Advances of Plastic & Reconstructive Surgery

Chapter 3

# Stem Cells and their Place in Fat Grafting

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## 1. Introduction

Fat grafting involves removing fat from one area of the body and transferring it to another to add or restore volume and shape [8,9]. The procedure has become increasingly popular as more patients seek to improve their appearance without implantation of foreign bodies such as breast implants or fillers. Fat grafting is most often performed to augment or reconstruct the breasts and face or augment the buttocks. Before the fat can be injected, it must be removed from elsewhere through liposuction. Several devices are marketed to collect, wash, and concentrate lipoaspirate to aid in the collection of better quality fat for injection [10[. Before injection, the surgeon must attempt to remove as much fluid and oil as possible to deliver as much fat per volume injected as can be achieved [11]. This purification step can in addition be utilized for cell extraction and is described later in this chapter. The processed fat is then transferred to a special injector cannula and injected in small paths, a process also known as structural fat grafting [12]. Once the fat is injected, it must integrate with the recipient tissue to survive [13]. This process can take several weeks, and the amount of fat that remains is often low and unpredictable [4–6]. The advantages of fat grafting include a natural look and feel, biocompatibility, and minimal scarring. The procedure is considered safe with a low-risk profile [14]. While the results of fat grafting are immediate and noticeable, most of the grafted fat does not survive the initial period after grafting. Over the first several weeks and months, the fat cells may be reabsorbed by the body, and the results of the procedure may not be as notice-

able as they were immediately after the procedure [5].

Despite optimizing conventional fat grafting, additional fat grafting procedures are often needed to achieve a desired cosmetic result [15,16]. To avoid this, researchers have investigated multiple angles to improve fat grafts (**Figure 1**). One of the more promising is the supplementation of stem cell products to improve graft retention and provide patients with a more reliable and natural outcome.

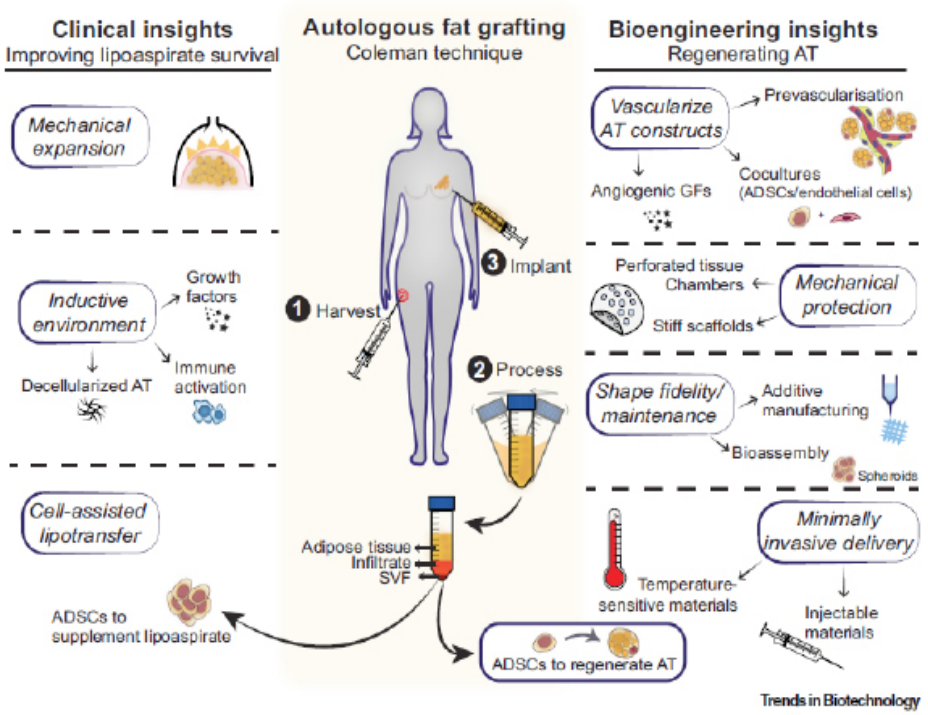



Image published by Major et al. 2+21 Trends in Bio Tech. Demonstrates the various areas of investigation for fat grafting (17).

