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Concise Review: Using Fat to Fight Disease: A Systematic Review of Nonhomologous Adipose-Derived Stromal/Stem Cell Therapies

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Key Words. Adipose stem/stromal cells • Adult stem cells • Autologous stem cell transplantation • Cellular therapy • Mesenchymal stem cells • Stromal vascular fraction cells • Tissue regeneration

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Received February 23, 2018; accepted for publication April 22, 2018; first published online in STEM CELLS *EXPRESS* May 15, 2018.

http://dx.doi.org/10.1002/stem.2847

Available online without subscription through the open access option

ABSTRACT

The objective of this Review is to describe the safety and efficacy of adipose stem/stromal cells (ASC) and stromal vascular fraction (SVF) in treating common diseases and the next steps in research that must occur prior to clinical use. Pubmed, Ovid Medline, Embase, Web of Science, and the Cochrane Library were searched for articles about use of SVF or ASC for disease therapy published between 2012 and 2017. One meta-analysis, 2 randomized controlled trials, and 16 case series were included, representing 844 human patients. Sixty-nine studies were performed in preclinical models of disease. ASCs improved symptoms, fistula healing, remission, and recurrence rates in severe cases of inflammatory bowel disease. In osteoarthritis, ASC and SVF improved symptom-related, functional, radiographic, and histological scores. ASC and SVF were also shown to improve clinical outcomes in ischemic stroke, multiple sclerosis, myocardial ischemia, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, chronic liver failure, glioblastoma, acute kidney injury, and chronic skin wounds. These effects were primarily paracrine in nature and mediated through reduction of inflammation and promotion of tissue repair. In the majority of human studies, autologous ASC and SVF from liposuction procedures were used, minimizing the risk to recipients. Very few serious, treatment-related adverse events were reported. The main adverse event was postprocedural pain. SVF and ASC are promising therapies for a variety of human diseases, particularly for patients with severe cases refractory to current medical treatments. Further randomized controlled trials must be performed to elaborate potential safety and efficacy prior to clinical use. STEM CELLS *2018;36:1311–1328*

SIGNIFICANCE STATEMENT

Stem cell therapy has shown potential benefit in a variety of human diseases. However, there are limitations to the widespread clinical application including the use of invasive procedures to isolate cells and the need for processing. Adipose-derived stromal/stem cells are adult cells that possess the capacity for homing, immunomodulation, promotion of repair, and direct regeneration of damaged tissues, which make them promising therapeutic candidates. Furthermore, these cells can be easily obtained in large quantities from subcutaneous tissue, allowing for an abundance of cells to be isolated relatively easily.

INTRODUCTION

Mechanisms of Action

Mesenchymal stem cells, also known as multipotent stromal cells, (MSC) are therapeutic candidates for a wide range of human diseases. Their therapeutic potential is derived from their natural ability to maintain homeostasis. These cells can migrate to areas of tissue injury in the body to facilitate tissue repair [1–3]. Upon arrival to the area of damage, MSC may be stimulated to differentiate into components of the injured tissue [4]. However, their key effect is likely their ability to exert immunomodulatory effects and to secrete factors that promote tissue repair [2].

Sources of Mesenchymal Stem Cells

The two main questions with regard to cellular therapy sources are the cell donor and the location from which the cells are isolated. The cell donor can be the same as the cell recipient (autologous) or different from the cell recipient (allogeneic). Autologous therapy options are ideal

because they ensure histocompatibility and make rejection very unlikely [5,6]. Notably, allogeneic MSC also carry a minimal risk of rejection because they lack major histocompatibility complex II (MHC-II) molecules and express low quantities of MHC-I [5].

With regard to location, bone marrow is the most common source of MSC cellular therapy in current preclinical and clinical trials [2,7]. However, bone marrow harvest from the iliac crest is painful and increases the risk of infection [7,8]. In contrast, MSC can be isolated from subcutaneous adipose tissue with no complications and with up to 500 times the yield of bone marrow isolation [9]. These adipose-derived stromal cells (ASC) can be isolated from the stromal vascular fraction (SVF) of adipose tissue. The cells are collected through liposuction and processed with washing, collagenase digestion, and centrifugation. SVF contains circulating blood cells, fibroblasts, pericytes, endothelial cells, and ASC [6]. The ASC are obtained by plating the SVF cells, thereby enriching for the adherent ASC (Fig. 1) [6]. Over 400,000 liposuction procedures are performed annually with up to 3 liters of lipoaspirate discarded after each procedure. By collecting and processing the entirety of the discarded tissue, it may be possible to collect up to 6 billion ASC after a single passage [6,8].

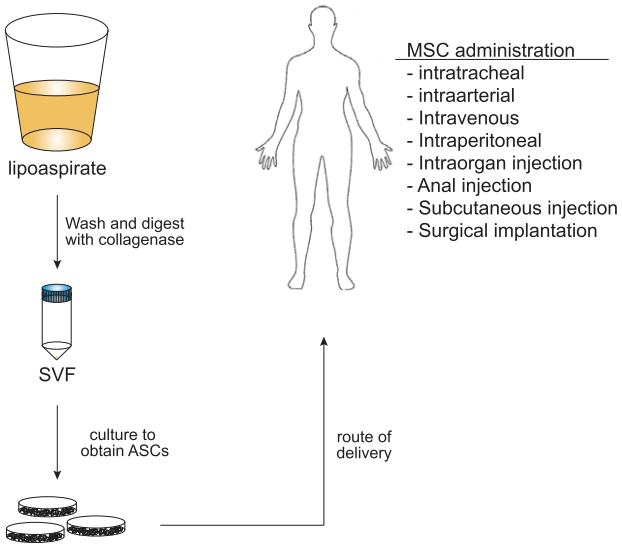

Figure 1. SVF and ASCs are isolated from liposuction procedures for cell-based therapies. Abbreviations: ASC, adipose-derived stromal cells; MSC, mesenchymal stem cells; SVF, stromal vascular fraction.

Potential Roles in Disease Therapy

ASC have been investigated as a therapy for a variety of human diseases. They may represent promising adjunctive therapy for patients with diseases for which current therapies are inadequate such as ischemic stroke, multiple sclerosis, myocardial ischemia, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, chronic liver failure, acute kidney injury, chronic skin wounds, and glioma. ASC also hold potential for treatment of severe cases of inflammatory bowel disease and osteoarthritis that are refractory to current treatment options [10–23]. Development of therapies that can reduce the complications associated with these diseases also has the potential to reduce costs via decreasing disability and hospitalizations.

ASC can aid in tissue repair through multiple mechanisms and are an easily isolated and abundant option for cellular therapy. Patients may be treated with their own ASC or with ASC from other patients with minimal risk of cellular rejection. The majority of studies of ASC safety and efficacy have occurred in the last 5 years, and the most significant studies will be highlighted in this review.

Methods

The authors searched Pubmed, Ovid Medline, Embase, Web of Science, and the Cochrane Database of Systematic Reviews for English language articles with the key words "adipose stem cell and disease" between 2012 and 2017. The authors collectively reviewed 5,815 titles for relevance to the efficacy and safety of SVF and ASC as cellular therapy. Diseases from each organ system with the highest number of studies were included. Notably, this review focuses on nonhomologous use of these cells and thus excludes studies of homologous use such as soft tissue reconstruction or cosmesis. The authors MEB and ALS then reviewed all remaining abstracts. Studies were excluded if they did not test efficacy or safety of stem cell therapy in disease, tested efficacy or safety in a disease other than those selected, did not contain original analyses (i.e., review articles), used stem cells not derived from adipose tissue, or were not written in English. The remaining full-text articles were assessed for eligibility.

