**Abstract:** Adipose tissue is an abundant source of mesenchymal stem cells, which have shown promise in the field of regenerative medicine. Furthermore, these cells can be readily harvested in large numbers with low donor-site morbidity. During the past decade, numerous studies have provided preclinical data on the safety and efficacy of adipose-derived stem cells, supporting the use of these cells in future clinical applications. Various clinical trials have shown the regenerative capability of adipose-derived stem cells in subspecialties of medical fields such as plastic surgery, orthopedic surgery, oral and maxillofacial surgery, and cardiac surgery. In addition, a great deal of knowledge concerning the harvesting, characterization, and culture of adipose-derived stem cells has been reported. This review will summarize data from *in vitro* studies, pre-clinical animal models, and recent clinical trials concerning the use of adipose-derived stem cells in regenerative medicine.

**Introduction**

In the field of [regenerative medicine](http://www.discoverymedicine.com/category/medical-specialties/regenerative-medicine/), basic research and preclinical studies have been conducted to overcome clinical shortcomings with the use of mesenchymal stem cells (MSCs). MSCs are present in adult tissues, including [bone marrow](http://www.discoverymedicine.com/category/species-and-cell-types/human/bone-marrow/) and adipose tissue. For many years, bone marrow-derived stem cells (BSCs) were the primary source of stem cells for [tissue engineering](http://www.discoverymedicine.com/category/research-technology/tissue-engineering/) applications (Caplan, 1991; Pittenger et al., 1999; Caplan, 2007). However, recent studies have shown that subcutaneous adipose tissue provides a clear advantage over other [stem cell](http://www.discoverymedicine.com/category/species-and-cell-types/human/bone-marrow/stem-cell/) sources due to the ease with which adipose tissue can be accessed as well as the ease of isolating stem cells from harvested tissue (Schäffler et al., 2007). Initial enzymatic digestion of adipose tissue yields a mixture of stromal and vascular cells referred to as the stromal-vascular fraction (SVF) (Traktuev et al., 2008). A putative stem cell population within this SVF was first identified by Zuk *et al.* and named processed lipoaspirate (PLA) cells (Zuk et al., 2001; Zuk et al., 2002).

There is no consensus when it comes to the nomenclature used to describe progenitor cells from adipose tissue-derived stroma, which can sometimes lead to confusion. The term PLA refers to adipose-derived stromal cells and adipose-derived stem cells (ASCs) and describes cells obtained immediately after collagenase digestion. Accordingly, the term ASC will be used throughout this review.

ASCs exhibit stable growth and proliferation kinetics and can differentiate toward osteogenic, chondrogenic, adipogenic, myogenic, or neurogenic lineages *in vitro* (Zuk et al., 2002; Izadpanah et al., 2006; Romanov et al., 2005). Furthermore, a group has recently described the isolation and culture of ASCs with multipotent differentiation capacity at the single-cell level (Rodriguez, et al., 2005).

Using these attractive cell populations, recent studies have explored the safety and efficacy of implanted/administrated ASCs in various animal models. Furthermore, clinical trials using ASCs have been initiated in some medical subspecialties. This review summarizes the current preclinical data and ongoing clinical trials and their outcomes in a variety of medical fields.

**Characterization and Localization**

ASCs express the [mesenchymal stem cell](http://www.discoverymedicine.com/category/species-and-cell-types/human/bone-marrow/stem-cell/mesenchymal-stem-cell/) markers CD10, CD13, CD29, [CD34](http://www.discoverymedicine.com/tag/cd34/), CD44, CD54, CD71, CD90, CD105, CD106, CD117, and STRO-1. They are negative for the hematopoietic lineage markers CD45, CD14, CD16, CD56, CD61, CD62E, CD104, and CD106 and for the endothelial cell (EC) markers CD31, CD144, and von Willebrand factor (Zuk et al., 2002; Musina et al., 2005; Romanov et al., 2005). Morphologically, they are fibroblast-like and preserve their shape after expansion *in vitro* (Zuk et al., 2002; Arrigoni et al., 2009; Zannettino et al., 2008).

