The power of fat and its adipose-derived stromal cells: emerging concepts for fibrotic scar treatment

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Lipofilling or lipografting is a novel and promising treatment method for reduction or prevention of dermal scars after injury. Ample anecdotal evidence from case reports supports the scar-reducing properties of adipose tissue grafts. However, only a few properly controlled and designed clinical trials have been conducted thus far on this topic. Also the underlying mechanism, by which lipofilling improves scar aspect and reduces neuropathic scar pain, remains largely undiscovered. Adipose-derived stromal or stem cells are often described to be responsible for this therapeutic effect of lipofilling. We review the recent literature and discuss anticipated mechanisms that govern anti-scarring capacity of adipose tissue and its adipose-derived stem/stromal cells. Both clinical and animal studies clearly demonstrated that lipofilling and ADSC influence processes associated with wound healing including extracellular matrix remodeling, angiogenesis and modulation of inflammation in dermal scars. However, randomized clinical trials, providing sufficient level of evidence for lipofilling and/or ADSC as an anti-scarring treatment, are lacking yet warranted in the near future.

Transfer of adipose tissue, also known as fat grafting, lipografting or lipofilling is recognized as a promising and novel technique for correction of volume deficiency, skin rejuvenation and as treatment for scars. This is strongly supported by evidence-based clinical trials as well as fundamental studies in animals and in vitro. The first case of lipofilling in literature dates from 1893, when Gustav Neuber described the first free fat transfer for a scar which had left a young man with a soft tissue defect of the face.

As soon as liposuction was further developed in the mid 1980’s, also interest developed of re-using the lipoaspirated subcutaneous adipose tissue. Liposuction pioneers such as Illouz and co-workers developed the first clinical applications and methods for lipofilling to restore or gain volume. The real breakthrough in lipofilling came with fat harvesting, subsequent processing and subcutaneous administration as described by Coleman, which allowed better survival of the lipograft. Centrifugation was the first successful attempt to improve fat graft survival by removing oil, fluid and dead cells from the harvested fat tissue. This method also inspired clinical trials to assess volumetric augmentation of the breast and buttocks.

Initially, introduced by Coleman in the early nineties, the use of small liposuction and lipofilling cannulas also opened the door for lipofilling of the face and hands for both reconstructive and aesthetic purposes. Especially in these applications with rather superficial lipofilling, effects described as ‘more than volume alone’ were often observed. This included an improved appearance and quality of the skin and has subsequently been described in many case reports. Yet a mechanistic underpinning was still lacking. These clinical observations initiated a wide range of clinical applications for lipofilling other than just volume adjustment. This novel idea to use lipofilling for treatment of (the consequences of) tissue damage, has led to the use of lipofilling to treat burn scars and even to alleviate scar-associated pain as occurring e.g. after mastectomy.

In 2001, Zuk and colleagues demonstrated that adipose tissue had a source of endogenous mesenchymal stem cells, which were named adipose-derived stem or stromal cells (ADSC). This discovery significantly advanced the use of lipofilling as a regenerative therapy, as it had been shown that at least one of the components of adipose tissue had therapeutic potential. Since then, many of the beneficial effects observed after lipofilling have been attributed to ADSC.

In this review the authors, both clinicians and biologist, try to bridge the gap between both worlds, provide a review of recent literature and summarize possible mechanisms behind the anti-scarring effect of adipose tissue and its adipose-derived stem/stromal cells.
Adipose tissue, the energy storehouse of the human body, consists of a parenchymal mass of adipocytes that is structurally supported by connective tissue and perfused by blood vessels. All non-adipocyte tissue is called stroma or stromal tissue. Adipocytes are the main volumetric component of adipose tissue although they only comprise up to 20% of all cells. Adipocytes consist of a thin layer of cytoplasm with an eccentric nucleus, while most of the volume is made up by the large central vacuole in which triglycerides predominantly are stored. Adipocytes are sensitive to hypoxia and as a consequence prone to apoptosis. Depending on the technique and time that is required for harvesting and lipofilling, 40-90% of the injected lipograft volume will remain, while the rest is resorbed within months after grafting. Oily cysts may remain in the grafted area as a consequence of this fat necrosis. To improve fat graft survival, different processing techniques are used (e.g. centrifugation, decantation, gauze-towel technique). In a systematic review, these techniques are compared for viability of the fat graft as a whole in terms of number of viable cells and in terms of graft volume survival in human and animal models. For fat graft survival, the gauze-towel processing technique is found to be superior to centrifugation or decantation. However, if the focus lies on the number of ADSC in adipose grafts, centrifugation improves the number of ADSC that can be isolated, compared to a non-centrifuged fat. Thus, depending on the goal of lipofilling, different fat processing techniques need to be considered carefully.

During development, adipose tissue is derived from the mesodermal germ layer. The mesenchymal stem cells (MSC) that reside in the mesoderm differentiate into adipocytes to form adipose tissue. However, after the embryogenic formation of adipose tissue, some of the mesenchymal stem or stromal cells remain. In the adult situation, these MSC are the previously mentioned ADSC. In the adipose tissue, ADSC reside around the vasculature. Furthermore, ADSC retain the ability to differentiate into adipocytes, thus functioning as a source to regenerate adipose tissue.

Liposuction simply implicates the harvest of adipose tissue under negative pressure with small-bore suction cannulas. By this, the architecture of the fat tissue is disrupted and small lumps of adipose tissue are harvested and collected in a sterile environment (bag or collector), which can then be used for lipofilling subsequently. Inevitably, some degree of hypoxia occurs around the grafting of the lipospirate. In the recipient, the integration of the graft requires extensive (re)vascularization, which is primed by the occurring hypoxia as well as by the pre-existing microvasculature in the graft. Too large ‘lumps’ of lipograft obviously develop necrotic cores due to diffusion insufficiency, as a result of which the graft ‘take’ may be reduced. Adipocytes are sensitive to hypoxia and as a consequence prone to apoptosis. Depending on the technique and time that is required for harvesting and lipofilling, 40-90% of the injected lipograft volume will remain, while the rest is resorbed within months after grafting. Oily cysts may remain in the grafted area as a consequence of this fat necrosis. To improve fat graft survival, different processing techniques are used (e.g. centrifugation, decantation, gauze-towel technique). In a systematic review, these techniques are compared for viability of the fat graft as a whole in terms of number of viable cells and in terms of graft volume survival in human and animal models. For fat graft survival, the gauze-towel processing technique is found to be superior to centrifugation or decantation. However, if the focus lies on the number of ADSC in adipose grafts, centrifugation improves the number of ADSC that can be isolated, compared to a non-centrifuged fat. Thus, depending on the goal of lipofilling, different fat processing techniques need to be considered carefully.

