscript{114} as well as IDO\textsuperscript{111} and TSG-6\textsuperscript{65,116} may contribute to the effect as well. Intravenously infused MSCs have been shown to block the TLR4 induced activation of dendritic cells (DCs). This prevents cytokine secretion and migration of DCs to regional lymph nodes to present their antigen to T cells alleviating the inflammation.\textsuperscript{117}

**Neutrophils**

Neutrophils are phagocytic myeloid cells that are attracted to microbes. They have an extensive arsenal of weapons at their disposal, including reactive oxygen molecules, bactericidal agents, and unique extracellular traps.\textsuperscript{118} These neutrophil extracellular traps (NETs) are made of DNA-derived extracellular fibers, which can physically trap the pathogens similarly to a fishnet trapping fish.

Neutrophils are attracted to sites of inflammation/infection by IL-8 and macrophage inhibitory factor (MIF) released by local or invading MSCs.\textsuperscript{119,120} MSCs then modulate NO-based oxidative damage caused by neutrophils, stimulate their phagocytic function, and decrease their apoptosis.\textsuperscript{115} In an allergic/inflammatory environment the increased histamine will stimulate the H1 receptor of the MSCs. This stimulation will result in increased secretion of IL8 by the MSCs that attract more neutrophils to the site. MSCs will also increase their IL-6 production that is a strong anti-apoptotic agent and will help to keep more live neutrophils in the immediate area\textsuperscript{121} leading to faster resolution of the inflammation/infection.

**Mast Cells**

Mast cells (MCs) are inflammatory cells of myeloid lineage that play a very significant role in allergic disorders including asthma, rheumatoid arthritis, and dermatological diseases. MSCs when they are in contact with them, suppress MC degranulation, inflammatory cytokine production, and chemotaxis. The effect is driven by increased Cox2 production by the BMSCs resulting in PGE2 release and stimulation E4 receptors on MCs.\textsuperscript{76}

**Use of MSCs Versus MSC Medium/Exosome**

Bone marrow MSCs are a heterogeneous cell population. Whether the cells that make up this population have fixed phenotypes or can change in response to environmental alterations is not known. In the former case, we should learn how to purify and exploit various MSC subtypes. In the latter case, we should try to discover how to differentiate the cells according to our needs—ie, make cells that are strong immunomodulators, or bone, cartilage, or fat cell precursors. To solve these problems, we will have to find specific combinations of markers to use in identifying cells of interest.

The advantage of MSCs over exosomes should be obvious. MSCs respond to signals in their environment.\textsuperscript{9,122} Exosomes have a fixed set of contents and, presumably, are optimal for treating some conditions but not others. While they may not be as flexible as MSCs, one can imagine building a bank of EVs that have been tested and found to be optimal for treating certain conditions. Unlike cells, frozen aliquots of such EV preparations can easily and quickly be readied for administration. Both more basic science research and testing are necessary to achieve this. However, we know that when MSCs are injected and “reprogram” the area of injury (immune cells, endothelial cells, bacteria, etc.) then the conversation between the MSC and its environment continues and is not steady. The MSC will change its cytokine/small nucleic acid, anti-bacterial peptide, etc. production depending on the first response from the environment after the MSC arrived.

This is something we cannot do with exosomes — they remain as they were harvested. Thus, we lose some flexibility of the applied MSCs. Interestingly, it has been shown that even if the MSC is short-lived, when the immune cells phagocytose the apoptotic MSCs — the phagocytic host immune cells will produce IDO that is needed for immune suppression. The authors suggested either screening patients for their ability to kill MSCs or treating them with pre-treated apoptotic MSCs.\textsuperscript{123} However, similarly to the exosome scenario — we lose the plasticity of the infused MSC since it is not likely that apoptotic cells would respond to the environmental signal the same way how healthy MSCs would. While secretomes cannot respond to environmental signals, they can teach us how MSCs have responded to specific perturbations. Consequently, they are worth examining. For instance, studies of amniotic fluid-derived stem cell secretomes have shown that a variety of miRNAs may inhibit apoptotic factors and promote neuronal survival following strokes. Based on this, one may be able to select or prime cells that are especially efficient at making factors with beneficial effects on strokes or other disorders.\textsuperscript{124,125}
State of Trials and State of the Field
On December 13, 2016, the 21st Century Cures Act was signed into law with the hope of significantly accelerating product development and speeding up their use in patients. The law provides means to the FDA to expedite programs for use of certain biological products. Proposals to be included in this concept were included in the RMAT (Regenerative Medicine Advanced Therapy) process that aims to see novel clinical trials designs and the use of “Real-world evidence”. Within this framework, the FDA so far granted RMAT designation to 64 proposals. Only 54 of these have available information and 4 of those included studying MSC therapy focusing on their immune-regulatory roles. These 4 proposals include (companies are in alphabetical order):