After exclusion, 88 studies were ranked as most relevant to the clinical application based on the use of human patients, human ASC, disease model if not in human patients, and outcomes assessed (Table 1). Initially, five studies per disease were going to be included, but these were not sufficient to capture the scope of ASC effects and were expanded to eight per disease. Four studies were included for chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis due to the lower number of available studies.

One meta-analysis, two randomized controlled trials, and 16 case series were included, representing 844 patients. Sixty-nine studies were performed in preclinical models. These articles were agreed upon by all authors and are organized by disease. For additional details of these studies, please refer to Table 1.

Results

Beneficial Effects in Human Disease

Stroke. In preclinical studies, ASC administered through intravenous and intracarotid injection have shown the potential to reduce disability and improve motor function up to 56 days after ischemic stroke (Fig. 2A) [24–30]. ASC also reduced the size of the infarct, reduced acute brain swelling, improved in myelination, increased vascular supply, reduced scar formation, and decreased chronic atrophy (Fig. 2A) [28–31]. These improvements may be secondary to the capacity of ASC to reduce apoptosis, reduce inflammation, reduce glial scar formation, increase angiogenesis, increase neurogenesis, and differentiate into astrocytes and neurons. Most of these effects were demonstrated several hours or more after stroke induction in animal models, which is clinically relevant to stroke patients who may present hours after the onset of symptoms.

Table 1. The most relevant preclinical and clinical studies for each disease are highlighted along with the year, the species or subject, the cell type used, the model for disease or clinical disease, the cell dose, the number of injections, the length of follow up (days), the clinical outcomes affected, and the grade of the evidence

Disease	Subject	Cell type	Model	Dose	No.	Follow up (days)	Clinical outcomes	Grade
Stroke	Rats	Rat ASC	Intravenous injection 30 minutes after MCA branch ligation	2×10^6	1	1, 14	ASC improved Rogers and rotarod test performance but did not change the lesion size [24].	5
	Rats	Human ASC	Intracerebral injection 1 day after MCA occlusion	3.5×10^5, 1.5×10^5	1	1, 7, 14, 21, 28	ASC attenuated neurological deficits at multiple time points [25].	5
	Rats	Rat Autologous ASC	Intracarotid injection 3 days after MCA occlusion	2×10^6	1	1, 7, 14, 21, 28	ASC improved mNSS scores but did not change the lesion size [26].	5
	Rats	Rat ASC, Human ASC	Intravenous injection 30 minutes after MCA branch ligation	2×10^6	1	1, 14	ASC improved functional recovery on Rogers' test but did not change the lesion size. There were no toxic effects or tumor formation [27].	5
	Rats	Rat ASC	Intravenous 1 day after induction of subcortical stroke	2×10^6	1	1, 3, 7, 14, 28	ASC improved performance on walking beam test, Rotarod test, and Rogers' functional scale. ASC decreased infarct size and improved white matter tract connectivity [28].	5
	Rats	Human ASC	Intracarotid injection 1, 3, and 7 days after MCA occlusion	5×10^5	1	1, 7, 14, 21, 28, 35, 42, 49, 56	ASC improved performance in rotarod test and mNSS test. ASC reduced final infarct size [29].	5
	Rats	Pig ASC	Intravenous injection of ASC and exosomes 3 hrs after left middle cerebral artery occlusion	1.2×10^6	1	1, 3, 14, 28	ASC and exosomes reduced acute brain swelling, late brain shrinkage, and infarct area. ASC and exosomes improved performance on Corner test. There were no toxic effects or tumor formation [30].	5
	Rats	ASC	Intracarotid injection 45 minutes after MCA occlusion	10^6, 3×10^5, 5×10^4	1	2, 9	The 3×10^5 ASC dose decreased infarction size. MRI showed ASC migration to the infarction site [31].	5
Multiple Sclerosis	Mice	Murine ASC	Intravenous administration after 42 days of cuprizone induction	10^6	1	10	ASC remyelinated corpus callosum axons with increased myelin fibers, axonal diameter, and myelin sheath thickness [32].	5
	Mice	Murine ASC	Intraperitoneal and intravenous 12 and 14 days after MOG, mycobacterium tuberculosis, and pertussis induction	0.5×10^6, 1×10^6	1 2	60	ASC reduced clinical symptoms and increased body weight in the acute and chronic phases of EAE. ASC reduced inflammatory infiltrations in the brains of EAE mice [33].	5
	Mice	Murine ASC, SVF	Intraperitoneal administration with MOG, mycobacterium tuberculosis, and pertussis induction	10^6	1	10–14, 26–30	SVF and ASC decreased disease scores, progression, and demyelinated lesion size. They also delayed onset of disease [34].	5

(Continues)

Table 1. *Continued*

Disease	Subject	Cell type	Model	Dose	No.	Follow up (days)	Clinical outcomes	Grade
	Mice	Human ASC, SVF	Intraperitoneal administration with MOG, mycobacterium tuberculosis, and pertussis induction	10^6	1	10–14, 26–30	ASC and SVF decreased disease incidence, scores, progression, immune cell infiltration, and number of demyelinated regions. They did not alter disease onset timing [35].	5
	Mice	Murine autologous and allogeneic ASC	Intraperitoneal administration with MOG, mycobacterium tuberculosis, and pertussis induction	10^6	1	30	Wild-type ASC reduced symptoms and progression. ASC delayed onset by reducing demyelination, immune cell infiltration, lesion number, and lesion size [36].	5
	Mice	Murine ASC, SVF	Intraperitoneal injection 20 days after MOG induction	10^6	1	5, 10, 15, 20, 25, 30	ASC and SVF reduced disease severity, restored deficits, reduced immune cell CNS infiltration, restored myelination, and decreased lesion size and frequency [37].	5
	Mice	Human ASC	Intraperitoneal administration with and 15 days after MOG, mycobacterium tuberculosis, and pertussis induction	10^6	1	5, 10, 15, 20, 25, 30	ASC delivered before disease onset reduced clinical symptoms, delayed disease onset, reduced disease severity. When delivered at the peak of disease, ASC resulted in improvement in symptoms, reduction in number and area of lesions, and reduced demyelination [38]	5
	Mice	Murine ASC	Intraperitoneal administration 10 days after MOG, mycobacterium tuberculosis, and pertussis induction	10^6	1	60	ASC and conditioned media groups had significantly fewer clinical signs of EAE, improved clinical scores, and higher body weights [39].	5
Myocardial Ischemia	Nude, Athymic Rats	Human ASC	Injection into peri-infarction area 7 days after LAD occlusion	3×10^6	1	35	ASC increased LVEF, increased FS, reduced infarct size, and increased highly vascularized granulation tissue in border zone [40].	5
	Nude, Athymic Rats	Human ASC	Injection into peri-infarction area 10 days after cryo-injury of LV wall	10^6	1	38, 39, 40	ASC increased LVEF and reduced myocardial infarct area [41].	5
	NOD/ SCID Mice	Human ASC	Injection into peri-infarction area immediately after LAD occlusion	10^6	1	28	ASC reduced LVEDD, reduced LVESD, increased LVEF, decreased scar area, and increased vascular density in the border zone [42].	5
	SCID-beige Mice	Human ASC	Injection into peri-infarction area immediately after LAD occlusion	10^5	1	21	ASC increased LVEF, increased wall thickness, and reduced infarct perimeter [43].	5
	Lewis Rats	Human ASC	Injection into peri-infarction area immediately after LAD occlusion	3×10^6	1	7, 28, 42	ASC decreased infarct size, increased left ventricle wall thickness, and increased LVEF [44].	5