**Figure 1:** Fat grafting – Areas of investigation.

## 1. Stromal vascular fraction

### 1.1. The procedure

The most investigated cell product in fat grafting is the stromal vascular fraction (SVF). Adipose-derived SVF is defined as the cell pellet within adipose tissue [18,19]. To isolate the cell pellet, one must first harvest fat. Enzymes such as collagenase or mechanical sheer are applied to harvested fat tissue to separate the cells from the extracellular matrix (ECM) [20,21]. The processed fat is centrifuged to separate the lipid layer, connective tissue, aqueous layer, and, at the bottom, the cell pellet – the SVF (**Figure 2**). The process takes from minutes to a couple of hours depending on the isolation method, and the SVF can be collected from the bottom of the centrifugation vessel after centrifugation. The SVF pellet is mixed with freshly harvested fat and injected in the same structural manner as it is performed for conventional fat grafting. The procedure is performed in a single step but can lengthen the surgical time due to the additional isolation steps.

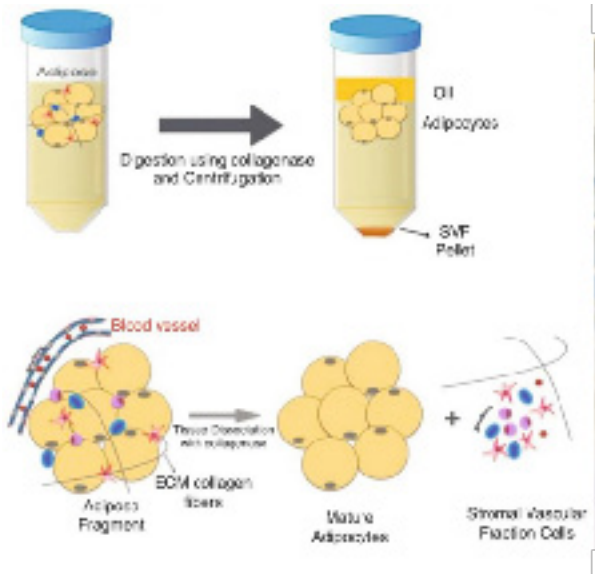



Image published by London spine Unit 2019. Demonstrates the process of SVF isolation.

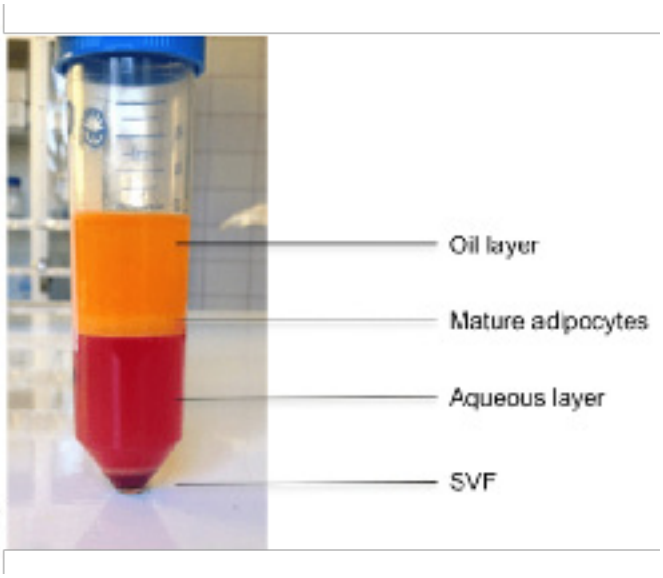



Image published by Malec et al. 2013. Int. Jour. Nano Med. Demonstration of the components of adipose tissue after enzymatic digestion and centrifugation (22)

**Figure 2:** SVF cell pellet.

## 1.2. Mode of action

The SVF comprises a heterogenic population of cells, including adipocytes, preadipocytes, macrophages, endothelial cells, fibroblasts, and mesenchymal stem cells (MSC(AT)). Additionally, SVF contains numerous growth factors, cytokines, and other factors that help promote cell survival, proliferation, and differentiation [23]. Several proposals have been made to explain why SVF could improve fat graft retention. First, SVF cells have been proven to withstand the ischaemic environment after engraftment better than adipocytes and to facilitate neoangiogenesis and adipogenesis crucial for the integration and survival of the fat graft [24,25]. Another potential mode of action is the anti-inflammatory effect by regulation of various cytokines and macrophage conversion [26]. The heterogenic cell population can vary in composition and cell numbers, and the clinician must pay attention to the quality of the SVF before use.