The similarities between ASCs and BSCs may indicate that ASCs are derived from circulating BSCs, which infiltrate into the adipose compartment through vessel walls (Zuk et al., 2002; Zannettino et al., 2008; Brighton et al., 1992; Canfield et al., 2000; Bianco et al., 2001). On the other hand, according to a recent theory, these stem cells are actually pericytes (Traktuev et al., 2008; Chen et al., 2009; Crisan et al., 2008; Zannettino et al., 2008; Tintut et al., 2003; Abedin et al., 2004; Amos et al., 2008). Pericytes around microvessels express alpha-smooth muscle actin (α-SMA) as well as certain MSC markers (CD44, CD73, CD90, CD105); however, they do not express endothelial or hematopoietic cell markers (Chen et al., 2009). Pericytes adhere, proliferate in culture, sustain their initial antigenic profile, and can differentiate into bone, cartilage and fat cells (Chen et al., 2009). Moreover, injected MSCs migrate to the blood vessels *in vivo* and become pericytes (Chen et al., 2009). Considering the above-mentioned data, it can be speculated that pericytes are the ancestors of MSCs, but this does not mean that all MSCs are descendants of pericytes (Chen et al., 2009) or that all pericytes are necessarily stem cells (Lin et al., 2008; Traktuev et al., 2008; da Silva et al., 2008; Abedin et al., 2004; Tintut et al., 2003; Zannettino et al., 2008; Amos et al., 2008).

Traktuev et al. (2008) defined a periendothelial [pericyte](http://www.discoverymedicine.com/category/species-and-cell-types/human/blood-vessel/pericyte/)-like subpopulation of ASCs. These cells were CD34+, CD31-, CD45-, and CD144- and expressed mesenchymal cell markers, smooth muscle antigens, and pericytic markers, including chondroitin sulfate [proteoglycan](http://www.discoverymedicine.com/tag/proteoglycan/) (NG2), CD140a, and CD140b ([PDGF](http://www.discoverymedicine.com/tag/pdgf/) receptor α and β, respectively) (Traktuev et al., 2008; Amos et al., 2008). However, Lin et al. (2008) could not co-localize CD34 and CD104b, and thus concluded that CD34+/CD31- cells of adipose [vasculature](http://www.discoverymedicine.com/tag/vasculature/) are not pericytes.

The differences in the expression of surface markers in these studies may be explained by the stage of culture growth (Romanov et al., 2005). Similarly, the variability of CD34 positivity in several reports is likely a consequence of the down-regulation of expression of this marker within the first few days of *in vitro* expansion (Traktuev et al., 2008).

**Paracrine Secretion**

Adipose tissue actively participates in endocrine processes by secreting cytokines and growth factors (Kilroy et al., 2007). ASCs secrete high levels of [epidermal growth factor](http://www.discoverymedicine.com/tag/epidermal-growth-factor/) ([EGF](http://www.discoverymedicine.com/tag/egf/)), [vascular endothelial growth factor](http://www.discoverymedicine.com/tag/vascular-endothelial-growth-factor/) ([VEGF](http://www.discoverymedicine.com/category/therapeutic-technology-and-methodology/therapy/targeted-therapy/vegf-targeted-therapy-therapy/)), basic fibroblast growth factor ([bFGF](http://www.discoverymedicine.com/tag/bfgf/)), [keratinocyte](http://www.discoverymedicine.com/category/species-and-cell-types/human/skin/keratinocyte/) growth factor (KGF), platelet-derived growth factor (PDGF), [hepatocyte](http://www.discoverymedicine.com/category/species-and-cell-types/human/liver/hepatocyte/) growth factor (HGF), transforming growth factor-beta (TGF-β), insulin-like growth factor (IGF), and [brain-derived neurotrophic factor](http://www.discoverymedicine.com/tag/brain-derived-neurotrophic-factor/) ([BDNF](http://www.discoverymedicine.com/tag/bdnf/)) (Chen et al., 2009; Kilroy et al., 2007; Rehman et al 2004; Cai et al., 2007; Ebrahimian et al., 2009; Kim et al., 2009; Kim et al., 2007; Wei et al., 2009). They also secrete cytokines such as Flt-3 ligand, [granulocyte](http://www.discoverymedicine.com/category/species-and-cell-types/human/blood/granulocyte/) colony stimulating factor ([G-CSF](http://www.discoverymedicine.com/tag/g-csf/)), granulocyte/[macrophage](http://www.discoverymedicine.com/category/species-and-cell-types/human/immune-system/macrophage/) colony stimulating factor ([GM-CSF](http://www.discoverymedicine.com/tag/gm-csf/)), macrophage colony stimulating factor (M-CSF), interleukin-6 ([IL-6](http://www.discoverymedicine.com/tag/il-6/)), [interleukin-7](http://www.discoverymedicine.com/tag/interleukin-7/) ([IL-7](http://www.discoverymedicine.com/tag/il-7/)), interleukin-8 ([IL-8](http://www.discoverymedicine.com/tag/il-8/)), interleukin-11 (IL-11), [interleukin-12](http://www.discoverymedicine.com/tag/interleukin-12/) ([IL-12](http://www.discoverymedicine.com/tag/il-12/)), [leukemia](http://www.discoverymedicine.com/category/medical-specialties/oncology/leukemia/) inhibitory factor (LIF), and [tumor necrosis factor](http://www.discoverymedicine.com/tag/tumor-necrosis-factor/)-alpha ([TNF](http://www.discoverymedicine.com/tag/tnf/)-α) (Kilroy et al., 2007; Rehman et al 2004). This secretion of paracrine factors by the adipose tissue likely contributes to the elevated levels of these cytokines in cases of [obesity](http://www.discoverymedicine.com/category/medical-specialties/endocrinology/obesity/) (Kilroy et al., 2007; Hotamisligil et al., 1995).