- Athersys proposed to study ARDS (NCT04367077) with 400 and stroke (NCT03545607) with 300 participants; both conditions with interventional clinical trials using iv infusion of bone marrow stem cells, called Multistem. The proposed completion date of the phase II/III and 3 trials are December 2023 and September 2022, respectively. Fortress Biotech in Texas uses autologous bone marrow mononuclear cells to alleviate symptoms of childhood (NCT01851083, 47 participants) and adult (NCT02525432, 55 participants) traumatic brain injury. However, this phase I/III study uses a mixture of BM cells, thus the results might or might not be relevant for MSCs. The Australian company, Mesoblast applies transendocardial delivery of human bone marrow-derived allogeneic MPCs in patients (466) with chronic heart failure in their phase III study (NCT02032004). Finally, the fourth RMAT proposal was by Vericel Corporation to treat chronically dilated heart (NCT01670981, NCT00765518) and osteonecrosis (NCT00505219) using their unique mixture of bone marrow MSCs and M2, anti-inflammatory, macrophages in a multi-cellular approach. The company’s proprietary technology expands the MSCs and the M2 macrophages from the patient’s bone marrow while retaining the other hematopoietic cells. The MSC/M2 cells regulate the immune response and secrete factors that have pro-angiogenic and regenerative effects and bear anti-inflammatory actions.

Most of the trials seeking to exploit the unique features of MSCs took place in the last 2 decades. Initially, the cells were tested for regenerative abilities, but later their immune-modulatory effects were appreciated and many immune-related diseases (autoimmune diseases, sepsis, chronic inflammatory disease, etc.) were identified as potential targets. There were over 1000 clinical trials world-wide to test these opportunities and very few consistent therapeutic successes emerged. As of today, there are 2 approved clinical applications for MSCs. In 2016, stem cells were approved for use in steroid-resistant acute GVHD in Japan. The history of this trial and the results from the first 3 years can be found in a recent review. The cells (called Tencell) used in the Japanese trial and for clinical therapy are “off-the-shelf” MSCs produced from healthy human donor bone marrow samples. The harvesting, culture, and storage conditions used are like those used but used unsuccessfully by Osiris (Prochymal). Compared to thymoglobulin treatments, the responses to MSCs are similar, but there is less non-relapse mortality in the MSC group due to a lower incidence of infections. The other success story as I said in the GI section above, was the use of allogeneic, off-the-shelf adipose-derived MSCs in the treatment of complex peri-anal fistulas in Crohn’s disease, which received approval in 2018 by the EMA. At present, there are 24 phase III clinical trials in 10 different countries listed at Clinicaltrials.gov for a wide variety of diseases. All but 3 were first posted in the last 3 years. To have more approved treatments using off-the-shelf MSCs (BM, adipose-derived, umbilical cord, placenta) there are lessons that we should have learned from the nearly 1000 unsuccessful or marginally successful trials performed to date. We need to learn how best to culture the cells and how to expand them so that they retain their activities. We know that they can be “primed”, but we do not know which methods increase their activities most. The therapeutic target should be selected carefully and tested in animal models when possible. The inclusion and exclusion criteria should be carefully selected. The source of the stem cells, how they are cultured, and how many passages they undergo before use should be well controlled and compared. The route of administration (local or systemic) should be picked thoughtfully. The primary and secondary endpoints should be well thought out and the study should be well powered. Right now, the only sure thing is that the stem cells appear to do no harm. It is hard to make this claim for many other therapies.

In summary, MSCs can potentially be used to treat a variety of diseases. They appear to be safe to give and respond to environmental cues by secreting factors that rebalance harmful inflammatory conditions. In individualizing their responses, they are “smarter” than drugs which have fixed efficacies and toxicities.

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Conflict of Interest
The author declared no potential conflicts of interest.

Data Availability
No new data were generated or analyzed in support of this research.

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