## 1.2. Surgeon and facility demand

The process of SVF isolation can be time consuming, as the SVF must be isolated from the extracellular matrix and fluids. However, some time can be used to harvest additional fat, thus minimizing or eradicating the time extension of the surgery. SVF isolation requires training and commitment by the surgeon and nursing staff, which can hinder some advancement in treatment. Furthermore, additional equipment may have to be purchased, such as an incubator, enzymes or a mechanical isolation device, and a centrifuge, thus complicating the availability of the procedure.

## 1.3. Safety of SVF

In addition to the oncological concerns regarding conventional fat grafting [27], there is

an ongoing debate regarding the possible oncological risks after autologous fat grafting with cell enrichment. In this respect, clinical studies investigating SVF-enriched fat tissue in breast augmentation and in patients with volume defects after breast cancer surgery have shown no increased incidence of cancer recurrence [28]. Thousands of patients in more than 500 clinical studies have received MSC(AT) (as SVF or expanded) without reports of serious adverse events (29).

### 1.4. Clinical outcomes

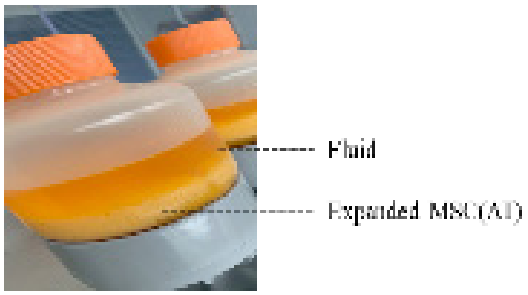
The proposed mode of action for SVF-enriched fat grafting is aimed at improving fat graft retention. Naturally, the most important outcome is therefore the retention rate. Although it can be difficult to evaluate results between studies due to the large number of factors in the fat processing technique prior to injection and intersurgeon variance, most randomized controlled clinical trials report degrees of improved fat graft retention, with some showing no statistical improvements [24,31–33]. There has been speculation as to whether the number of SVF cells contributes to the difference in findings. Dos Anjos et al. reported improved graft retention of higher numbers of SVF cells compared to a lower SVF cell dose and also reported the benefit of increasing the number of SVF cells per ml of fat [34]. The issue with SVF is that patients do not have unlimited fat reserves, thereby restricting the amount of fat available for isolation. In addition, isolating a large amount of SVF is time consuming and can leave patients with low amounts of fat for grafting. The SVF is a heterogenic cell population, as mentioned earlier in the chapter. The proposed effects of SVF have largely contributed to the MSC(AT) fraction of the SVF. To utilize the potential of MSC(AT), researchers have succeeded in culturing MSC(AT) from SVF, thereby significantly expanding the number of cells.

## 2. Mesenchymal Stem Cells

### 2.1 The procedure

The expansion of MSC(AT)s is comprehensive and requires isolation of SVF and a couple of weeks of ex vivo culture. This cannot be performed in a standard hospital setting, as it requires special laboratory equipment and regulations. However, for surgeons, the procedure is simplified, as the harvested lipoaspirate can be sent to a manufacturer with the required approvals. The surgeon does not have to learn SVF isolation techniques but will harvest a small amount of lipoaspirate, approximately 150 ml, to send to the stem cell manufacturer, and a couple of weeks later, the patient can be booked for a second surgery to harvest fat for the reconstruction or augmentation procedure. The autologous ex vivo expanded MSC(AT)s will be delivered to the hospital and can be sterilely unpackaged and placed on the operating table. The MSC(AT)s are mixed with freshly harvested and washed fat and injected following the standard structural fat grafting techniques as are used for the SVF and conventional fat grafting procedure. The MSC(AT) product comprises 200 million MSC(AT)s per millilitre,

and researchers have achieved expansion of more than 16 billion MSC(AT)s per patient during three weeks of expansion (**Figure 3**).