It is important to note that these angiogenic and anti-apoptotic growth factors are secreted in bioactive levels by ASCs and that their secretion increases significantly under hypoxic conditions (Rehman et al., 2004; Cai et al., 2007; Lee et al., 2009). HGF is possibly the main angiogenic factor secreted by ASCs and it plays a central role in the paracrine effects on ASCs. Its suppression has been shown to impair the angiogenic and regenerative effects of ASCs in ischemic tissues. Silencing HGF reduces the ability of ASCs to promote EC proliferation and inhibits the pro-angiogenic effects of HGF *in vitro* (Cai et al., 2007).

**Soft** [**Tissue Regeneration**](http://www.discoverymedicine.com/category/medical-specialties/regenerative-medicine/tissue-regeneration/) **and** [**Wound Healing**](http://www.discoverymedicine.com/category/medical-specialties/surgery/wound-healing/)

The materials currently used in soft tissue regeneration, which include collagen, hyaluronic acid, silicon, and other filler materials, have several disadvantages such as high cost, immunogenicity/allergenicity, and the risk of transmitting [infectious diseases](http://www.discoverymedicine.com/category/medical-specialties/infectious-diseases/). Meanwhile, autologous fat grafts are more widely available; however, one limitation of this technique is the poor long-term graft retention in current clinical practice (Min et al., 2010). The transplanted fat grafts can lose volume over time due to tissue resorption that can result in the loss of 20-90% of the original graft volume (Cherubino et al., 2009). The ideal solution for soft tissue regeneration would promote the regeneration of vascularized adipose tissue to completely fill the defect volume (Brayfield et al., 2010).

Recently, Frerich et al. (2005) reported an in vitro co-culture model using human adipose stromal cells and human umbilical vein ECs, where perfused tubes formed capillary-like networks that sprouted from the central lumen wall. Kang et al. (2009) developed an *in vitro* 3D model of tissue regeneration in which human vascularized adipose tissue, human ASCs, and human umbilical vein ECs were co-cultured on 3D aqueous silk scaffolds. After two weeks of co-culture, continuous endothelial lumens formed. Furthermore, Min et al. (2010) demonstrated in an *in vivo* murine model that the [transplantation](http://www.discoverymedicine.com/category/medical-specialties/transplantation/) of [fat tissue](http://www.discoverymedicine.com/category/species-and-cell-types/human/fat-tissue/) with non-cultured ASCs improved long-term graft retention. Compared with transplanted fat tissue alone, fat tissue transplanted with non-cultured ASCs had a higher density of capillaries six and nine months after transplantation. The reasons for these successful results might be the pro-angiogenic growth factors secreted by ASCs, as described previously.