Clinical studies
Clinical efficacy of lipofilling in scar areas is determined either by improvement of the appearance of a scar, such as size, thickness, stiffness, discoloration of the scar. In the case of painful scars, this effect can also be measured by a decrease in pain. In the first subsection of this summary of clinical studies, the focus lies on the ability of lipografts to improve several of the above mentioned appearance of scars, whereas in the second subsection focus lies on the ability to reduce pain.

Scar appearance
Macroscopically, scars are characterized by different appearance than the surrounding skin: discoloration, stiffness and roughness are features of scarring. In clinical studies, different outcome measures are used to quantify the degree of scarring on a macroscopic level. The first method often used to assess scar severity are patient or observer rated grading scales, in which several aspects of scarring (e.g. color, stiffness, thickness, irregularity) are rated. A second method is to use measuring devices for skin elasticity or dermal pigmentation.

As stated above, lipofilling is beneficial for skin and scar treatment. In recent years, a limited number of retrospective and prospective supported previous anecdotal clinical observation (Table 1).

Clinical studies
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The efficacy of lipofilling to improve scar appearance has been investigated in sixteen case reports or clinical trials (see Table 1). In ten studies of these publications, comprising of a total of 156 patients, complications were recorded: in nine of these ten studies, no complications were recorded whereas in one study with 12 patients there was a case of cellulitis reported as a complication. Hence, it seems that risks of lipofilling in scar areas is rather low. All fourteen case reports or clinical trials reported some degree of amelioration in scar appearance after lipofilling: in other words, scars became less different from normal skin and/or became less visible. However, overall result of these clinical studies is not unequivocal. Firstly, not all studies use the same outcome measurements to report scar appearance: most studies used patient satisfaction or patient and observer rated grading scales for scar severity to report the effect of lipofilling, whereas other studies used measuring devices for skin elasticity or dermal pigmentation. Secondly, whether or not there is improvement in scar appearance varies within these studies: some studies report improvement in most patients, contrasted by no effect in a few other patients. Lastly, also, within the same study, improvement after lipofilling in one outcome measure (e.g. less stiffness of the scar) is reported, but there is no improvement in other outcome measures (e.g. no improvement in discoloration). Thus, the overall trend is that lipofilling improves scar appearance in several different outcome measures, which is confirmed by two systematic reviews. However, due to lack of uniformity in intervention and follow up, no definitive conclusions can be drawn. Only five well designed controlled studies had well-defined objectives and outcome parameters and had included both non-treated or placebo controls. Four of these studies focused on clinical outcomes and are discussed below and one addresses histological changes and is discussed in the next section.
Table 1a | Clinical studies on lipofilling to improve scar appearance

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
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<tbody>
<tr>
<td>Balkin et al. 2014</td>
<td>Retrospective, controlled</td>
<td>Patients with cleft lip repair (n=30, 37 sides), Immediately treated.</td>
<td>Intervention: submu-coal, subcutaneous, intra-muscular and periosteal lipofilling (n=20) Control: no lipofilling treatment (n=10)</td>
<td>Photographic analysis by 3 independent observers using a visual 5-grade scale (mean follow-up of 24.7 months).</td>
<td>Less cleft lip related deformity in overall facial, upper lip, nose and midface appearance in treated group.*</td>
<td>No complications reported</td>
</tr>
<tr>
<td>Benjamin et al. 2015</td>
<td>Case-report</td>
<td>1 Patient with scarring of the lower extremity after trauma.</td>
<td>Intervention: subcutaneous lipofilling (2 interventions)</td>
<td>Visual evaluation of the lower extremity.</td>
<td>Patient noted improvement in mobility and appearance, less neuralgic pain,</td>
<td>No complications reported</td>
</tr>
<tr>
<td>Bollero et al. 2014</td>
<td>Prospective, non-controlled, non-blinded, non-randomized</td>
<td>Patients with scars after trauma (n=19).</td>
<td>Intervention: subcutaneous lipofilling (28 interventions)</td>
<td>Visual evaluation of photographs (pre-operative, 1 month and 3 months postoperative).</td>
<td>Among 28 interventions, 24 showed visual improvement in skin quality. 1 case showed improvement initially, but not after 3 months.</td>
<td>No complications reported</td>
</tr>
<tr>
<td>Bruno et al. 2013</td>
<td>Prospective, controlled, non-blinded, non-randomized</td>
<td>Patients with burn wound scars (n=93 scars). Mean scar age of 2.3 years.</td>
<td>Intervention: intra-and subcutaneous lipofilling (n=93) Control: saline injection (n=93)</td>
<td>Immunohistochemical analysis of scar biopsies, subjective evaluation using a questionnaire, photographic analysis by independent observers using the VSS (preoperative, 3 months and 6 months postoperative).</td>
<td>After 6 months, a decrease in Langenharhs cells and increase in P53 and Ki67. No difference in P67 count. Improvements in VSS scores from 41 (preoperative) to 15 (6 months postoperative) and questionnaire scores from 31 (preoperative) to 95 (6 months postoperative) compared to untreated group. The mobility improved*, but there was no grip strength and DASH improvement. A trend towards significant improvement in MHQ scores was noticed. A significant improvement in the POSAS scores was visible, except the scores for pain and itch.</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Byrne et al. 2015</td>
<td>Retrospective, non-controlled</td>
<td>Patients with burn wounds scars of hand (n=13). Mean scar age of 2.3 years.</td>
<td>Intervention: subdermal lipofilling</td>
<td>Aesthetic, functional and satisfaction scores were measured using a TAM (Goniometer), GSM (Dynamometer), DASH, MHQ and POSAS after 9.1 months (range 3 months – 1.3 years)</td>
<td>Improvement in skin quality, 5 cases obtained a score of 4 and 3 cases obtained a score of 3.</td>
<td>No complications reported</td>
</tr>
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Table 1a (continued) | Clinical studies on lipofilling to improve scar appearance

