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Therapeutic Applications for Adipose-Derived Stem Cells in Wound Healing and Tissue Engineering

Michelle E. McCarthy[1] · Theodore A. Brown[1] · Joanna Bukowska[1,2] · Bruce A. Bunnell[1,3,4] · Trivia Frazier[5,8] · Xiying Wu[8] · Jeffrey M. Gimble[1,5,6,7,8]

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Abstract

Purpose of Review The use of adipose-derived stem cells (ASCs) has garnered recent interest for their accessibility and potential utility in wound healing applications. The purpose of this review is to provide an overview of developments within the last 5 years regarding therapeutic use of ASCs in wound healing applications.

Recent Findings Recent studies have demonstrated that ASCs do not exert the majority of their effects through differentiation, as previously believed. Rather, when they improve healing, it is via secreted factors that promote vascularization and control inflammation. New therapeutic approaches reflect this shift in belief.

Summary ASC-based therapies can improve outcomes in the treatment of a variety of wound types. Questions about how to best implement ASCs in the clinical setting remain, and their answers will profoundly influence the utility and availability of ASC-based therapies.

Keywords Adipose-derived stem cells · Cytokine · Pressure ulcers · Scaffold · Skin wound healing · Stromal vascular fraction

Introduction

Pathophysiology of Wound Healing and Chronic Wounds

A skin wound is defined as an injury in which the protective barrier of the integument is compromised, limiting its defensive functionality against the outer environment [1]. Wound healing is the process following injury which leads to restoration of the body's protective skin barrier [1]. This process encompasses a complexly organized cascade of cellular signals that include four main overlapping phases: hemostasis, inflammation, proliferation, and remodeling [2]. However, the ability of the human body to regenerate is limited and, in the adult, often results in formation of a fibrotic scar at the injury site during the process recognized as repair [1].

While scar formation does restore the skin's major functionality as a barrier to water loss and pathogens, it has significant drawbacks. Beyond unappealing esthetics, scar formation accompanied by tissue fibrosis also results in reduced skin elasticity [3]. In extreme cases, such as large full-thickness burns, developing scar tissue pulls the margins of the wound together, resulting in skin contracture [4]. Indeed, skin contracture is a feared sequela of burns on the thorax and neck regions, as it can result in respiratory compromise and

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✉ Michelle E. McCarthy
mmccart@tulane.edu

[1] Center for Stem Cell Research and Regenerative Medicine, Tulane University, New Orleans, LA, USA

[2] Polish Academy of Science, Olsztyn, Poland

[3] Department of Pharmacology, Tulane University, New Orleans, LA, USA

[4] Tulane National Primate Research Center, Tulane University, New Orleans, LA, USA

[5] Department of Structural and Cell Biology, Tulane University, New Orleans, LA, USA

[6] Department of Medicine, Tulane University, New Orleans, LA, USA

[7] Department of Surgery, Tulane University, New Orleans, LA, USA

[8] LaCell LLC and Obatala Sciences Inc., New Orleans, LA, USA

even suffocation [5]. Also, scars do not regrow hair follicles or sebaceous glands.

The role of inflammation is critical to scar formation. Upon entry to the wound site, inflammatory cells such as macrophages and neutrophils release numerous growth factors such as FGF and TGF-β to promote fibroblast proliferation and deposition of collagen [1, 2]. However unlike intact skin which incorporates collagen fibers arranged in a "basket-weave" formation, the collagen fibers within scars are fibrous and uni-directional, resulting in a visually distinct and often undesirable cosmetic appearance [6, 7]. Interestingly, fetal animals, including humans, are able to undergo complete skin regeneration without scar formation potentially due to the as yet underdeveloped immune systems [6, 8]. Indeed, immunodeficient nude mice, which carry the mutation that inactivates transcription factor Foxn1, display scarless healing of skin injuries [9]. These observations have led to the hypothesis that reducing the inflammatory response at the site of a wound can result in reduced scarring [10]. Furthermore, transcriptomic analysis of skin tissues from Foxn1 active (B6) and Foxn1 deficient (nude) mice has revealed that Foxn1 inactivity in nude mice keeps their skin in the immature stage, resembling the phenomena of neoteny that provides the correct *environment* to *facilitate regeneration* [11].