	Sprague-Dawley Rats	Human ASC	Injection into peri-infarction area 7 days after LAD occlusion	10^6	1	7, 35	ASC increased LVEF and increased wall diameter [45].	5
	Athymic Nude Rats	Human ASC	Surgical transplantation of cell sheets 14 days after LAD occlusion	7.5×10^5	1	14, 28, 42, 56	ASC increased LVEF, FS, anterior wall thickness, contractility, and capillary density. They reduced remodeling and fibrosis [46].	5
	Human, NYHA II-IV and LVEF <40%	Human Autologous SVF	Injection into myocardial scar via MyoCath catheter delivery system	Unc	1	30, 90, 180	Mean LVEF increased from 29% to 35% at 3 and 6 months. For the 4 patients that completed 12 month follow up, LVEF increased from 25% to 31%. 6MWT and wall thickness also improved [47].	4
Chronic Obstructive Pulmonary Disease	Mice	Murine ASC	Intravenous or intratracheal administration after 28 days of weekly elastase administration	10^5	1	7	ASC reduced MLI, fractional area of alveolar collapse, and damage of the alveolar-capillary membrane. ASC reduced PAT/PET ratio and normalized right ventricular area [48].	5
	Guinea Pigs	Guinea Pig ASC	Intratracheal and intravenous administration after 90 days of smoke exposure	10^6	1	14	ASC reduced oxidative stress but did not significantly change the emphysema score [49].	5
	Mice	Human ASC	Intravenous administration 7 days after elastase intratracheal administration or after 180 days of smoke exposure	10^5	1	7, 14	ASC reduced the MLI in the elastase model but not in the smoke-induced emphysema model [50].	5
	Mice	Human ASC	Intrapleural injection 7 days after the start of intratracheal elastase administration	10^5	1	14	ASC led to recovery from alveolar damage and reduction of MLI [51].	5
Idiopathic Pulmonary Fibrosis	Humans with IPF, 64.4 $\pm$ 7 years old	Human Autologous SVF	Endobronchial infusion	5×10^5	3	180, 365, 730	There were no serious adverse events. SVF prevented deterioration in mMRC dyspnea scale, 6MWT, and exercise capacity. Quality of life was improved on SGRQ. Systolic pulmonary artery pressure increased nonsignificantly [12].	4
	C57BL/6 Mice	Murine ASC	Intravenous injection 1 day after bleomycin administration	5×10^5	1	21	Young ASC decreased the fibrosis Ashcroft score while old ASC did not [52].	5
	Humans with CPFE, 44–75 years old	Human Autologous ASC	Intravenous or endobronchial infusion	1.6×10^8	3	365	There were no serious adverse events and was no significant mean change in FVC, FEV1, TLC, TLco tests in 8 COPD patients and 5 combined pulmonary fibrosis and emphysema patients [53].	4
	Swiss-albino Mice	Human ASC	Intravenous injection on days 3, 6, and 9 after bleomycin administration	8×10^5	3	24	ASC prolonged survival and reduced the modified Ashcroft's score, more than pirfenidone. ASC attenuated fibrosis and helped maintain alveolar architecture [54].	5

(Continues)

Table 1. *Continued*

Disease	Subject	Cell type	Model	Dose	No.	Follow up (days)	Clinical outcomes	Grade
Chronic Liver Failure	Rats	Rat ASC	Intravenous injection into portal vein and tail vein 2 days after 84 days of CCl4 treatment	2×10^6	1	84, 126	ASC improved mortality from 60% to 73%–93%, increased PVP and TLP, decreased HPI, improved microcirculation, reduced steatosis, and reduced fibrosis. ASC decreased ALT and AST, decreased bilirubin, and increased albumin [55].	5
	Mice	Murine ASC	Injection into splenic subcapsule after 224 or 252 days of high-fat diet and intravenously every 24 days after	10^5, 2×10^4	2	3, 7, 14, 84, 238, 490	ASC restored albumin expression in hepatic parenchymal cells of cirrhotic mice and reduced fibrosis [56].	5
	Mice	Human ASC	Intravenous injection after 42 days of CCl4 treatment	2.5×10^4	1	84	ASC reduced the mean fibrotic area, increased the area with hepatocytes, and decreased AST and ALT levels [57].	5
	Rats	Rat ASC	Intravenous injection into the portal vein every 14 days after 70–84 days of CCl4 administration	5×10^6	2	28	ASC reduced fibrotic area through effects on hepatic stellate cells [58].	5
	Rats	Rat ASC	Intravenous injection weekly for 60 days after 42 days of thioacetamide administration	3×10^6	-	60	ASC decreased ALT and increased fibrinogen [59].	5
	Mice	Human ASC	Intravenous injection after 28 days of CCl4 treatment	10^6	1	28	ASC reduced fibrosis, improved albumin, decreased ALT and AST, and decreased bilirubin [60].	5
	Rats	Rat ASC	Intraperitoneal administration 14 days after methotrexate exposure	2×10^6	1	42	ASC reduced ALP, AST, and ALT while increasing serum albumin and total protein [61].	5
	Humans with cirrhosis 30–69 years old	Autologous Human ASC	Intraarterial injection into the common hepatic artery	3.3×10^5, 6.6×10^5	1	30	No serious adverse events or worsening of AST or ALT were seen. Patients maintained or improved synthetic function (prothrombin time, albumin) at follow up [62].	4
Inflammatory Bowel Disease	Humans with Crohn's Diagnosis and perianal fistula, 36 ± 9 years old	Human ASC	Intravenous injection into fistula at day 0 and at 12 weeks if incomplete closure	2×10^6, 4×10^6	1 2	70, 84, 154, 168	ASC reduced at least one fistula in 69.2% of patients, PDAI, and MRI score of severity. 30% had fistula closure with absence of suppuration, re-epithelialization, and MRI absence of collections at 24 weeks. 5 ASC-related adverse events were reported (anal abscess, pyrexia, and uterine leiomyoma) [63].	4
	Humans with Crohn's Disease and perianal fistula, 26.5 ± 6 years old	Human Autologous ASC	Injection into fistula	10^7, 2×10^7, 4×10^7	1	56, 240	Healing was observed in 50% of patients treated with at least 2×10^7 cells/ml. Three patients showed complete healing at week 8 and had no recurrence by	4