Wound healing might be interrupted by a variety of pathological conditions, such as [diabetes](http://www.discoverymedicine.com/category/medical-specialties/endocrinology/diabetes/), radiation and [immunosuppression](http://www.discoverymedicine.com/tag/immunosuppression/), resulting in refractory chronic wounds (Lorens et al., 2006). Growth factors involved in wound healing have been individually applied to the wound to promote wound healing in unfavorable conditions. However, the theoretical promise of this approach was unfulfilled due to the complex nature of wound healing, which involves a number of different growth factors (Ebrahimian et al., 2009; Brem et al., 2009). To achieve optimal results, all these growth factors should be applied continuously, as opposed to the intermittent applications of individual growth factors (Brem et al., 2009; Blanton et al., 2009).

ASCs secrete nearly all of the growth factors that take part in normal wound healing (Ebrahimian et al., 2009; Blanton et al., 2009; Kim et al., 2007; Rehman et al., 2004). After application, ASCs may remain viable at the wound site and secrete growth factors in a continuous and regulated manner in response to environmental cues, just as occurs in the natural wound healing process (Badillo et al., 2007). ASCs promote wound healing by increasing vessel density, granulation tissue thickness, and collagen deposition (Ebrahimian et al., 2009), and they also improve the cosmetic appearance of resultant scars (Blanton et al., 2009).

A ready blood supply is crucial for wound healing. [VEGF](http://www.discoverymedicine.com/tag/vegf/) secreted from ASCs induces the migration and proliferation of ECs, increasing the vascularity of the wound bed (Lorens et al., 2006; Rehman et al., 2004). It was both experimentally and clinically shown that the topical administration of ASCs to full-thickness radiated wounds increase the healing rate of the wound (Ebrahimian et al., 2009; Rigotti et al., 2007). Kim et al. (2007) demonstrated that ASCs stimulate fibroblast proliferation and migration and type I collagen secretion in an *in vitro* wound model. These findings suggest that ASCs may promote *in vivo* wound healing.

**Musculoskeletal Regeneration**

Current therapeutic approaches for muscle loss cannot restore muscle function effectively. ASCs can differentiate into chondrogenic, osteogenic, and myogenic cells *in vitro,* and thus could potentially be used to regenerate tissue in musculoskeletal system disorders (Zuk et al., 2001; Mizuno et al., 2002).

Muscle tissue contains muscle progenitor cells called satellite cells that lie underneath the basal lamina (Kim et al., 2006; Di Rocco et al., 2006; Mizuno et al., 2002). These cells can divide and fuse to repair or replace damaged ﬁbers in response to acute muscle injury or in chronic degenerative myopathies (Kim et al., 2006; Mizuno et al., 2002). However, continuous muscle degeneration-regeneration cycles in chronic cases lead to a depletion of the satellite cell pool. Moreover, it is difficult to expand satellite cells *in vitro* and they rapidly undergo [senescence](http://www.discoverymedicine.com/tag/senescence/) (Di Rocco et al., 2006; Mizuno et al., 2002).

ASCs may provide an easily accessible and expandable alternative cell source for the cellular therapy of muscular disorders. ASCs were successfully differentiated into skeletal muscle cells and smooth muscle cells *in vitro* (Jeon et al., 2010; Mizuno et al., 2002; Di Rocco et al., 2006). Differentiated ASCs even exhibited a contractile function similar to that of smooth muscle cells *in vivo* (Rodríguez et al., 2006). ASCs have also shown a capacity for myogenic differentiation *in vivo*. Allogeneic ASCs injected intravenously or directly into the affected muscle could restore muscle function in a murine [muscular dystrophy](http://www.discoverymedicine.com/category/medical-specialties/neurology/muscular-dystrophy/) model without any signs of immune rejection (Di Rocco et al., 2006). In another study, poly lactic-co glycolic acid (PLGA) spheres attached to myogenically-induced ASCs were injected subcutaneously into athymic nude mice. Injected ASCs diﬀerentiated into muscle cells and regenerated into new muscular tissue (Kim et al., 2006). However, it is still unclear whether ASCs directly differentiate into myogenic lineage cells or whether they become incorporated into muscle ﬁbers via [cell fusion](http://www.discoverymedicine.com/category/research-technology/cell-fusion/). It is likely that ASCs contain different subsets of cells capable of either function (Di Rocco et al., 2006).