(Unpublished image of >12 billion expanded MSC(AT)s from StemMedical archives)

**Figure 3:** Ex vivo expanded MSC(AT)s pellet.

## 2.2 Mode of Action

MSCs are multipotent "spindle shape" adult cells that reside in many connective tissues, including bone marrow and adipose tissue MSC(AT) (35–38). These cells have high growth potential and can differentiate into adipose, bone, cartilage, tendon, skin, endothelial, and muscle tissue (**Figure 4**).

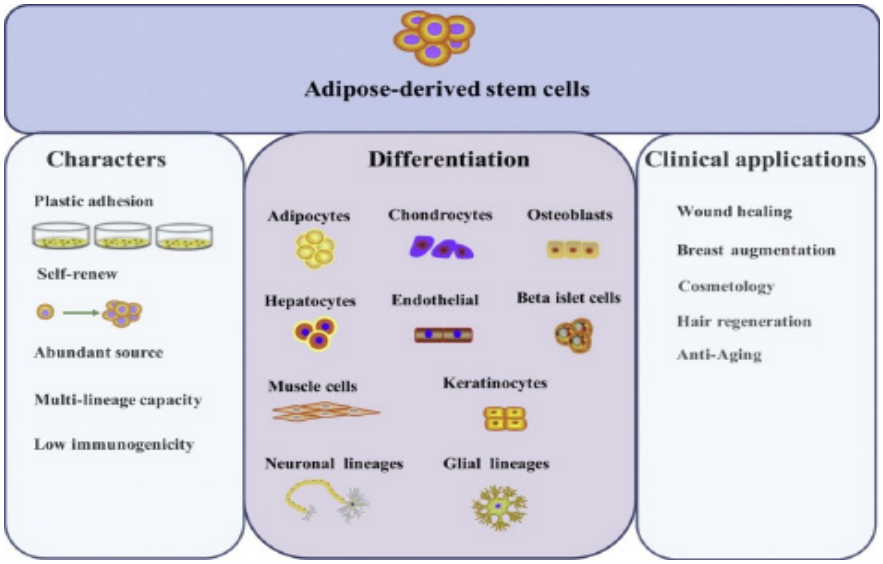



Image published by Si et al. 2019. Bio. Med. and Pharm. Thera. Demonstrates the clinical regenerative clinical application for MSC(AT) (39).

**Figure 4:** MSC(AT) properties.

MSCs have similarities with adventitial cells and perivascular pericytes, which are found near small vessels and play a role in inflammation homeostasis and tissue regeneration [40,41]. Currently, there is no specific marker for MSCs. To define them, the International Society for Cell and Gene Therapy (ISCT) and International Federation for Adipose Therapeutics and Science (IFATS) have suggested a set of minimal criteria that includes adherence to a plastic culture surface, expression of the surface markers CD73, CD90, CD105 and absence of primarily haematopoietic surface markers CD14, CD34, CD45; for MSC(AT), CD45 and CD31 should be excluded, and there should be potential to differentiate in vitro into adipocytes, chondroblasts and osteoblasts when subjected to the proper inductive factors and culturing media [18,42].