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<tr>
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<tr>
<td>Guisantes et al. 2012</td>
<td>Cases-report</td>
<td>Patients with retractile and dystrophic scars (n=8)</td>
<td>Intervention: intrascar lipofilling depending on treated area (11 interventions)</td>
<td>Photographic analysis by 2 independent observers using a visual 4-grade scale (mean follow-up of 18 months).</td>
<td>Improvement in skin quality, 5 cases obtained a score of 4 and 3 cases obtained a score of 3.</td>
<td>No complications reported</td>
</tr>
<tr>
<td>Klinger et al. 2008</td>
<td>Cases-report</td>
<td>Patients with scars as a result of hemifacial 2nd and 3rd degree burns (n=8)</td>
<td>Intervention: dermal-hypodermal junction lipofilling (2 interventions per patient)</td>
<td>Histological evaluation of scar biopsies and MRS (preoperative, 13 months postoperative during operation 2, 3 months postoperative).</td>
<td>Histological improvement; patterns of new collagen deposition and more dermal hyperplasia and neoangiogenesis. Presence of amniotic structures is nearly normal. MRS revealed similar signal enhancement of soft tissue between affected and unaffected facial sides.</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Maione et al. 2014</td>
<td>Prospective, controlled, non-blinded, non-randomized</td>
<td>Patients with short limb deformity syndrome presented with retractile and painful scars (age &gt;1 year) cured by surgical procedures (n=98).</td>
<td>Intervention: dermal-hypodermal junction lipofilling (n=36) Control: saline injection (n=36)</td>
<td>A modified POSAS and durometer measurements to measure skin hardness were performed (preoperative and 3 months postoperative).</td>
<td>Reduction of scar hardness after treatment*, while no significant reduction occurred in the control group. Reduction of all POSAS parameters, except itching in the treatment group.* No POSAS scores in control group reported.</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Mazza et al. 2013</td>
<td>Retrospective, non-controlled</td>
<td>Patients who underwent tracheostomy healed by secondary intention resulting in a retracting scar (n=1). Scar age of 4-10 years.</td>
<td>Intervention: lipofilling in the plane between skin and subcutaneous tissue (2 interventions, interval of 6-12 months)</td>
<td>Evaluation of patient satisfaction (mean follow up of 21.3 months)</td>
<td>Patients described functional and aesthetic improvement and were all satisfied. 2 cases with severe retraction needed a additional lipofilling procedure.</td>
<td>No complications reported</td>
</tr>
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<td>Pallua et al. 2014</td>
<td>Prospective, non-controlled, non-blinded, non-randomized</td>
<td>Patients with facial scars of different causes (n=35)</td>
<td>Intervention: subcutaneous lipofilling</td>
<td>A POSAS, tissue oxygen saturation, hemoglobin levels and microcirculation (Doppler spectrometry) measurements performed (pre-operative, 1 month, 3 months, 6 months and 12 months follow-up).</td>
<td>Improvement in overall POSAS scores, both patient score as observer score.** Only 12 months scores mentioned. Early postoperative measurements revealed increased hemoglobin levels and reduced microcirculation, but both normalized after 7-90 days.</td>
<td>No complications reported</td>
</tr>
<tr>
<td>Phulpin et al. 2009</td>
<td>Retrospective, non-controlled</td>
<td>Patients with aesthetic subcutaneous or sub-mucous head and neck reconstruction after radiotherapy (n=11).</td>
<td>Intervention: subcutaneous lipofilling</td>
<td>Aesthetic and functional scores were measured using a 5-grade scale (mean follow-up of 39.9 months).</td>
<td>Skin scoring tests revealed more softness, more pliability and improvement of skin quality of the irradiated skin. No scores mentioned.</td>
<td>No complications reported</td>
</tr>
<tr>
<td>Ribuffo et al. 2013</td>
<td>Retrospective, controlled</td>
<td>Patients underwent MRM and IIBR + PMRT (n=32). Lipofilling performed 6 weeks after PMRT.</td>
<td>Intervention: deep and superficial subcutaneous lipofilling</td>
<td>Capsular contracture was measured using Baker’s classification. Patients’ satisfaction was evaluated using a 3-grade scale. (Mean follow-up of 18 months).</td>
<td>7 complications reported in the control group compared to none in the lipofilling group.* Higher capsular contracture rates in the control group compared to the lipofilling group. Patient satisfaction increased, but no scores were mentioned.</td>
<td>No complications reported</td>
</tr>
<tr>
<td>Sardesai et al. 2007</td>
<td>Prospective, non-controlled, non-blinded, non-randomized</td>
<td>Patients with various scar types (n=14). Scar age of &gt;1 year, 8.5 years on average.</td>
<td>Intervention: subcutaneous lipofilling</td>
<td>Dermal elasticity (Custometer), vascularity and pigmentation (Dermaspectrometer) measured. Patients’ perception (POAS) and observers’ perceptions (POAS and VSS) evaluated. Preoperative and 12-16 months postoperative.</td>
<td>Increase of dermal elasticity** and no difference in vasculation and pigmentation. Decrease of scar stiffness and thickness in patients’ perception.** * Less relief and pliability in observers’ perception using a POSAS, pliability decrease was confirmed using a VSS.** No differences in vascularization and pigmentation (POAS and VSS).</td>
<td>Not mentioned</td>
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</tbody>
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Table 1a (continued) | Clinical studies on lipofilling to improve scar appearance

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<tr>
<td>Wang et al. 2013</td>
<td>Retrospective, non-controlled</td>
<td>Patients with bilateral gluteal concave deformities associated with intragluteal injections. (n=12)</td>
<td>Intervention: deep, intermediate and superficial layer lipofilling of the gluteal</td>
<td>Effect of fat grafting on the skin was evaluated by severity of irregularity, quality of skin patterns and visual impact. Overall satisfaction was evaluated using a 5-grade scale. (Follow up of 3-44 months).</td>
<td>9 cases scored 4-5 and 3 cases scored 3 on the satisfaction scale after treatment. Improvement in skin texture was observed in all cases. Softening of hypertrophic scars was observed, started 1 month postoperative and continued to 12 months postoperative. No preoperative scores mentioned.</td>
<td>1 case with cellulitis in the feet and calves</td>
</tr>
<tr>
<td>Zellner et al. 2014</td>
<td>Retrospective, controlled</td>
<td>Patients with cleft lip repair (n=35, 44 sides). Immediately treated with lipofilling.</td>
<td>Intervention: submucoanal, subcutaneous, intra-muscular and periosteal lipofilling (n=19)</td>
<td>Control: no lipofilling treatment (n=16)</td>
<td>Photographic analysis by 3 independent observers using a visual 5-grade scale (mean follow-up of 266 days).</td>
<td>9 cases scored 4-5 and 3 cases scored 3 on the satisfaction scale after treatment. Improvement in skin texture was observed in all cases. Softening of hypertrophic scars was observed, started 1 month postoperative and continued to 12 months postoperative. No preoperative scores mentioned.</td>
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Abbreviations: VSS = Vancouver Scar Scale, TAM = Total Active Movement, GSM = Grip Strength Measurement, DASH = The Disabilities of the Arm, Shoulder and Hand, MHQ = Michigan Hand outcome Questionnaire, POSAS = Patient and Observer Scar Assessment Scale, MRS = Magnetic Resonance Scan, MRM = Modified Radical Mastectomy, IIBR = Immediate Implant-Based Reconstruction,