						month 8. Injection of ASC was safe and tolerable at all doses [64].	
Dogs	Dog ASC	Intravenous injection	2×10^6/kg	1	42	ASC improved digestive symptoms and weight loss. Disease scores decreased with 9/11 dogs achieving remission. No adverse events were related to the ACS [65].	5
Humans with Crohn's Disease, 26.2 ± 5.5 years old	Human Autologous ASC	Injection into fistula with fibrin glue	3×10^7, 4.5×10^7, 6×10^7	12	365, 730	ASC treatment resulted in 80% (28 of 35) and 75% (27 of 36) patients having complete fistula healing at 12 and 24 months. There were no ASC-related adverse events [66].	4
Humans with Crohn's Disease and perianal fistula, 32.17 ± 7.96	Human ASC	Injection into fistula with fibrin glue	10^7, 3×10^7	12	56, 120, 180, 240	ASC led to complete healing of the fistula in 50% of patients at 8 months as assessed clinically and by MRI. There were no serious adverse events. Adverse events included postoperative pain and complications of Crohn's Disease [67].	4
Humans with Crohn's Disease and perianal fistulas, 39 ±13.1 years old	Human ASC	Injection into fistula	1.2×10^7	1	42, 84, 126, 168	At week 24, combined remission as assessed clinically and with MRI was achieved for 50% (53/107) patients versus 35% (36 of 105) for placebo. ASCs also reduced median time to remission and PDAI score. There was no difference in adverse event rates as compared with placebo with most common adverse events of anal abscess and proctalgia [18].	1b
Humans with Crohn's Disease and rectovaginal fistula, 31–55 years old	Human ASC	Injection into fistula at day 0 and at 12 weeks if incomplete re-epithelialization	2×10^6, 4×10^6	1 2	7, 28, 56, 84, 168, 365	ASC cured 60% (3/5) at 365 days. In 90% (9/10), the fistula was cured at some point during the trial but reopened prior to final follow up. No adverse events were related to the ASC [68].	4
Humans with Crohn's Disease, 26.1–53.57 years old	—	—	10^7 –9.5×10^7	-	—	In this meta-analysis of 477 patients, ASC had a significant healing rate and clinical response for patients with CDAI>150. ASC had lower recurrence rate than BMSCs. 2–4 $\times 10^7$ cells per ml had higher healing rate and lower recurrence rate than other doses [69].	1

(Continues)

Table 1. *Continued*

Disease	Subject	Cell type	Model	Dose	No.	Follow up (days)	Clinical outcomes	Grade
Glioma and Glioblastoma	Rats	Human ASC with UPRT	Intracerebral injection with glioblastoma	10^5, 10^6	1, 2	74, 90, 124	ASC increased survival from 31 to 90 days. Increasing ratios of ASC to tumor cells improved survival. Tumor-free survival increased from 63% with 1 dose to 88% with 2 [70].	5
	Rats	Human ASC with CE	Intracerebral injection 2 days after glioma injection	2×10^5	1	Unc	Rats treated with transfected ASC survived longer than control or unmodified ASC [71].	5
	Rats	Human ASC with UPRT	Intracerebral injection at varying times after glioblastoma injection	10^6 5×10^6 7.6×10^6	2	165, 237	2 doses caused complete regression in 43–50% of rats. Continuous administration led to regression in 33% [72].	5
	Mice	Human ASC with BMP2/4	Intracerebral injection with glioblastoma and intracardiac injection 14 days after glioblastoma injection	5×10^5	1	7, 14, 28, 125	The intracranial ASC group had a smaller mean tumor area than control. After cardiac injection, ASC increased survival [73].	5
	Mice	Human ASC with ICOVIR17	Intracerebral injection at varying times after glioblastoma injection	2×10^5	1	3, 7, 11, 15, 24, 42	ASC-ICOVIR17 resulted in a drastic tumor volume reduction and extension in survival time relative to control and ASC alone [74].	5
	Mice	Human ASC with CE and/or sTRAIL	Intracerebral injection 3 days after glioma injection	1.2×10^5	2	27, 100	Mice treated with ASC expressing sTRAIL with and without CE had smaller tumor volumes and longer survival than the unmodified ASC [75].	5
	Mice	Human ASC with Tk	Intracerebral injection 7 days after glioblastoma injection	5×10^5	1	21	Injection of ASC-Tk cells reduced tumor size relative to control. Mice treated with ASC had a nonsignificant tumor size reduction [76].	5
	Rats	Human ASC with PTX	Intracerebral, intraarterial, or intravenous injection with or 14 days after glioblastoma injection	10^5, 2×10^5	1	3, 7, 21	After intracerebral injection, ASC reduced tumor size, reduced microvascular density, and improved survival, even in the absence of PTX. Intraarterially and intravenously administered ASC homed to tumors and inducted cytotoxic damage to tumor cells [77].	5
Acute Kidney Injury	Rats	Human ASC	Intravenous injection on day 1 and intraperitoneal injection of conditioned medium on day 1 and 2 of cisplatin induction	5×10^5	1	1, 3, 10, 22	ASC reduced mortality at 7 days from 100% to 20%. ASC reduced BUN and creatinine and attenuated histopathological tubular injury [78].	5
	Rats	Human SVF	Injection into kidney subcapsular space or intraperitoneal injection on day 1 of cisplatin injection	10^6	1	0, 2, 4, 6, 8, 14	SVF reduced creatinine, reduced tubular damage, and dilated renal cortical peritubular capillaries [79].	5

	Rats	Rat ASC	Intravenous and intraarterial injection 45 minutes after ischemia-reperfusion	10^7, 5×10^4, 10^5, 5×10^5, 10^7, 5×10^7	1	2	ASC reduced BUN, creatinine, and tubular cell injury. Survival was increased in all groups except for the 5×10^7 intravenous group in which all rats died from pulmonary emboli. Optimal dose was 1.67×10^6 cells per kilogram [80].	5
	Rats	Rat Autologous ASC	Intravenous at 1, 6, and 24 hours after ischemia-reperfusion	1.2×10^6	1	3	ASC reduced BUN, creatinine, and urine protein to creatinine ratio. ASC reduced histological injury and increased the number of small vessels in kidney parenchyma [81].	5
	Rats	Human ASC	Intravenous injection 1 day after cisplatin induction	$1–2 \times 10^6$	1	5	ASC decreased BUN and creatinine. Histopathological injury was reduced and similar to the healthy control group after ASC treatment [82].	5
	Rats	Human ASC	Intravenous injection at 1 day after cisplatin induction	5×10^6	1	4, 7, 11, 30	ASC reduced BUN and creatinine. ASC decreased tubular necrosis, atrophy, and fibrosis [83].	5
	Rats	Rat ASC	Intravenous administration of ASC or exosomes at 3 hours after ischemia-reperfusion	100 micrograms, 1.2×10^6	1	3	ASC and exosomes decreased BUN, creatinine, urine protein to creatinine ratio, and histopathological injury. ASC and exosomes increased urine quantity. ASC and exosomes increased the number of podocytes while decreasing renal tubular and glomerular damage markers [84].	5
	Rats	Human ASC	Intravenous injection 1 day after cisplatin induction	5×10^6	1	4, 7, 11, 30	ASC reduced BUN and creatinine. ASC decreased injury with less tubular necrosis and atrophy while increasing regeneration [85].	5
Osteoarthritis	Humans with grade 2–3 knee OA, 65–80 years old	Human Autologous ASC	Intra-articular injection with platelet-rich plasma into the most severe cartilage defect	4.2×10^7	1	90, 365, 730	ASC increased Lysholm score, decreased VAS, and improved KOOS subscales. ASCs helped to improve or maintain cartilage status in elderly patients with OA. There were no serious adverse events [86].	4
	Humans with grade 2–3 OA, >18 years old	Human Autologous SVF	Intra-articular injection of SVF and activated PRP	N/a	1	30, 90, 180	SVF improved joint function, Lysholm score, and VAS score. SVF increased cartilage regeneration. There were no side effects or complications [87].	4

(Continues)