Whereas scarring results in a functional, albeit imperfect, repair of the skin barrier, an even more feared consequence of wounds is their failure to heal, resulting in a chronic wound. Wounds induced by surgery, pressure ulcers, venous ulcers, diabetic ulcers, and burns all have the potential to become chronic wounds [12]. Chronic wounds most often remain arrested within the inflammatory phase of healing, resulting in persistently increased levels of inflammatory cytokines and neutrophils, degradation of the extracellular matrix, and depletion of growth factors within the wound environment. Since poor circulation is a major risk factor for the development of chronic wounds, most patients are elderly individuals with significant comorbidities such as diabetes mellitus and vascular disease. As a result, most chronic wounds present as diabetic, venous, or pressure ulcers that can remain unhealed for months at a time [13]. Chronic wounds that occur affect an estimated 5.7 million people and account for US$20 billion in treatment costs per year in the USA alone [14]. Beyond causing severe pain, chronic wounds act as a nidus for many more serious conditions: a majority of amputations are preceded by an ulcer, and infections are a common cause of death for chronic wound patients [14, 15].

Stem Cells in Wound Healing

Recent advances in wound healing have focused on developing therapies that address the molecular mechanisms at work within the wound microenvironment [16]. By focusing on the molecular mechanisms, new therapies have the potential to provide better outcomes for conventional wounds and treatment-resistant chronic wounds. One of the key mechanisms targeted by new treatments is the activation of angiogenesixs, a critical process to the wound healing process. Adequate blood supply to the wound provides the nutrients, oxygen, and pathways for cell migration that are required for healthy tissue regeneration. Poor circulation due to vascular insufficiency or diabetes mellitus is a major risk factor for the development of chronic wounds which fail to heal spontaneously or respond to conventional treatments. Of these new treatments, the therapeutic use of adipose-derived stem cells to accelerate or support the wound healing process has gained increased attention in recent years [17].

Stem cells are characterized by their self-renewal ability and multi-potency. Mesenchymal stromal/stem cells (MSCs) are a type of adult stem cell originally isolated from bone marrow which are capable of contributing to the regeneration of connective tissues such as skin, bone, cartilage, and fat [18]. These properties make MSCs useful in various medical therapies, such as bone marrow transplantation. However, the clinical utility of bone marrow MSCs has been limited by the difficulty of harvesting sufficient numbers of cells spurring investigation into alternative sources of MSCs [19]. While MSCs have been isolated from nearly every tissue in the body, MSC derived from fat, known as adipose-derived stem cells (ASCs), has emerged as one of the most promising alternatives due to their abundance and ease of collection [20]. ASCs can be found in large numbers within lipoaspirated adipose tissue, which can then be enzymatically digested and centrifuged to isolate an ASC containing mixture called the stromal vascular fraction (SVF) [17]. While ASCs can be further purified from SVF by plastic adherence and culture expansion, recent clinical applications have focused on the use of freshly isolated SVF cells at point of care [12].

Wound Healing Using Adipose-Derived Cells: Molecular Foundations

Role of Cytokines in ASC Paracrine Activity

Adipose-derived stem cells have been shown in animal trials to reduce inflammation and promote an enhanced healing process that is often blocked in chronic wounds, particularly through the promotion of neovascularization [21, 22]. The mechanisms through which ASCs enact their effects on the surrounding wound microenvironment fall into two paradigms: (1) the differentiation of the ASCs into keratinocytes, pericytes, and other cell lineages, which act to restore normalized wound bed architecture, and (2) the secretion by the ACSs of cytokines and chemokines, which lead to enhanced tissue regeneration [12, 23]. Of these two modalities, the current literature favors the later process as the primary

mechanism exerted by ASCs on wound healing [24–26]. One of the strongest findings in support of factors secreted by ACSs in promoting wound healing is that wounds treated with conditioned media from ASC cultures show enhanced tissue regeneration [27–29]. The ASC conditioned medium comprises a "secretome" containing cytokines [12, 23], growth factors, microRNAs [30–32], and exosomes [30, 33, 34], each of which may contribute to the regenerative effect. In contrast, there is a growing body of evidence against the former process, i.e., direct cell participation. Multiple studies have demonstrated that transplanted ASCs do not survive for extended periods of time in wound beds or injury sites [20, 35–37]. However, this remains a debated topic in the field and may depend upon the specific cell types administered and the type of tissue injury [38, 39].

The secretory activity of ASCs can result in angiogenesis, decreased inflammation, promotion of re-epithelization, and increased ratio of type III to type I collagen formation [33]. These effects are at least in part, if not primarily, accomplished through the secretion of a wide variety of cytokines, immunomodulatory factors, and growth factors, the full gamut of which was effectively summarized by Blaber et al. and Toyserkani et al. [21, 25]. Although there are many secreted factors, the majority of pre-clinical studies investigating the mechanisms by which ASCs promote wound healing to date have focused on a few cytokines that have major effects on overall wound healing architecture and rate (Table 1).