* Significant difference (p<0.05)  
** Significant difference (p<0.001)
In two studies, performed under supervision of the same senior researcher27,37, the effect of lipofilling as adjuvant procedure to reduce formation of new scars after surgery is evaluated. During primary cleft lip repair surgery, efficacy of lipofilling is examined by comparison of pre- and post-operative pictures for residual cleft stigmata by a blinded reviewer panel. Compared to primary cleft lip repair without lipofilling, it resulted in significantly less residual cleft stigmata and thus in better scar appearance. Apparently lipofilling led to reduction of scar formation. Also already existing scars can be treated by means of lipofilling: in prosthetic breast reconstruction in the setting of post mastectomy radiotherapy, post-radiotherapy lipofilling can reduce the degree of capsular contracture as measured by the Baker classification44. Here, lipofilling apparently is able to prevent or even (partially) revert the fibrotic process of capsular contracture. Another example is the treatment of post-surgical scars in patients with achondroplasia that require surgical limb lengthening45. In this study, lipofilling was compared to saline injection: lipofilling significantly increased skin pliability and all but one parameter of the patient and observer scar assessment scale improved. Thus, lipofilling apparently improves appearance of scars.

Pain reduction

Efficacy of lipofilling as a means for pain reduction was investigated in six case reports or studies3,9,41-45 (see Table 1b). No complications were recorded in six of seven studies with a total of 204 patients; one study did not mention any complications. All studies reported a significant reduction of pain after treatment of painful scars: only in two of these studies there was no difference found in one41 and in two45 patients out of the entire population. Three studies included control groups, where lipofilling was compared to no treatment41,44,45. Two of these studies, performed at the same institute, focused on lipofilling as treatment for neuropathic pain after total mastectomy27 or breast conserving surgery42. In both studies, it was shown that lipofilling can reduce pain as measured on a visual analogue scale by approximately 3 points in the lipofilling group, compared to about 1 point in the control group. The third study compared results with a representative patient cohort: women who have undergone breast reconstruction and irradiation after mastectomy44. In the lipofilling group there was a significant improvement of all parameters of the LENT-SOMA classification (pain, telangiectasias, breast edema, atrophy and fibrosis) after treatment. For unknown reasons, the authors did not compare and analyze the treatment group with a control group, still but they concluded that lipofilling leads to pain relief as well as amelioration of scar appearance.

Influence of lipofilling in scars at the tissue level

Microscopically, scars display a loss of rete ridges, sebaceous glands and hair follicles. Also, they are characterized by increased dermal and epidermal thickness. The epidermal thickening is caused by excessive proliferation of keratinocytes. In the dermis, the thickening is caused by excessive ECM production by myofibroblasts, mainly consisting of collagen type I44. Not only is there an increase in the amount of collagens, but also in the collagen fiber thickness, maturation and degree of disorganization46,47. Even though there is an increase in the amount of ECM in scarring, some components of normal skin (e.g. elastin, decorin) are less abundant in scars49.

In two patient studies, skin biopsies have been acquired before and after treatment of scars with lipofilling23, one study evaluating a complete series of biopsies from a single patient4. After lipofilling, the general structure of the skin improved, collagen was remodeled, and there was an increase in vascularization.

In a large, placebo-controlled study, lipofilling in large burn scars was compared to saline injection49. In 96 patients, half of the scar was injected with saline (placebo or sham treated group), the other half was injected with lipoaspirate. Skin biopsies were taken and analyzed after three and six months. Overall, the histological structure of the scars reached near to that of normal skin: a better organization and alignment of collagen fibrils, better vascularization of the dermal papillae, less melanocytic activity in the epidermis and an increase of the amount of elastin fibers. On cellular level, there was an increase in cell divisions in the basal layer of the epidermis and Langerhans cells migrated downwards into this basal layer. Also, levels of pro-fibrotic factor Transforming Growth Factor beta 1 (TGF-β1) and pro-angiogenic factors Vascular Endothelial Growth Factor (VEGF) decreased.

In summary, histological improvement in scar appearance was noted in both studies, expressed as a plethora of changes on both histological as well as cellular level. However, why and how lipofilling results in the improvement of all these aforementioned aspects of scarring including pain reduction, remains to be elucidated.

Animal studies

In contrast to clinical studies thus far, experimental animal models have been able to demonstrate the mechanisms and influence of lipofilling on dermal scars, scar exterior and scar pain (table 2). Scar histology has been investigated in two studies using irradiation skin damage models in rodents40,51 (table 2A). Skin fibrosis after radiation in general is a clinical relevant problem, which can easily be reproduced in rodents. After radiation, dermatitis develops, which eventually gives rise to fibrotic skin characterized by epidermal thickening and irregular deposition of collagen in the dermis. Also, compared to normal skin, irradiated skin areas have an increased vessel density. In two studies in mice, it has been shown that treatment with lipofilling can reduce all these hallmark features of radiation-damaged skin40,51. Decrease in SMAD3 protein levels, a key protein in the pro-fibrotic pathway TGF-β/Smad signal transduction pathway, partly explains the mechanism of scar improvement40. In a slightly different model in mice with full thickness burn wounds, it has been shown that lipofilling leads to better scar appearance by increasing pro-angiogenic factors VEGF and stromal cell-derived factor 1 (SDF-1) and decreasing pro-fibrotic factor TGF-β142.
### Table 1b | Clinical studies on lipofilling to reduce pain