Table 1. *Continued*

Disease	Subject	Cell type	Model	Dose	No.	Follow up (days)	Clinical outcomes	Grade
	Humans with grade ≥2 OA, 18–75 years old	Human Autologous ASC	Intra-articular injection 3 weeks after liposuction	10^7, 5×10^7, 10^8	1	30, 60, 90, 180	The high dose of ASC improved WOMAC score, VAS score, ICRS grade, and KSS score with regeneration of articular cartilage on MRI. There were no serious or treatment-related adverse events [21].	4
	Humans with knee OA, 23–74 years old	Human Autologous SVF	Intra-articular injection of SVF and PRP followed by monthly PRP injections for 4 months	1.15×10^7–5×10^7	4	365	SVF increased KOOS subscores and improved functional activity for the 4 patients [88].	4
	Humans with grade 3–4 ICRS lesions, aged 18 to 50 years	Human Autologous SVF	Surgical implantation of SVF-thrombin-fibrinogen suspension in wells on the cartilage surface after microfracture induction	Unc	1	90, 365, 730, est 767	SVF improved degree of defect repair with increased MOCART score, increased KOOS subscores, improved Lysholm score, increased ICRS scores, and decreased VAS scores [89].	4
	Humans with grade 2–3 OA, >18 years old	Human Autologous SVF	Intra-articular injection with SVF and activated PRP after arthroscopic microfracture	5×10^7	1	30, 180, 365, 540	SVF improved WOMAC scores, Lysholm scores, VAS scores, OS scores, bone marrow edema, and cartilage layer thickness on MRI. Improvements in WOMAC and Lysholm were greater in the stage 2 OA group than in the stage 3 group. Joint function and motion amplitude also improved. No adverse events were noted [90].	1b
	Humans with grade 3–4 knee OA, 50–75 years old	Human Autologous ASC	Intra-articular injection	2×10^6, 10^7, 5×10^7	1	7, 90, 180	ASC reduced WOMAC score, VAS score, and multiple clinical outcome parameters. No adverse events were associated with liposuction and intra-articular injection [91].	4
	Humans with grade 3–4 knee OA, 65–82 years old	Human Autologous SVF	Intra-articular injection	3×10^7	1	30, 180	SVF improved WOMAC, VAS, and JKOM. No serious adverse events occurred [92].	4
Chronic Skin Wounds	Human Skin	Human ASC	Organotypic 3D skin culture with laser wounding	6–9×10^4	1	11	ASC treatment resulted in accelerated healing and decreased defect size relative to control [93].	5
	Mice	Human ASC	Intradermal injection or carrier application to 6-mm full thickness wounds	10^5	1	3, 5, 7, 9	ASC accelerated wound closure at all time points and enhanced granulation tissue formation [94].	5
	Mice	Human ASC	Intradermal injection into 10-mm full thickness wounds	10^6	1	3, 7, 10, 14, 21	ASC treated mice had greater wound closure at all time points. ASC enhanced re-epithelialization and granulation tissue formation [95].	5

Mice	Human ASC	Carrier application to 5-mm punch biopsy wounds	3×10^4	1	3, 10, 14	ASC treatment accelerated wound closure, increased microvascular density, and led to greater tissue organization with near complete epithelialization by day 10 [96].	5
Mice	Human ASC	Carrier application to 6-mm full thickness wounds	$3–5 \times 10^5$	1	5	ASC delivered in fibrin form vascular tubes. ASC treatment resulted in wounds with more granulation tissue and collagen [97].	5
Pig	Human ASC	Carrier application to 30-mm full thickness wounds	Unc	1	7, 14, 21, 28	ASC treatment led to a more complex collagen structure and increased vascularity. ASC reduced scar formation [98].	5
Mice	Human ASC	Intravenous injection of ASC exosomes for 20 × 15-mm full thickness wounds	—	1	1, 3, 5, 7, 14, 21	In vivo: ASC exosomes migrated to the wound where they accelerated wound closure and increased collagen synthesis and maturity [99].	5
Mice	Human ASC, SVF	Carrier application to 6-mm full thickness wounds	10^6	1	14, 28	SVF and ASC accelerated healing and enhanced re-epithelialization. SVF increased capillary density [100].	5

Abbreviations: ASC, adipose-derived stromal cells; ICRS, International Cartilage Regeneration and Joint Preservation Society; MCA, middle cerebral artery; MOG, myelin oligodendrocyte glycoprotein; NOD, non-obese diabetic. OA, osteoarthritis; PTX, paclitaxel; SCID, severe combined immunodeficiency; SVF, stromal vascular fraction; VAS, visual analogue scale.

The preliminary safety data was encouraging. In one study, ASC administration did not cause any harmful effects on the brains, hearts, lungs, livers, or kidneys of healthy animals and did not promote tumor formation [30]. Another study demonstrated that no toxic effects on spleen, liver, lung, or kidneys were present at three months after ASC administration [27]. No tumors had formed by this time [27]. While studies in human patients are lacking, the preclinical data suggests that ASC may be a safe cellular therapy that can reduce the acute damage and chronic disability caused by ischemic stroke.

Multiple Sclerosis. Intraperitoneal administration of SVF and ASC has been shown to significantly delay onset of disease, reduce signs of motor impairment, and slow disease progression in animal models of multiple sclerosis (Fig. 2J) [33–39]. The primary animal model of multiple sclerosis is experimental autoimmune encephalomyelitis (EAE). In one study, SVF and ASC reduced disease incidence from 100% in the control group to 75% and 83%, respectively [35]. This effect is likely secondary to the ability of SVF and ASC to reduce immune infiltrates, decrease lesion number and size, decrease demyelination, and improve remyelination in the central nervous system [32–39]. Several studies have directly compared the effects of SVF and ASC and found that SVF-treated subjects had delayed onset of disease (by 5 days) and lower clinical disease scores at 30 days after onset of disease [34,37]. The only noted significant differences in the two types of therapy were that SVF had a more pronounced effect to increase IL-10 in the peripheral blood, lymphoid, and CNS tissues, to decrease serum IL-12 levels, and to induce regulatory T cells in the lymph nodes [34,35,37]. The ability of SVF and ASC to alter the clinical course through immunomodulatory effects in the central nervous system may improve the lives of young adults affected by this disease.

Myocardial Ischemia. ASC have been shown to be effective in improving myocardial dysfunction after myocardial ischemia. SVF and ASC improve functional parameters as shown by increasing left ventricular ejection fraction (LVEF), fractional shortening [101], wall thickness, contractility, and six-minute walk test distance while decreasing left ventricular end diastolic diameter, left ventricular end systolic diameter, and overall remodeling (Fig. 2C) [40,42–47]. Possible explanations for these changes include the capacity of ASC to reduce the infarct size through reduction of apoptosis, inflammation, and fibrosis and to improve the vascular density in the infarct border zone through increase in angiogenesis [40,42–44,46]. In preclinical studies, ASC were injected into the peri-infarction area up to two weeks from myocardial infarction induction, which indicates that improvement in functional parameters can be achieved from effects delivered during the acute ischemic state and subacute remodeling state. In contrast, a study in 28 patients with New York Heart Association class II to IV heart failure found that SVF may improve functional parameters after scar formation has occurred in those with a left ventricular ejection fraction <40% or akinetic myocardial scarring [47].