ASCs can form osteoid *in vitro* and *in vivo* (Hattori et al., 2004). ASCs combined with biomaterials were successfully used to repair critical bone defects (Di Bella et al., 2008; Yoon et al., 2007). Moreover, ASCs secrete osteoinductive growth factors, which may potentially recruit host bone-forming cells and induce osteogenesis when implanted *in vivo* (Hao et al., 2010). ASCs genetically modified to secrete bone morphogenic protein-2 ([BMP-2](http://www.discoverymedicine.com/tag/bmp-2/)) may also be an effective method for enhancing bone healing (Peterson et al., 2005).

Use of ASCs in intervertebral disc regeneration has also been reported (Hoogendoorn et al., 2008). Other applications of ASCs in musculoskeletal system are periodontal tissue regeneration and [tendon](http://www.discoverymedicine.com/category/species-and-cell-types/human/muscle/tendon/) regeneration. Tobita et al. (2008) reported that implanted ASCs were differentiated into the periodontal tissues including alveolar bone, cementum, and periodontal ligament in a rat model. In addition, topical administration of ASCs to [tendon repair](http://www.discoverymedicine.com/category/medical-specialties/orthopedics/tendon-injury/tendon-repair/) sites in rabbits accelerated tendon repair and significantly increased tensile strength (Uysal et al., 2011).

**Cardiovascular Regeneration**

Acute and chronic ischemic heart diseases are among the leading causes of mortality worldwide (Bai et al., 2010; Psaltis et al., 2008). Conventional management generally does not replace lost [cardiomyocyte](http://www.discoverymedicine.com/category/species-and-cell-types/human/heart/cardiomyocyte/) mass or myocardial fibrotic tissue (Psaltis et al., 2008). The injection of both cultured and freshly-isolated ASCs has the potential to improve cardiac function in experimentally-induced myocardial injury (Danoviz et al., 2010; Cai et al., 2009; Miyahara et al., 2006; Schenke-Layland et al., 2009; Valina et al., 2007; van der Bogt et al., 2009; van der Bogt et al., 2008; Wang et al., 2009; Van’t Hof et al., 2007; Léobon et al., 2009). Bai et al. (2010) injected human ASCs into the peri-infarct region of the hearts of mice. Cardiac function was preserved; moreover, left ventricular end-systolic volume was signiﬁcantly lower in the mice that received injections of ASCs. Valinaet al. (2007) reported similar results in a porcine model.

Human ASCs spontaneously differentiate into cardiomyocytes *in vitro*, express the cardiac-speciﬁc markers troponin-I and myosin light chain 2 (Song et al., 2007; Choi et al., 2010), and even contract rhythmically (Planat-Bénard et al., 2004). However, as with smooth muscle differentiation, the *in vivo* differentiation of ASCs into cardiomyocytes is still controversial. Strem et al. (2005) reported that ASCs expressed cardiac markers *in vivo* two weeks after injection, but Cai et al. (2009) found that intramyocardially-injected human ASCs differentiated into smooth muscle cells but not into cardiomyocytes in rats. Intramyocardially-injected ASCs can promote [angiogenesis](http://www.discoverymedicine.com/tag/angiogenesis/) and inhibit [apoptosis](http://www.discoverymedicine.com/tag/apoptosis/) of cells in injured hearts via the secretion of pro-angiogenic growth factors (Bai et al., 2010). Moreover, ASCs may also directly stimulate nerve sprouting in ischemic myocardium, thereby increasing cardiac contractile performance (Bai et al., 2007; Cai et al., 2010).

The conventional method of delivery of ASCs is needle-based intramyocardial injection. However, significant cell death or cell washout may occur, which can decrease the efficacy of treatment (Shimizu et al., 2009). An alternative method is epicardial delivery via scaffold-free cell sheets that are prepared on temperature-responsive dishes. The advantages of these cell sheets are the absence of any foreign material, the preservation of cell cohesiveness, and the possibility of incorporating different cell populations (Bel et al., 2010; Shimizu et al., 2009). Several types of cell sheet-based patches have improved damaged heart function in rat, canine, and porcine models (Shimizu et al., 2009).