<table>
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<tr>
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<tr>
<td>Caviggioli et al. 2011</td>
<td>Retrospective, controlled</td>
<td>Patients with severe scar retraction and PMPS after mastectomy with auxiliary dissection and radiotherapy (n=113)</td>
<td>Intervention: dermal-hypodermal junction lipofilling (n=72) Control: no lipofilling treatment (n=41).</td>
<td>Pain evaluation using a VAS (mean follow-up of 13 months).</td>
<td>Decrease of pain in treated group compared to untreated group.**</td>
<td>No complications reported</td>
</tr>
<tr>
<td>Huang et al. 2015</td>
<td>Prospective, non-controlled, non-blinded, non-randomized</td>
<td>Patients with painful neuropathic scars with persistent symptoms (n=13). Range 3 months - 13 months</td>
<td>Intervention: dermal-hypodermal junction and subcutaneous lipofilling.</td>
<td>Pain evaluation using VAS and NPSI scores (pre-operative, 1 week, 4 weeks and 24 weeks postoperative).</td>
<td>Decrease of VAS and VSS scores after 1, 4 and 24 weeks compared to preoperative scores.** No other comparisons between postoperative measurements performed.</td>
<td>No complications reported</td>
</tr>
<tr>
<td>Klinger et al. 2013</td>
<td>Retrospective, semi-controlled, non-blinded, non-randomized</td>
<td>Patients with retractile and painful scars compromising daily activity (n=20). Scar age of &gt;2 years.</td>
<td>Intervention: dermo-hypodermic junction lipofilling. Control: saline injection.</td>
<td>Pain and skin quality of the scar was evaluated using the POSAS questionnaire (without central group). Scar hardness was measured using the durometer (with control group). Both after 3 months.</td>
<td>All POSAS scores (patient and observer scores) decreased significantly except for itching. Scars hardness decreased postoperative compared to preoperative in the treated group.* No significant decrease of scar hardness mentioned</td>
<td>No complications reported</td>
</tr>
<tr>
<td>Maione et al. 2014</td>
<td>Prospective, controlled, non-blinded, non-randomized</td>
<td>Patients with PMPS after lumpectomy and radiotherapy (n=96). Lipofilling performed &gt;1 year after radiotherapy.</td>
<td>Intervention: dermal-hypodermal junction lipofilling (n=59). Control: no lipofilling treatment (n=37).</td>
<td>Evaluation of spontaneous pain using a VAS (preoperative and 1 year postoperative).</td>
<td>A mean decrease of pain of 3.1 in the treated group and 0.9 in the control group. More decrease of pain in the treated group compared to the control group.**</td>
<td>No complications reported</td>
</tr>
<tr>
<td>Panettiere et al. 2009</td>
<td>Prospective, controlled, non-randomized</td>
<td>Patients with irradiated reconstructed breasts after mastectomy for carcinomas (n=61, 62 breasts).</td>
<td>Intervention: subscar lipofilling (serial interventions till patient was satisfied or result was stable). (n=20) Control: no lipofilling treatment (n=41).</td>
<td>Functional results were evaluated using the LENT-SOMA scoring system, 3 months after the last treatment.</td>
<td>Scores for pain, telangiectasia, breast edema, atrophy and fibrosis decreased in the intervention group after 3 months. Aesthetic results were evaluated using a 5-grade scale. No significant difference for above mentioned scores compared to the control group after 3 months. Aesthetic outcome improved in the intervention group compared to the control group.*</td>
<td>No significant complications reported</td>
</tr>
<tr>
<td>Rigotti et al. 2007</td>
<td>Prospective, non-controlled, non-blinded, non-randomized</td>
<td>Patients with side effects of radiotherapy with severe symptoms and irreversible function damage (LENT-SOMA scale grade 3 and 4) (n=20). Scar age 1-30 years.</td>
<td>Intervention: purified lipofilling.</td>
<td>LENT-SOMA grading scale scores evaluation (mean follow-up of 30 months).</td>
<td>Improvement in all patients, except 1 case. Reduction of LENT-SOMA grading scale scores.**</td>
<td>No complications reported</td>
</tr>
<tr>
<td>Ulrich et al. 2012</td>
<td>Prospective, non-controlled, non-randomized</td>
<td>Patients with painful episiotomy scars (n=20). Mean time after episiotomy was 10.3 months.</td>
<td>Intervention: subscar lipofilling.</td>
<td>Perineal pain evaluation using a MQPQ, a PPI and VAS. The SSSRS was used to evaluate the sexual satisfaction of the patients. (preoperative, 1, 3, and 6 months).</td>
<td>Reduction of pain after 1, 3 and 6 months in all pain questionnaires.* Improvement in sexual satisfaction after 1, 3 and 6 months.* No comparison performed between postoperative time points.</td>
<td>No major complications reported</td>
</tr>
</tbody>
</table>

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**Table 1b (continued) | Clinical studies on lipofilling to reduce pain**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Study population</th>
<th>Intervention</th>
<th>Follow up</th>
<th>Results</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panettiere et al. 2009</td>
<td>Prospective, controlled, non-randomized</td>
<td>Patients with irradiated reconstructed breasts after mastectomy for carcinomas (n=61, 62 breasts).</td>
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<td>Reduction of pain after 1, 3 and 6 months in all pain questionnaires.* Improvement in sexual satisfaction after 1, 3 and 6 months.* No comparison performed between postoperative time points.</td>
<td>No major complications reported</td>
</tr>
</tbody>
</table>

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**Abbreviations:** PMPS = Post-Mastectomy Pain Syndrome, VAS = Visual Analogue Scale, NPSI = Neuropathic Pain Symptom Inventory, VSS = Vancouver Scar Scale, POSAS = Patient and Observer Scar Assessment Scale, LENT-SOMA = Late Effects Normal Tissue Task Force (LENT)-Subjective, Objective, Management, Analytic, MQPQ = McGill Pain Questionnaire, PPI = Present Pain Intensity Index, SSSRS = Sabbatsberg Sexual Self-Rating Scale

* Significant difference (p<0.05)