A safety analysis was performed in the patients who underwent liposuction and direct intramyocardial injection of SVF [47]. Three patients in this study died weeks to months after the stem cell administration from a cardiac arrest after bowel obstruction, of unknown cause, and a pulmonary thromboembolism. While

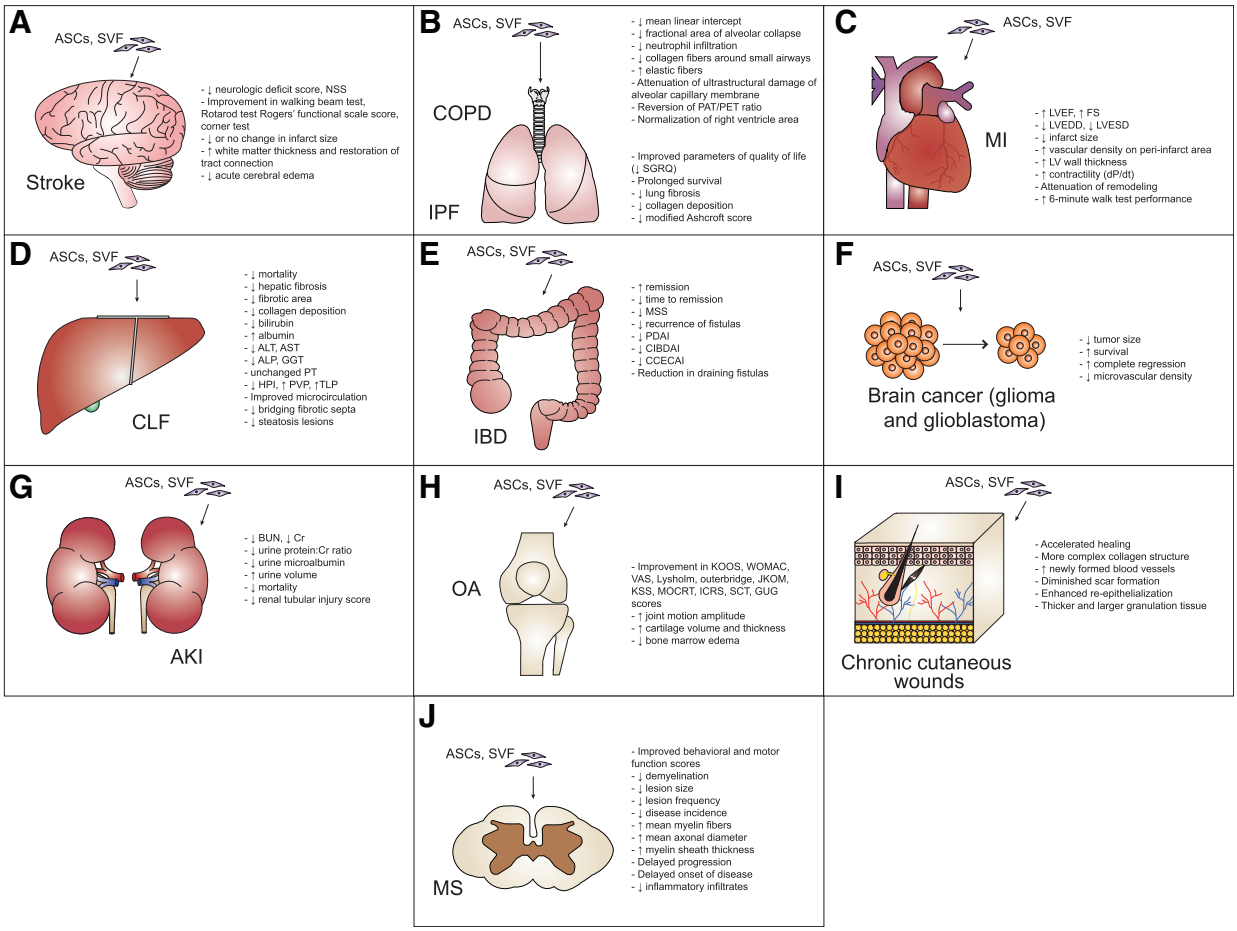

Figure 2. Stromal vascular fraction and adipose-derived stromal cells have positive effects on clinical outcomes in **(A)** ischemic stroke, **(B)** multiple sclerosis, **(C)** myocardial ischemia, **(D)** chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis, **(E)** chronic liver failure, **(F)** inflammatory bowel disease, **(G)** glioma and glioblastoma, **(H)** acute kidney injury, **(I)** osteoarthritis, **(J)** cutaneous chronic wounds. Abbreviations: ASC, adipose-derived stromal cells; SVF, stromal vascular fraction.

these events were serious, they were unlikely related to the SVF cells given the timeline of development. Adverse events that occurred immediately after liposuction included soreness, headache, nausea, and a small hematoma [47]. This study performed by Comella and colleagues also found that intramyocardial injection resulted in brief episodes of bradycardia or tachyarrhythmia that spontaneously resolved [47]. While further safety and efficacy studies must be performed, SVF cells and ASC show promise in treatment of the acute and chronic phases of myocardial ischemia.

Chronic Obstructive Pulmonary Disease. In several preclinical studies, ASC have demonstrated the capacity to reduce emphysematous structural changes in the lung parenchyma, including increasing elastic fibers in the lung and decreasing the damage to the alveolar-capillary membrane (Fig. 2B) [48,50,51]. One such parameter improved in these studies was the mean linear intercept (MLI) which measures the mean free distance in the airspaces. These studies involved intravenous and intratracheal administration of ASC. ASC can also play a role in reducing changes associated with chronically increased pulmonary vasculature pressures and resulting cor pulmonale [48]. While results are preliminary, these effects may ultimately be driven by the immunomodulatory capacity of ASC and their ability to reduce the presence of neutrophils, apoptosis, oxidative damage, and inflammation in the airways in chronic obstructive pulmonary disease [49].

Idiopathic Pulmonary Fibrosis. In one preclinical study, ASC were shown to prolong survival significantly more than current standard of care pirfenidone administration (Fig. 2B) [54]. In a Phase Ib clinical trial of 14 patients with idiopathic pulmonary fibrosis, endobronchial infusion of SVF cells contributed to the maintenance of exercise capacity and six-minute walk test (6MWT) performance while preventing worsening of dyspnea (Fig. 2B). SVF cells also improved the overall scores on the St. George's Respiratory Questionnaire which measures symptomatology, ability to participate in activities without difficulty breathing, and impact of airflow limitation on daily life at 6 and 12 months after treatment [12]. In a Phase I clinical trial of 5 combined pulmonary fibrosis-emphysema patients receiving intravenous or endobronchial ASC, pulmonary function was maintained over a 12 month period [53]. These effects may be secondary to the ability of ASC to decrease inflammation, oxidative stress, and apoptotic pathways to ultimately decrease lung fibrosis [52,54].

Safety analyses were performed in both clinical trials of patients with IPF. In these studies, endobronchial infusion of SVF cells or ASC was well tolerated with no serious or clinically significant side effects over the 12 month study period [12,53].

The only noted side effects after the procedure were worsening of cough and dyspnea (2 patients), oxygen desaturation to 92%–94% (2 patients), increase in heart rate (2 patients), and transient fever (7 patients) [12]. The cough, dyspnea, oxygen desaturation, and increase in heart rate were successfully managed with supplemental oxygen alone. Monitoring up to 2 years showed no ectopic tissue formation on whole body CT scan [12]. Both SVF cells and ASC may represent a safe adjunctive therapy for IPF with the potential to slow the rate of disease progression and prolong survival.

Chronic Liver Failure. Several studies, including one in four patients with cirrhosis, have shown that ASC can reduce alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin while increasing albumin and maintaining prothrombin activity (Fig. 2D) [55–57,59–62]. This may be due to the ability of ASC to reduce liver fibrosis through reduced inflammation, reduced apoptosis, and improved hepatocyte regeneration [55–58,60]. In the Phase I clinical study of four patients with cirrhosis, safety of intra-arterial infusion of ASC into the common hepatic artery was analyzed [62]. The subcutaneous color change to purple at the liposuction site resolved after one month, and no serious adverse events were noted over this period. No patients had chest pain or dyspnea concerning for pulmonary thromboembolism, and hematomas did not occur [62]. There were no exacerbations of serum AST, ALT, lactic acid dehydrogenase (LDH), or creatine kinase (CK) enzyme levels nor severe anemia requiring blood transfusion [62]. Preliminary data suggests that ASC may represent promising candidates for prevention and treatment of cirrhosis.