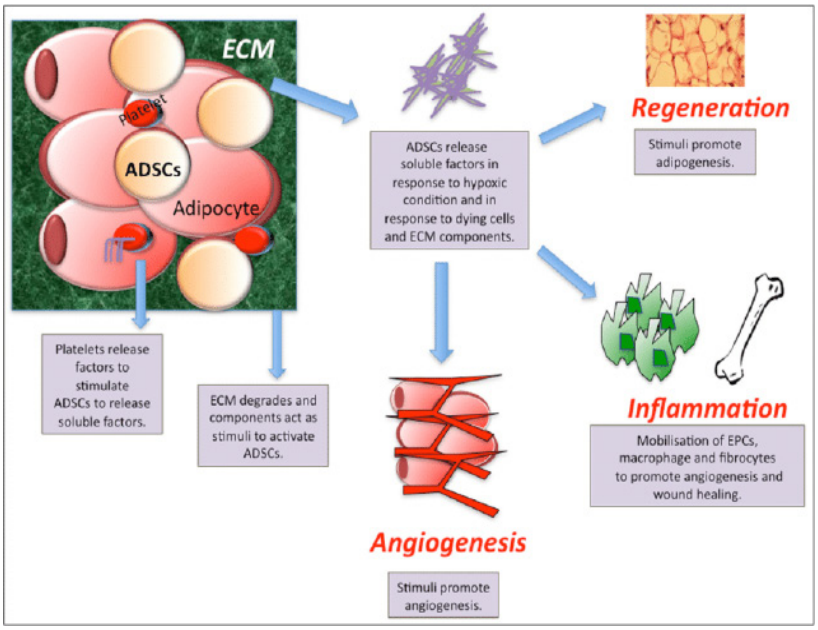



Image published by Griffin et al. 2014. Stem Cell Rev and Rep. This study demonstrates the proposed mechanism for improved fat retention using MSC(AT) (43).

**Figure 5:** MSC(AT) mode of action.

In addition to their ability to differentiate, MSCs, including MSC(AT)s, have been found to stimulate innate tissue repair, modulate immune and inflammatory responses, support stem and progenitor cell growth and differentiation and have antifibrotic, antiapoptotic and angiogenetic effects [44] (**Figure 5**). These effects have been demonstrated to be mediated by cell contact-dependent mechanisms and by secreted factors [45].

## 2.3 Surgeon and facility demand

The surgeon must perform an additional 100-150 ml small liposuction on the patient a couple of weeks before the fat grafting procedure to allow time for expansion of the MSC(AT)s. In the operating theatre, the surgical time is the same as for conventional fat grafting procedures plus an additional five minutes for mixing of the expanded MSC(AT)s and fat. The facility must ship lipoaspirate and receive expanded MSC(AT)s.

## 2.4 Safety

The primary concern regarding stem cell therapies is the oncological risk. For MSC(AT)s, the oncological risks have been assessed, especially with respect to increasing angiogenesis after autologous fat grafting with or without the addition of *ex vivo* expanded MSC(AT)s [14,46–49]. No clinical findings have suggested increased oncological risk; however, the ability of MSC(AT)s to promote angiogenesis has prevented researchers from treating patients in oncological breast follow-up programs. Apart from theoretical de novo MSC(AT)-derived tumorigenesis, several studies have investigated the possible effect of MSC on tumour growth. A range of in vitro and in vivo animal studies have been conducted with different types of cancer cells cocultured or cotransplanted with MSCs. No conclusions have been made thus far because MSCs have shown both promoting and inhibitory effects on tumour cell growth

[50,51]. Additionally, there are no data indicating that malignant transformation of expanded human MSCs occurs [50]. An in vitro study demonstrated no signs of chromosome abnormalities, as indicated by array comparative genomic hybridization analyses in cultured MSC(AT)s [52]. As reflected in the literature, more than 1000 patients in clinical studies have received MSC (AT)s, and no serious adverse events have been reported. This is in addition to a more recent publication, cited above, in which more than 950 registered MSC clinical studies were listed with the FDA, with more than 10,000 treated participants showing no safety issues [53]. Additionally, a very high MSC(AT) dose ($240 \times 10^6$ MSC(AT)s per kilogram) was tested in a murine study and produced no signs of cancer, organ toxicity, or changes in body weight after 12 months [54]. However, long-term follow-up of human recipients is still needed.

### 2.5 Clinical outcomes

Only a few clinical studies have been published investigating ex vivo expanded MSC(AT)s in fat grafting. The first study by Kølle et al. demonstrated significant improvement in fat graft retention when enriching a bolus injection of fat with approximately $20x10^6$ MSC(AT)s per ml of fat compared to conventional fat grafts. The results showed 80.9% graft retention in the MSC(AT)-enriched group compared to 16.3% in controls with conventional fat grafts [55]. The same author later validated the findings in a clinically relevant breast augmentation setting where participants received MSC(AT)-enriched fat grafts or conventional fat grafts. The study reported graft retention rates of 80.2% and 45.1% in the enriched and conventional groups, respectively. Another clinical study was conducted but did not show any effect of adding $10x10^6$ MSC(AT) per ml of fat for breast augmentations. The study reported 54.0% retention for enriched grafts vs. 55.9% for conventional fat grafts [56]. The reason for the negative results published by Vester-Glovinski has been discussed in the response by Kølle et al. [57]. The essence of the discussion is that the implementation of an ex vivo expanded product is subject to variation depending on the culture, handling and preparation.