** Significant difference (p<0.001)
### Table 2a | Animal studies on lipofilling to improve scar appearance

<table>
<thead>
<tr>
<th>Reference</th>
<th>Animal model</th>
<th>Intervention</th>
<th>Follow up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garza et al. 2014</td>
<td>Mouse</td>
<td>Radiation of scalp skin</td>
<td>Treatment: lipofilling (human adipose tissue) 4 weeks after irradiation. Control: no lipofilling and/or no radiation</td>
<td>Histology of skin for epidermal thickness (H&amp;E), collagen arrangement (picrosirius red) and vessel density (CD31), CT for fat graft retention. Histology of fat graft. Assessments 2 and/or 8 weeks after lipofilling.</td>
</tr>
<tr>
<td>Sultan et al. 2011</td>
<td>Mouse</td>
<td>Full thickness burn wound on dorsum</td>
<td>Treatment: lipofilling (human adipose tissue) 2 weeks after injury. Control: saline injection</td>
<td>Blood flow measurement by Laser-Doppler. Photographs. Histology for collagen arrangement (picrosirius red) and vessel density (CD31). Gene and protein expression analysis of skin. Assessment 4 and/or 8 weeks after lipofilling.</td>
</tr>
<tr>
<td>Sultan et al. 2011</td>
<td>Mouse</td>
<td>Radiation of dorsum skin</td>
<td>Treatment: lipofilling (human adipose tissue) 4 weeks after irradiation. Control: saline injection and/or no radiation</td>
<td>Photographs. Histology for epidermal thickness (H&amp;E), collagen arrangement (picrosirius red), vessel density (CD31) and pro-fibrotic marker (Smad3). All at 4 and/or 8 weeks after lipofilling.</td>
</tr>
</tbody>
</table>

**Abbreviations:** H&E = hematoxilin and eosin

### Table 2b | Animal studies on lipofilling to reduce pain

<table>
<thead>
<tr>
<th>Reference</th>
<th>Animal model</th>
<th>Intervention</th>
<th>Follow up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang et al. 2014</td>
<td>Rat</td>
<td>Full thickness burn wound of hind paw</td>
<td>Treatment: lipofilling (rat adipose tissue) 4 weeks after injury Controls: saline injection or no treatment, and/or sham burn wound.</td>
<td>Behavioral testing for neuropathic pain: paw withdrawal test with mechanical and heat stimuli. Histology of hind paw skin (H&amp;E, MTC) and of spinal cord (microglial activation). All at 4 weeks after lipofilling.</td>
</tr>
<tr>
<td>Huang et al. 2015</td>
<td>Rat</td>
<td>Full thickness burn wound of hind paw</td>
<td>Treatment: lipofilling (human adipose tissue) 2 weeks after injury. Control: saline injection</td>
<td>Behavioral testing for neuropathic pain: paw withdrawal tests. Assessment of inflammatory markers in hind paw skin (COX-2, iNOS, nNOS) and spinal cord (IL-1B, TNFα, p-IkB and p-NFkB). All at 4 weeks lipofilling.</td>
</tr>
</tbody>
</table>

**Abbreviations:** MTC = Masson's trichrome, IL-1B = interleukin 1 beta, COX-2 = cyclo-xygenase 2, TNFα = tumor necrosis factor alpha, CD31 = cluster of differentiation 31, iNOS = inducible nitric oxide synthase, nNOS = neuronal nitric oxide synthase
Reduction of neuropathic pain has been reported in two studies of Huang and co-workers (table 2b). Allodynia, painful perception of a normally non-painful stimulus, after burn wound injury was tested in rats by means of behavioral testing. After burn injury, lipofilling reduced burn induced allodynia. On the one hand, lipofilling reduces skin fibrosis and scarring after burn injury and lowers expression of pro-inflammatory mediators in the skin. On the other hand, lipofilling induces changes in the spinal cord as well decreases microglial activation and by lessens activation of the pro-inflammatory NFkB signal transduction pathway in spinal cord cells.

It can be concluded that lipofilling in rodent models for skin injury and fibrosis, reduces adverse fibrotic changes. This appears to be mediated by factors from the lipograft that can inhibit activation of both fibrotic and inflammatory signal transduction pathways. All changes caused by lipofilling in a dermal scar have been drawn schematically in Figure 1.

**THERAPEUTIC MODE OF ACTION OF ADSC**

**ADSC: stem or stromal cells?**

Because of their ability to differentiate into different cell types, ADSC are sometimes referred to as adipose stem cells. However, a true stem cell has the potential to differentiate into other cell types, while maintaining a stable population of stem cells by the process of self-renewal with indefinite proliferation capability due to telomerase activity. Embryonic stem cells are an example of such pluripotent stem cells: they can undergo an infinite number of cell divisions and can differentiate into all cell types of the three germ layers during embryonic development. ADSC, on the other hand, are a type of adult stem cell that have no telomerase activity and therefore have a limited capacity of proliferation. ADSC can only differentiate into a limited number of cell types, which makes them multipotent progenitor cells. Hence, in the case of ADSC, the authors prefer to speak of adipose-derived stromal cells instead of adipose-derived stem cells.

**Isolation**

ADSC can be isolated either from intact adipose tissue or from lipoaspirates. The adipose tissue or lipoaspirate is subjected to enzymatic digestion using proteases such as collagenase, dispase or trypsin. After digestion, the Stromal Vascular Fraction (SVF) that contains ADSC as well as several other cell types, is separated from the mature adipocytes by differential or density gradient centrifugation. For cell culture, the SVF is then seeded into cell culture dishes. Only ADSC adhere to the tissue culture plastic, whereas other, non-adherent cell types such as erythrocytes, endothelial cells and immune cells, are removed by washing. Then, the remaining ADSC are culture-expanded or cryopreserved until further use.
ADSC in vivo versus in vitro

Adipose tissue contains two major components: SVF and adipocytes. SVF is a heterogeneous mix of cells of eleven main subpopulations based on CD-surface marker expression: seven adipose derived populations (CD45-) and four blood derived populations (CD45+) [31]. Three important subpopulations of CD45- cells are pericytes (in vivo: CD34+/CD34+/CD146+/CD31-), supra adventitial cells (in vivo: CD34+/CD146+/CD31-) and ADSC (in vivo: CD34+/CD90+/CD31- / CD105-) in a very low number [41,42]. Pericytes and supra-adventitial cells are both identified as precursor cells of ADSC, but there remains controversy [31,32,43].