**Nervous System Regeneration**

A variety of growth factors, such as [nerve growth factor](http://www.discoverymedicine.com/tag/nerve-growth-factor/) ([NGF](http://www.discoverymedicine.com/tag/ngf/)), ciliary neurotrophic factor (CNF), IGF, and FGF, are secreted from nerve stumps following injury (Bixby et al., 1988; Longo et al., 1983). These growth factors stimulate axonal growth in close contact with Schwann cells, which are the primary support cells of the peripheral nervous system (Shimizu et al., 2007; Sofroniew et al., 2001). Since the above-mentioned regeneration sequence is known to fail in long nerve defects, cellular treatments, such as [stem cell therapy](http://www.discoverymedicine.com/category/therapeutic-technology-and-methodology/therapy/stem-cell-therapy/), might be useful (Lundborg et al., 1982) as a means to introduce growth factors into the gap and thereby promote nerve regeneration. ASCs can secrete some nerve growth factors, including IGF and FGF (Rehman et al., 2004; Zavan et al., 2010), so these cells might have the capacity to promote nerve healing. In addition, a number of recent studies reported the successful differentiation of ASCs into neural lineage cells and Schwann cells *in vitro* (Safford et al., 2002; Fujimura et al., 2005; Xu et al., 2008; Kingham et al., 2007; Oh et al., 2010). When compared to BSCs, ASCs express a significantly higher proportion of nestin, which is commonly used to identify proliferating adult neural progenitor cells (Safford et al., 2002). Several results suggest that the differentiation of ASCs into Schwann cells, the mechanism of which has been described in detail (Deng et al., 2001; Cohen et al., 1999; Shah et al., 1999; di Summa et al., 2010),is not an incomplete, reversible process resulting from the disruption of the cytoskeleton (Safford et al., 2002; Fujimura et al., 2005; Kingham et al., 2007).

A study testing the effects of ASCs, which were differentiated into a [Schwann cell](http://www.discoverymedicine.com/category/species-and-cell-types/human/brain/schwann-cell/)-like phenotype, on peripheral nerve healing has been reported by di Summa et al. (2010). However, more experimental data must be gathered using larger animal models before these methods can be safely tested in the clinic.

ASCs can be used not only in peripheral nerve injuries but also in central nervous system injuries (Chi et al., 2010; Zhang et al., 2009; Ohta et al., 2008; Kang et al., 2006; Ryu et al., 2009). Ryu et al. (2009) used ASCs to treat acute spinal injuries in a canine model and reported an improvement in neurological function. They also could document the *in vivo* differentiation of ASCs into astrocytes, oligodendrocytes and neuronal cells. In another study, ASCs were used for [spinal cord injury](http://www.discoverymedicine.com/category/medical-specialties/neurology/cns-injury/spinal-cord-injury-cns-injury-neurology-medical-specialties/) in rats after *in vitro* differentiation into Schwann cells (Ohta et al., 2008). But in this study, the authors stated that functional improvement was not observed despite the significant histological improvement achieved at the primary injury site by the transplantation of Schwann cells. Therefore, it was speculated that a full recovery of [spinal cord](http://www.discoverymedicine.com/category/species-and-cell-types/human/spine/spinal-cord/) function requires a much more complex treatment combining different modalities rather than an injection of a single type of cell or cytokine.

It has been well established that ASCs can survive in the nervous system after injection and promote nerve healing either by direct differentiation or through the secretion of a number of paracrine factors. ASCs thus show promise for the future of the treatment of central nervous system injuries, as well as peripheral nerve injuries.