Inflammatory Bowel Disease. ASC have demonstrated the capacity to reduce clinical symptoms and histologic disease activity in multiple studies of patients with severe inflammatory bowel disease (IBD). Several studies specifically included patients refractory to antibiotics, immunomodulators, and surgical repair [18,68]. In this patient population, ASC fistula injections increased the rate of fistula closure as assessed clinically and by MRI and even reduced the median time to clinical remission in one placebo-controlled study (Fig. 2E) [18,63–68]. In most of these studies, at least 50% of patients treated with ASC had complete closure of the treated fistula at the final time point of 240 days. In one study, 80% and 75% of patients (n = 36) still had complete fistula closure at 1 and 2 years after ASC treatment, respectively [66]. Even in patients with rectovaginal fistulas, one of the most difficult types of fistulas to treat, ASC treatment resulted in 60% remission rate (3/5 patients) at one year after administration [68]. A meta-analysis of 477 patients demonstrated a significant improvement in healing rate and reduction in recurrence for patients treated with ASC relative to other treatments [69]. These improvements in clinical outcomes were likely secondary to the effects of ASCs to reduce inflammation through reduction of proinflammatory cytokines, induction of anti-inflammatory cytokines, increase in T regulatory cell populations, and conversion of macrophages to a regulatory phenotype [102–107].

The safety of ASC administration in IBD has been well established. In 6 studies of 198 patients total, a variety of adverse events were reported including postoperative anal pain, abdominal pain, new fistulas, seton placement, fistula discharge, new abscesses, increases in C reactive protein, musculoskeletal and connective tissue disorders, eczema, exacerbation of disease, anal inflammation, infections, diarrhea, fever, anxiety, psychiatric disorders, and nasopharyngitis [18,63,64,66–68]. No adverse events were related to the ASC in four studies [64,66–68]. Anal abscess was most commonly listed as a treatment-related adverse event [18,63]. Notably, in the placebo-controlled randomized study, approximately equal numbers of patients receiving ASC and placebo (66% and 65%, respectively), had treatment-emergent adverse events, and in this study, 5% (5 patients) in each group developed an anal abscess [18]. The available data suggest that ASC may be a beneficial adjunctive therapy for patients with severe, refractory IBD.

Glioma and Glioblastoma. Similar to their capacity for homing to damaged tissue, ASC have a tropism for tumors such as glioblastoma [73,77,108]. This feature has led to methods of using ASC to deliver chemotherapies locally, such as 5-fluorouracil, cisplatin, and paclitaxel. This can be done by transfection of ASC with genes that can convert prodrugs into chemotherapy or by direct loading of ASC [70,72,75,77]. Another method is transfection of ASC with oncolytic viruses such as ICOVIR17 or with viruses like herpes simplex that can infect cancer cells and be killed after treatment with ganciclovir [74].

Treatment of glioblastoma with intracerebral, intra-arterial, or intravenous injection of ASC has been shown to reduce tumor area, decrease the migratory ability of cancer cells, improve median survival time, and increase rate of remission (Fig. 2F) [70-7-77]. These effects are likely secondary to the ability of ASC to home to tumor sites and exert locally toxic effects [73,77,108]. In one study of treatment with unmodified ASC, glioblastomas were smaller than those in the control group, suggesting that using ASC as cellular therapy does not promote tumor progression [73]. ASC may represent a unique, adjunctive cellular therapy that can carry additional cancer therapies to the site of the tumor.

Acute Kidney Injury. SVF cells and ASC have been shown to reduce biomarkers of kidney injury such as creatinine, blood urea nitrogen (BUN), and urine protein to creatinine ratio [78–85]. Histological signs of tubular damage are decreased through reduction of apoptosis, reduction of inflammation, and increase in regeneration after SVF and ASC administration (Fig. 2G) [78–85]. In two preclinical studies, ASC even improved survival from 50% to 100% after ischemia-reperfusion-induced AKI and from 0% to 20% after cisplatin-induced AKI [78,80]. With regard to safety, doses up to 5×10^5 cells had no associated adverse events, but intravenous doses higher than this were shown to cause pulmonary emboli [80]. Cells were administered via intravenous, intra-arterial, and intraperitoneal injection. SVF cells and ASC may have the potential to reduce kidney damage after episodes of AKI.

Osteoarthritis. Various studies have been conducted in which human patients with osteoarthritis of the knee received an intra-articular injection with autologous SVF and ASC. Many of the studies specifically recruited patients with osteoarthritis which was refractory to oral medications, physical therapy, autologous cartilage transplantation, and hyaluronic acid injection [86,87,90,92]. Patients have experienced improvements in pain, function, mobility, and overall quality of life on various clinical questionnaires after SVF and ASC administration into the

affected joints (Fig. 2H) [21,86–92]. Clinical improvement persisted in these studies for several months to more than two years. Additionally, MRI and arthroscopy have demonstrated improvement or maintenance of cartilage status along the same time period after SVF or ASC administration [21,86,87,89,90]. Preclinical studies suggest that these effects of ASCs may be due to ASC-mediated reduction of pro-inflammatory cytokines and chemokines, apoptosis of chondrocytes, hypertrophic and fibrotic chondrocyte phenotypes, and collagenases [109–116].

Evidence of safety of SVF cell and ASC administration has been determined in multiple Phase I clinical trials. In six studies totaling 130 patients, adverse events reported by at least one patient included slight knee pain, joint effusion, pain in other joints, an increase in C reactive protein, a small increase in CK, a small increase in ALT, a small decrease in neutrophil count, eye problems, nasal symptoms, throat symptoms, diarrhea, urinary tract disease, high blood pressure, dyspnea, unstable angina, and right coronary artery stenosis [21,86,87,90–92]. The most common adverse event was joint pain. No adverse events were associated with liposuction or intraarticular injection of stem cells [87,90,91]. There was no tumor formation in the injected joint [87]. These results indicate that SVF cells and ASC may be therapeutic candidates for improving symptoms in patients with severe osteoarthritis of the knee.

Chronic Skin Wounds. In multiple preclinical studies, SVF cells and ASC have accelerated closure of wounds and decreased the defect size after application of cellular sheets or intradermal injection. These effects may be mediated by the immunomodulatory and angiogenic capacities of SVF and ASC, which lead to increased capillary density, enhanced re-epithelialization, and increased granulation tissue (Fig. 2I) [93–98,100]. ASC also reduce scar formation likely through inhibition of collagen synthesis in late phases of wound healing [98,99]. Chae et al. further explored the differences in effects between SVF and ASC and found that SVF led to faster wound healing [100]. This may be explained by SVF having greater differentiation into keratinocytes, cell survival properties, and expression of genes associated with wound healing and angiogenesis, including vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), fibroblast growth factors (FGF), and connective tissue growth factor (CTGF) [100]. SVF cells and ASC may have the capacity to improve the rate and process of healing of chronic wounds.