Enzymatic isolation and culture of those precursor cells or ADSC results in a large series of cells that can be used in regenerative medicine. After several days of culture the in vivo phenotype of precursor cells changes into an in vitro specific phenotype. Most of the cells will lose their CD34 expression and almost all of the cells gain expression of CD105 [45,51]. The CD105 marker is also known as endoglin and is a TGF-β type III receptor, which is expressed on virtually all cells of mesenchymal origin, but also on e.g. endothelial cells. Ten to twenty percent of the subpopulations remain CD34- [46,47], but their proliferation rate and adipogenic differentiation ability is significantly lower as compared to the CD34+ subpopulation [42,43]. This suggests that 80%-90% of the so-called ADSC, characterized by their phenotype in vitro (CD34+/CD105-), are not present in vivo: in other words: the majority of ADSC acquire their phenotype through culturing. Culturing of ADSC also causes dramatic shifts in secretome, as will be discussed within a few sentences below. The different components and cell types of all fractions of adipose tissue are summarized in Figure 2.

Some studies have described that regenerative potencies of ADSC is caused by secretion of trophic factors or differentiation into other cells [43]. In vivo, little is known about the secretion of trophic factors by ADSC. In vitro, secretion of trophic factors by ADSC in medium (called ADSC conditioned medium) is affected by many aspects: differences in culture conditions, donors, methods and medium and cell counts results in different expression of growth factors. For instance, hypoxia culture upregulates VEGF, platelet derived growth factor, placental growth factor and insulin-like growth factor II [48]. A 3D culture structure results in thousands of genes with a significant higher mRNA expression related to extracellular matrix (ECM), cell adhesion, wound healing and growth factors as compared to a 2D structure [49]. Concentrations of proteins related to angiogenesis, ECM remodeling and regeneration increase as well [50].

The regenerative potency of SVF might be caused by the interaction between cells and growth factors. For example, angiogenesis is significant greater when pericytes and endothelial cells are combined rather than the use of pericytes or endothelial cells alone [46]. Growth factors like VEGF, hepatocyte growth factor and TGF-β and extracellular matrix (ECM) stimulate angiogenesis [46]. ECM influences morphogenesis and migration speed depends on ECM density during angiogenesis [50]. Furthermore, ECM functions as a scaffold for other cell types at the site of injection. The interaction of cellular integrins, i.e. matrix receptors, suppresses pro-apoptotic signaling. Thus, applications

Figure 2 | Summary of different fractions of adipose tissue before, during and after mechanical or enzymatic isolation of ADSC. Cell types and their cell surface markers are represented for all different fraction.
ADSC AS AN ANTI-SCARRING TREATMENT

Clinical studies
To date, the use of ADSC as a cell therapy for treatment for fibrosis has not been thoroughly investigated in clinical studies. ADSC have been applied in two non-controlled, non-randomized studies investigating the effect of ADSC-enriched lipografts on healing of chronic, intractable radiation ulcers in 10 patients and for correction of soft tissue defects in 29 patients. It was concluded that ADSC improve wound healing and fat graft take and concomitantly decrease deep tissue fibrosis and dermal scarring. However, fundamentally, there is ample evidence for these effects: ADSC increase angiogenesis, can induce mitosis in resident tissue cells and are able to remodel ECM. Based on the design of both studies, no definitive conclusions can be drawn on the effectiveness of the use of ADSC as scar treatment.

On the other hand, studies in the field of cell-assisted lipotransfer (CAL), where lipografts are combined with ADSC in order to improve fat graft survival, have been several properly designed, controlled clinical trials to demonstrate the efficacy of CAL for improvement of lipograft survival over lipollfiling alone. In these studies no serious adverse events were reported after injection of autologous freshly isolated or culture expanded ADSC. It can be concluded that use of autologous ADSC in patients is safe. These clinical trials warrant the dissection of the underlying mechanism via animal models and in vitro investigations of underlying molecular pathways.

Animal studies
In animal wound healing models, where ADSC were used to speed up wound healing, it was observed that ADSC reduce severity of scarring after wound closure (Table 3). ADSC improved the wound healing rate in three out of four studies and smaller fibrotic areas remained after wound healing. Yet, the epidermal thickness increased, and the gene expression of the pro-fibrotic markers α-smooth muscle actin and TGF-β1 decreased while the gene expression of anti-fibrotic fibroblast growth factor and pro-angiogenic VEGF increased. Together, this indicates that ADSC suppress the formation of dermal scar, through augmented wound healing. The comparison with clinical treatment of pre-existing scars is hampered, because these animal studies more prevent scar formation than revert pre-existing scars.

FUTURE PERSPECTIVES
As discussed throughout, harnessing the power of fat for fibrotic scar treatment, is an emerging concept in regenerative medicine. Fat can however be used in several fashions: as whole adipose tissue in lipofilling, or in loose components such as SVF, ADSC or even ADSC conditioned medium. In our opinion, each of these forms has its own ideal application in regenerative medicine. The power of fat and ASC for scar treatment

In animal models specifically designed to study scarring and to study the fibrotic disorder of Peyronie’s disease (Table 3), it was noted that deposition of extracellular matrix components, such as collagen type I and III and elastin, was decreased after treatment of scars with ADSC. Also, collagen fiber alignment improved in the treated scar areas. Functionally, treatment of scars with ADSC lead to smaller scars and less scar elevation. Together, we surmise that the remodeling of the fibrotic matrix in a scar by ADSC is one of the components that governs scar reduction. Interestingly, ADSC are derived from connective tissue (SVF of fat), but appear to act as ‘good guys’ in contrast to the scar myofibroblasts, which are connective tissue cells too, but ‘bad guys’. The ADSC are capable of tilting the balance between ECM deposition and ECM degradation in favor of degradation. Whether this depends solely on matrix influence or also on direct influence on the scar-resident myofibroblast remains to be investigated. In conclusion, treatment of wounds or mature scars with ADSC in different animal models have shown to result in faster wound healing and reduction of scar tissue on both macroscopic and microscopic level. Thus, use of autologous ADSC to improve wound healing and to prevent or diminish scar tissue in patients, seems to be a very exciting and promising way to go.