[**Cancer Metastasis**](http://www.discoverymedicine.com/category/medical-specialties/oncology/cancer-metastasis/) **and Invasion**

Because stromal cells contribute to the development of a variety of tumors, it is important to consider the effect of implanted/administrated mesenchymal stromal/stem cells on cancer development before these cells can be used clinically in regenerative medicine. Stromal cell compartments contain a variety of cell types such as fibroblasts, pericytes, myofibroblasts, vasculature, and macrophages, which together form a microenvironment that tightly controls the proliferation and differentiation of epithelial cells (Bissell et al., 2002). During the initiation and progression of [breast cancer](http://www.discoverymedicine.com/category/medical-specialties/oncology/breast-cancer/), the tumor cells reorganize the tissue microenvironment to support their proliferation and invasion into the surrounding tissue (Pupa et al., 2002). Tumors recruit stromal fibroblasts in a process referred to as a desmoplasmic reaction. These tumor-associated fibroblasts are reprogrammed to produce growth factors, cytokines, and extracellular matrix-remodeling proteins (Orimo et al., 2005).

Recent studies have demonstrated that BSCs recruited by breast carcinomas promote breast cancer metastasis and invasion (Karnoub et al., 2007). BSCs produce chemokine ligand 5 (CCL5), which promotes breast tumor progression in direct co-cultures.

Compared with BSCs, ASCs are tissue-resident stem cells that occur locally adjacent to breast cancer cells, and interactions between adipocytes and breast cancer cells have been described previously (Iyengar et al., 2003; Manabe et al., 2003). Recent studies have linked white adipose-derived cells to cancer development. An *in vivo* murine model demonstrated that ASCs home to tumor sites when injected intravenously, and the stromal-derived growth factor-1 ([SDF-1](http://www.discoverymedicine.com/tag/sdf-1/))/CXC receptor 4 ([CXCR4](http://www.discoverymedicine.com/tag/cxcr4/)) axis plays an important role in mediating the tumor-promoting effect of ASCs (Muehlberg et al., 2009). Walter et al. (2009) reported that IL-6 secreted by ASCs is related to the migration and invasion of breast tumor cells. IL-6 is a critical growth factor for several types of cancer such as [multiple myeloma](http://www.discoverymedicine.com/category/medical-specialties/oncology/multiple-myeloma/) (MM) and [prostate cancer](http://www.discoverymedicine.com/category/medical-specialties/oncology/prostate-cancer/) (Smith et al., 2001). Furthermore, an *in vivo* study showed that SDF-1 secreted by ASCs promoted the invasion and metastasis of breast cancer (Muehlberg et al., 2009). Another study reported that human ASCs produce CCL5. Significant amounts of CCL5 were detected in conditioned medium from human ASCs after co-culture with MDA-MB-231 breast cancer cells (Pinilla et al., 2009).

However, the effect of ASCs against cancer tumor cells is controversial. Several studies have reported that implanted ASCs inhibited breast cancer metastasis and growth in a murine model (Sun et al., 2009).

Reciprocal interactions between breast tumor cells and stromal cells are mediated by inflammatory cytokines and chemokines, and may affect tumor development and progression. Therefore, the molecular basis of the effects of adipose tissue on the behavior of tumor cells should be carefully examined before the future clinical application of stem cell therapies.

**Current Clinical Trials**

Cell therapies using ASCs are widely promising in various clinical fields based on *in vitro* and *in vivo* research results. Currently, clinical trials for the regeneration of soft tissue, craniofacial tissue, and cardiovascular tissue enrolled a number of patients.

Breast reconstruction and augmentation trials have been reported by Yoshimura and colleagues (Yoshimura et al., 2008; Yoshimura et al., 2010). The stromal vascular fraction (SVF) was isolated from half of the aspirated fat tissue, recombined with the remaining half, and then used in combination with lipoinjection in over fifty patients. These results showed no evidence of fibrosis or adhesions and improved fat grafting by the SVF cells with retention of volume for over twelve months. Furthermore, a clinical trial was conducted for facial lipoatrophy using the same technique (Yoshimura et al., 2008). The authors note improved facial contour, although there was no statistically significant difference in clinical improvement score compared to the conventional lipoinjection.