Discussion

Current State of ASC as Cellular Therapy

This systematic review highlights a potential role for SVF cells and ASC in the nonhomologous treatment of a wide range of human diseases. In the majority of the clinical trials performed thus far, patients have undergone liposuction and subsequent treatment with their own SVF cells and ASC. Apart from postprocedural pain, very few treatment-related adverse events have been noted, indicating that the risk of treatment is minimal with autologous stem cell therapy [12,18,21,47,62–64,66–68,87,90–92]. While the formation of tumors was an initial concern with stem cell therapy, no ectopic tissue formation has been seen in any studies. In addition to being safe cellular therapies, SVF and ASC have been shown to improve outcomes through mediation of tissue repair. After transplantation, ASCs have been shown to home to the injured tissues, so their regenerative effects may be partially exerted locally [31,32,44,45,54,79]. Several studies have shown differentiation to repair damaged tissues directly [26,29,42,46,100]. However, most of the therapeutic efficacy of SVF and ASCs likely is likely a consequence of paracrine effects, as demonstrated by studies showing effects in the absence of direct cell migration to the target tissue, alterations in gene expression in transwell experiments, and effects of ASC-conditioned media and exosomes [24,27,28,30,39,43,50,60,78,84,95,96,99]. In addition to paracrine effects, ASC possess the capacity to home to sites of neurological tumors and provide local targeted therapy while reducing systemic exposure to drugs such as chemotherapy [70–73,75–77,108]. The strongest evidence for safety and efficacy of SVF and ASC as cellular therapy exists for treatment of inflammatory bowel disease and osteoarthritis, the two diseases with the greatest number of studies in humans.

Next Steps to Clinical Translation

While the preliminary results regarding safety and efficacy are promising, SVF cells and ASC are far from routine clinical use. In all disease states included in this article, additional studies must be performed in human subjects. At the time of this review, the majority of studies in humans were case series with no control group, which provide limited safety and efficacy data. Only one randomized, controlled trial had been performed in humans [18]. Two randomized, controlled trials for patients with chronic myocardial ischemia and acute ischemic stroke are ongoing [117,118]. Controlled trials in human patients are necessary to establish true safety and efficacy of SVF and ASC as cellular therapy.

Future studies need to explore the ideal administration method, dose, and timing for each disease state. These characteristics should be designed with clinical applications in mind. For example, SVF cells and ASC are commonly injected into the peri-infarction area in myocardial ischemia preclinical studies, which may improve delivery to the site of tissue repair but is very invasive and as noted in one study in humans, may cause bradycardia or arrhythmia at the time of injection [47]. Dosing is highly variable across studies, and few studies have investigated the therapeutic potential of administering multiple doses of ASC. Studies in which ASC are infused 30 and 45 minutes after the start of induced stroke or myocardial ischemia in animal models are likely not relevant to the treatment of these patients who rarely present to a hospital and receive treatment this quickly after their symptoms begin. Similarly, treatment of patients with SVF cells or ASC at the time that multiple sclerosis develops is impossible, as patients may not have symptoms until lesions have time to develop. Despite this, SVF cell and ASC treatment at the onset of multiple sclerosis symptoms is possible, and if effective, could provide an adjunctive therapy for newly diagnosed patients with a disabling disease. Thus, practical aspects of clinical use should always be carefully considered when preclinical and clinical trials are developed.

In regard to clinical outcomes, diseases that result in significant chronic disability, such as stroke, may require longer follow up periods. Even if ASC induce an improvement in neurologic function at 4 weeks after stroke, this result would mean more clinically if the effect persisted several months after stroke. Studies should aim to assess clinically meaningful outcomes including

improvements in patient quality of life, reduction in hospitalizations, and reduction in mortality. For certain diseases such as osteoarthritis, future studies assessing the length of nonsurgical treatment may be of utility if ASC can prolong the time to surgical intervention. Additionally, outcomes need to be compared with placebo, but placebo should account for the current standard of care. ASC should also be tested in addition to the standard of care treatments in an effort to determine whether adjunctive ASC therapy can be effective, even if ASC are not superior to the current standard of care. This is particularly important for diseases such as idiopathic pulmonary fibrosis and glioblastoma for which current therapies are inadequate to prevent rapid progression of disease.

Once the safest and most effective source, administration method, dose, and timing have been established, the question of the ideal source and processing for SVF cells and ASC remains. The majority of human studies to date have been performed using autologous SVF cells and ASC. However, studies of allogeneic SVF cells and ASC will be important for two reasons. For one, treatment of acute conditions such as myocardial ischemia and ischemic stroke require immediate availability of cells and do not allow time for liposuction and isolation of SVF cells or ASC. Second, autologous SVF and ASC may be less effective depending on the health characteristics of the donor. In studies of pulmonary fibrosis and myocardial ischemia, ASC have been shown to be less effective when isolated from older donor animals [52,119]. When isolated from animals with chronic inflammatory diseases such as obesity and the model for multiple sclerosis, ASC have also been shown to be less effective in immunomodulation [36,38]. Thus, studies comparing clinical outcomes after autologous and allogeneic SVF cells or ASC treatment may provide valuable information about the most effective source for cellular therapy.

Even after the question of autologous versus allogeneic stem cells is fully addressed, there are still multiple aspects of processing that must be explored before clinical application becomes widely applicable. The first is whether the lipoaspirate will undergo SVF cell isolation and/or expansion to isolate ASC. If SVF cells are not immediately re-administered to the patient, there must be processes for expansion, storage, and release of cells for clinical use [101,120]. ASC that have been isolated and expanded for multiple passages may begin to undergo replicative senescence, which could lead to genetic instability, increased potential for immune response, and reduced efficacy as a cellular therapy [121–123]. Additional studies should aim to compare SVF and ASC, as avoiding the need for culture and passage may reduce these risks. The few studies that have directly compared SVF and ASC have been promising, demonstrating more significant therapeutic effects for SVF with no additional adverse effects [34,35,37,100]. Good manufacturing processes will have to be developed to ensure the safety and quality of the cells and that the cells being isolated meet the criteria to be called mesenchymal stem cells as set by the International Society for Cellular Therapy [120,124,125].

The Food and Drug Administration regulates the use of stem cell-based products in the United States according to the Public Health Safety Act [107]. This act states that stem cells are subject to regulation if they are processed, used for purposes that are not their normal function, also known as "nonhomologous use," combined with non-tissue materials, or used for metabolic purposes [107,126]. However, some investigators claim that the use of stem cells for treatment of disease is not under the purview of the FDA as these stem cells are administered as part of medical procedures [126]. This viewpoint was recently exemplified by Regenerative Sciences, a company that treated patients with autologous mesenchymal stem cells for musculoskeletal injuries. Regenerative Sciences upheld that the stem cells they used were not drugs or biological products. The FDA issued an injunction by stating that these stem cells met criteria for regulation because they were more than minimally manipulated during the manufacturing process [126]. The FDA won the case in 2014, which may lead to increased regulation of stem cell use in clinics in the U.S.. While there is concern that this will limit progress in development of cellular therapies, the implications of this court decision remain to be determined.

Conclusion

SVF and ASC are promising candidates for use as cellular therapies due to their abundance, ease of isolation, and natural mechanisms for promoting tissue regeneration. Preclinical and clinical studies indicate that these stem cells may be able to improve the clinical outcomes and thus the lives of patients with diseases refractory to currently available therapies. Continued research of their safety and efficacy in human subjects will be needed before routine clinical use.

Author Contributions

M.E.B., A.L.S., and B.A.B.: conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript; J.M.G.: data analysis and interpretation, manuscript writing, final approval of manuscript.

Disclosure of Potential Conflicts of Interest

J.M.G. has compensated employment and is co-owner and co-founder of LaCell LLC, Obatala Sciences, Talaria Antibodies. The other authors indicated no potential conflicts of interest.

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