In vitro studies
Myofibroblasts play a major role in wound healing and scarring: activated myofibroblasts proliferate, produce extracellular matrix like collagens and have the ability to contract. After wound healing, myofibroblasts normally are resolved via apoptosis. However, if myofibroblasts persist, scarring will be the end result. In two in vitro studies, it has been shown that trophic factors, produced by ADSC, can inhibit the myofibroblast phenotype of dermal fibroblasts after stimulation with the pro-fibrotic cytokine TGF-β1 and can inhibit that of fibroblasts derived from Dupuytren’s nodules. Proliferation, extracellular matrix production and contraction of these fibroblasts were reduced, which indicates that growth factors and cytokines of ADSC have the ability to prevent or even to reverse dermal scarring.
Table 3 | Animal studies on ADSC as a treatment for wound healing and scar prevention or reduction

<table>
<thead>
<tr>
<th>Reference</th>
<th>Animal model</th>
<th>Biomaterial</th>
<th>Intervention</th>
<th>Follow up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castiglione et al. 2013</td>
<td>Rat</td>
<td>No</td>
<td>1x10³ labeled human ADSC Control: PB Local injection</td>
<td>Protein expression and histomorphometric analysis of the penis. Erectile function measurements 5 weeks after ADSC treatment.</td>
<td>Decrease in collagen III and elastin deposition (immunofluorescence). Improved erectile function. Both in ADSC-treated vs. control group.</td>
</tr>
<tr>
<td>Lam et al. 2012</td>
<td>Mouse Splinted excisional wound healing model</td>
<td>SIS</td>
<td>1x10³ mouse ADSC on SIS patch Control: patch alone or Topical application of ADSC</td>
<td>Wound healing speed, fibrosis (H&amp;E and MTC staining) after wound healing. Measured at day 14 after wounding.</td>
<td>Wound healing improved slightly with ADSC on SIS. Decreased fibrotic area with topical ADSCs and with ADSC on SIS. Both compared ADSC on SIS to untreated or SIS alone.</td>
</tr>
<tr>
<td>Lee et al. 2011</td>
<td>Nude mouse Splinted excisional wound healing model</td>
<td>Collagen gel</td>
<td>1x10³ human ADSC in collagen gel Control: human dermal fibroblast in collagen gel or collagen gel alone</td>
<td>Photographs of wound area size 10 days after wounding. Scar size 28 days after wounding (H&amp;E staining).</td>
<td>ADSC collagen gel group had a faster wound closure rate than control, but slower than DF collagen gel. Scar size increased in ADSC and DF collagen gel groups compared to control (based on H&amp;E staining alone).</td>
</tr>
<tr>
<td>Uysal et al. 2014</td>
<td>Rat</td>
<td>No</td>
<td>1x10³ labeled rat ADSC Control: 1x10³ rat BMSC or PBS Local injection</td>
<td>Wound healing speed. Histology for neovascularization, epithelial thickness (both H&amp;E). Immunostaining for cytokeratin, αSMA, FGF, VEGF, TGF-β1, β2 and β3. All at day 56 after wounding.</td>
<td>Increased wound healing speed, neo-vascularization and epithelial thickness. Lower αSMA, TGF-β1, β2 and β3 and higher FGF and VEGF expression. All outcomes for ADSC and BMSC treated groups vs. control group Slightly smaller scar area and slightly higher pliability. Higher amount of mature collagen. Lower mast cell count. Lower gene expression of αSMA and TIMP1, higher expression of MMP1. All outcomes for ADSC treated group vs. control group.</td>
</tr>
<tr>
<td>Yun et al. 2012</td>
<td>Pig</td>
<td>No</td>
<td>1x10³ labeled human ADSC Control: PBS Three consecutive local injections</td>
<td>Area, color and flexibility of scar. Histological assessment of collagen arrangement (MTC), number of mast cells. Gene expression analysis of scar tissue. All until 50 days after ADSC injection.</td>
<td>Lower scar elevation. Less deposition and better alignment of collagen. Lower gene expression of αSMA and collagen I. All outcomes for ADSC or ADSC CM treated groups vs. culture medium or untreated groups.</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADSC = Adipose Derived Stem/Stromal Cell, SIS = Small Intestinal Submucosa, H&E = Hematoxillin and Eosin, MTC = Masson’s Trichrome, DF = Dermal Fibroblast, αSMA = alpha Smooth Muscle Actin, FGF = Fibroblast Growth Factor, VEGF = Vascular Endothelial Growth Factor, TGF-β = Transforming Growth Factor beta, BMSC = Bone Marrow Mesenchymal Stem/Stromal Cell, PBS = Phosphate Buffered Saline, TIMP1 = Tissue Inhibitor of Metalloproteinase, MMP = Matrix Metalloproteinase, ADSC CM = ADSC Conditioned Medium, PHBV = Polyhydroxybutyrate-co-Hydroxyvalerate
Chapter 2

SVF however, would be a suitable alternative to combat organ fibrosis. SVF has all the requirements to act as a scaffold for repair, since it contains ready-to-use microvasculature, ECM and ADSC to orchestrate the repair process. For example acceleration of wound healing or alteration of early scar formation would be exemplary candidates for use of SVF. Nonetheless, in case of a pre-existing scars, a more rigorous remodeling of the mature scar tissue is necessary. Here, the microvasculature and ECM components of SVF are not a prerequisite. Thus, the application of ADSC would suffice. ADSC could orchestrate the remodeling, for example by immunomodulation or by instruction of the resident tissue cells from a synthetic to a proteolytic or a non-contractile phenotype. Last but not least, ADSC conditioned medium offers the ultimate solution when only instructive (growth) factors are required. In this way, use of allogeneic cells or xenogenic cell culture products can be circumvented, resulting in an off-the-shelf product. ADSC conditioned medium would be ideal for topical application or injection in wounds or developing scars.

CONCLUSION

Since Neuber’s first report in 1893, the use of adipose tissue has gradually developed into an exciting new way to be used in the treatment and prevention of scar tissue. After lipofilling or after application of ADSC, improvement of scar appearance or reduction in scar related pain has been reported in many case reports and clinical studies. Lipofilling and ADSC seem promising to lessen the severity of developing as well as pre-existent fibrotic scarring. A factor, which complicates definitive conclusions in the efficacy of lipofilling and ADSC, is the wide variety in experimental design of the studies. Each study uses different outcome measurements, at different time points in pre-existent as well as in developing scarring. Up to date, large randomized controlled clinical trials using lipofilling, ADSC, SVF or ADSC conditioned medium for fibrotic scar treatment, are still lacking. For future randomized controlled clinical trials, we recommend researchers to carefully select their source of stromal cells depending on their goal.

Figure 3 | Harnessing the power of fat for fibrotic scar treatment: as whole adipose tissue in lipofilling, or in loose components such as SVF, ADSC or ADSC conditioned medium. As listed, we propose each form has its own ideal application.
REFERENCES