Regarding craniofacial defects, ASCs were first used to stimulate bone repair in calvarial defects (Lendeckel et al., 2004). This surgical team used fibrin glue and autologous adipose-derived stromal cells including stem cells in a 7-year-old female, and new bone formation was evident three months after reconstruction. Meanwhile, a Finnish team reported clinical outcomes with autologous ASCs (Mesimäki et al., 2009). The authors harvested autologous fat tissue from a 65-year-old male who had undergone a hemimaxillectomy twenty-eight months earlier due to a large recurrent keratocyst, expanded the cells in culture, mixed them with BMP-2, and seeded them onto a β-tricalcium phosphate scaffold formed into the shape of the defect. Eight months after this construct was implanted into the patient’s rectus abdominis muscle, the construct was resected and transplanted into the maxillofacial defect. The patient regained full oral function for at least twelve months.

ASCs hold great promise for the treatment of cardiovascular diseases and no cardiac side effects (e.g., electrical instability) have been reported to date (Bai et al., 2010). Currently, an ongoing clinical trial using ASCs for cardiovascular treatment has been reported. The clinical trial is being carried out in patients with acute [myocardial infarction](http://www.discoverymedicine.com/category/medical-specialties/cardiology-and-circulation/myocardial-infarction/) (AMI) (Sanz-Ruiz et al., 2009), and it is a prospective, double-blind, randomized, placebo-controlled, sequential dose-escalation trial including up to forty-eight patients. Freshly-isolated ASCs are delivered through intracoronary infusion in patients with AMI and left ventricular (LV) ejection fraction impairment. For chronic myocardial [ischemia](http://www.discoverymedicine.com/category/medical-specialties/hematology/ischemia/), a clinical trial is also being carried out in up to thirty-six patients (Sanz-Ruiz et al., 2009). The freshly-isolated ASCs are delivered via transendocardial injections in patients with [coronary artery disease](http://www.discoverymedicine.com/category/medical-specialties/cardiology-and-circulation/coronary-artery-disease/). However, clinical trials of cardiac [cell therapy](http://www.discoverymedicine.com/category/therapeutic-technology-and-methodology/therapy/cell-therapy/) have yielded inconsistent results (Bel et al., 2010). A number of issues such as appropriate type and number of cells, timing and route of cell delivery, and the detailed mechanism of action should be optimized for more consistent clinical results (Danoviz et al., 2010).

ASCs were also used to heal chronic fistulas in Crohn’s disease (Garcia-Olmo et al., 2005; Garcia-Olmo et al., 2008). This disease is an inflammatory bowel disorder characterized by bloody stools, [diarrhea](http://www.discoverymedicine.com/category/medical-specialties/gastroenterology/diarrhea/), weight loss, and autoimmune-related symptoms. In a phase I trial with patients with fistulas unresponsive to standard treatment, cultured ASCs were directly injected into the rectal mucosa, and 75% of cases healed completely. In a phase IIb trial, the proportion of patients who achieved fistula healing was significantly higher with ASCs than with fibrin glue. Rigotti et al. (2007) reported successful results after injection of lipoaspirates containing ASCs to wounds caused by post-[mastectomy](http://www.discoverymedicine.com/category/medical-specialties/oncology/breast-cancer/mastectomy/) irradiation. According to ultrastructural analysis, the early stages of tissue mesenchymalization were observed after application of lipoaspirates and a tissue resembling normal mature adipose tissue was formed at the site of application. The authors commented that this effect of lipoaspirate on wound healing was largely due to the angiogenic growth factors secreted by ASCs (Rigotti et al., 2007). These results were valuable in terms of showing the safety and feasibility of ASCs for clinical wound management (Hanson et al., 2010; Garcia-Olmo et al., 2005).

**Conclusions**

ASCs are under investigation for a variety of therapeutic applications. These cells are known to home to some tissues such as injured tissue. Although the mechanisms underlying the migration of ASCs remain to be determined, clarification of the roles of chemokine receptors and adhesion molecules on ASCs may lead to the development of therapeutic strategies to enhance the recruitment of cultured ASCs to injured or damaged tissue.

Because human adipose tissue is a promising alternative source of stem cells, autologous ASCs will lead to novel clinical applications in various medical fields. However, a greater understanding of the mechanisms of interactions among ASCs, growth factors, and biomaterials on tissue regeneration is needed to advance the clinical utility of this therapy. Because chemokines derived from ASCs may also affect cancer metastasis or invasion, additional findings are necessary to address the safety of ASCs in the field of clinical tissue regeneration.

**Disclosure**

The authors report no conflicts of interest.

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