## 3. Summary of differences (SVF vs. MSC(AT)s)

The differences between the two cell products are noteworthy. First, SVF is a heterogeneous cell population with approximately 10-40% MSC(AT)s, and expanded MSC(AT)s are a homogeneous cell solution with >95% MSC(AT)s. Second, the number of cells is different between the two cell products. SVF contains approximately 100,000 cells per ml of fat corresponding to 10,000 to 40,000 MSC(AT)s [58]. On the other hand, from one ml of fat, homogeneous ex vivo expanded MSC(AT)s produce more than 1,200,000,000 MCS(AT)s [59]. Third, the expanded MSC(AT)s are morphologically different from those of the MSC(AT)s found in SVF [60] (**Figure 6**). Fourth, MSC(AT)s in culture express different surface markers than MSC(AT)s found in SVF [61]. Fifth, SVF-enriched fat grafting is a one-step procedure, whereas the MSC(AT) approach is a two-step procedure.

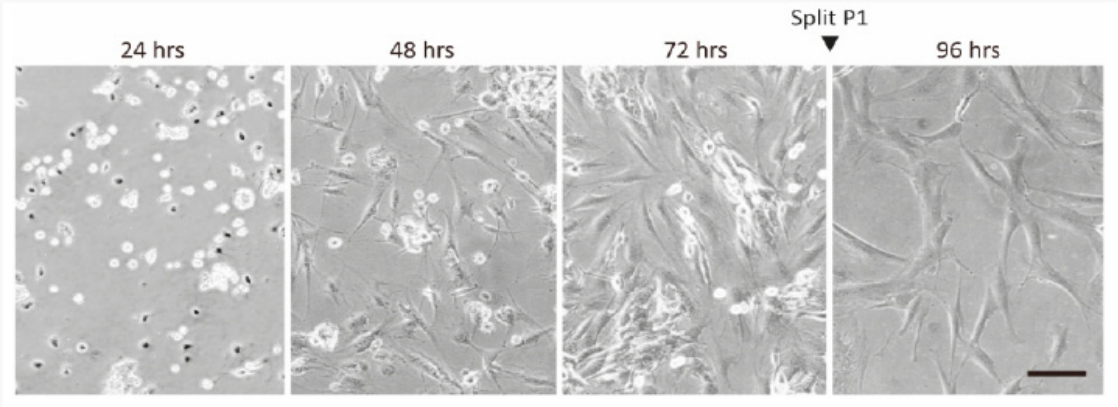



Image published by Peng et al. 2020. Int. J. Mol. Sci. Showing SVF that has been seeded in culture after 24 hours. The cell population is clearly heterogenic compared to the passaged MSC(AT)s shown after 96 hours. (62)

**Figure 6:** Morphology of SVF and expanded MSC(AT)s.

**Table 1:** Differences between SVF- and MSC(AT)-enriched fat grafting.

| Procedure | SVF | MSC(AT) |
|---|---|---|
| Surgical time | Can extend the surgical time substantially | Near equal to conventional fat grafting |
| Procedures | One-Step | Two-step |
| Procedure difficulty | Multiple additional steps to isolate the SVF, making it difficult | An easy mixing step |

## Call-to-action

SVF and MSC(AT) are currently being investigated with encouraging clinical efficacy in fat grafting. However, the mechanisms contributing to the beneficial effects are mostly thought to be contributed by the MSC(AT)s found in the SVF or ex vivo expanded MSC(AT)s themselves. The authors encourage other researchers to investigate the mechanisms responsible for the reported fat graft retention in clinical studies by collection of tissue samples for analysis in future RCTs. The proposed mechanisms are yet to be fully understood and the results of vascularization, cellular resilience, and the fate of SVF and MSC(AT)s still require investigation in human trials to obtain knowledge and understanding about the treatment in order to translate the findings from in vitro and animal studies.

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