Role of Exosomes in ASC Paracrine Activity

The role of ASC exosomes has also begun to garner attention. Exosomes are membrane bound luminal spheres which contain a variety of cellular signaling effectors such as microRNAs and proteins [43]. Preliminary research performed by Hu et al. indicates that exosomes secreted by ASCs can be taken up into the cytoplasm of fibroblasts, where release of their contents results in the promotion of fibroblast migration, proliferation, and secretion of collagen [33]. The same group subsequently noted that wounds treated with ASC exosomes had reduced scarring due to their regulation of fibroblasts and collagen deposition [34]. Interestingly, exosomes increased collagen deposition by fibroblasts at early stages of wound healing to promote formation of granulation tissue, yet inhibited collagen synthesis at later stages of wound healing resulting in reduced scar formation. Despite promising in vivo results, however, clinical application of exosomes must be met with caution, as exosomes have been linked with numerous tumor promoting factors. Most notably, Lin et al. linked ASC exosomes with promotion of migration signals in a breast cancer model [44].

Table 1 A summary of ASC-secreted cytokines and their putative role

A summary of ASC-secreted cytokines and their putative role	
Cytokine	Function
Vascular endothelial growth factor (VEGF-A)	Angiogenesis [40, 41]
Angiogenin (Ang-1)	Angiogenesis [41]
Basic fibroblast growth factor/Fibroblast growth factor 2 (bFGF or FGF-2)	Angiogenesis [40]
Transforming growth factor β1 TGF-β1	Angiogenesis Granulation tissue formation [40]
Interleukin 6 (IL-6)	Anti-inflammatory [25]
Interleukin 8 (IL-8/CXCL8)	Granulation tissue formation Angiogenesis Epithelialization [22, 42]
Epidermal growth factor (EGF)	Epithelialization [41]

Effects of Hypoxia on ASC Cytokine Secretion

In addition to modifying the extracellular environment for enhancing ASC activity, pre-exposing ASCs to hypoxic conditions not only improves in vitro and in vivo survival, but also increases ASC paracrine activity especially with respect to promotion of angiogenesis. Such effects are most likely through enhancing activity of the transcription factor hypoxia inducible factor-1α. Kang et al. found that the stabilization of HIF-1α under hypoxic conditions in ASCs led to increased secretion of VEGF [45]. Similarly, Kakudo et al. observed increased levels of VEGF and FGF-2 in ASCs in hypoxic conditions, and inhibition of FGF-2 upon knockdown of HIF-1α with siRNA [46]. Hsiao et al. showed increased angiogenesis in mice given conditioned media from hypoxic ASC [47]. While hypoxia pre-conditioning of ASCs is still a relatively new niche of research, the preliminary results highlighted here indicate that treatment with ASCs, or even conditioned medium from ASCs, can be ideal for use in chronic wounds and ischemia in vivo. It suggests that pre-treating of stem cells with hypoxia might become the gold standard in cell transplantation procedures.

Adipose-Derived Cells in Wound Healing: Skin and Soft Tissue Regeneration

Augmented Skin Healing

Autologous free skin grafting and skin flap transplantation are the first choices for the clinical treatment of skin injuries. While effective, these techniques are limited by the scarceness of donor sites and the risk of wound retraction and scar formation [48]. The requirement for donor sites is especially

problematic when treating second and third degree burns as the donor sites can additionally create disfiguring scars [49]. ASC-based therapies have the potential to address these issues by facilitating the healing process and minimizing fibrosis.

There is a large variety of wounds that could potentially benefit from an ASC augmented treatment and each type poses unique challenges. For simple cutaneous wounds, ASCs accelerate healing, either after injection of isolated cells or administration of cultured medium around the wound site [38]. Strong et al. found that subcutaneously injected ASCs accelerate and enhance recovery of a murine pressure ulcer model at the level of the dermis, subcutaneous adipose, and muscle layers [50]. However, without the protective effects of an extracellular matrix, injected ASCs often have poor cell retention and are rapidly eliminated by the immune system [51]. Various studies have demonstrated that treatment with human ASCs suspended within an injectable gel results in better local retention and improved function in murine full-thickness cutaneous wound models [52, 53].

ASC-based treatments tested in alternative murine injury models have yielded promising results for a variety of conditions where the natural wound healing response is inhibited. Huang et al. found that ASCs injected around wound sites in a chronic radiation wound model led to significantly smaller wound sizes when compared to controls after 3 weeks [39]. Similarly, Kuo et al. found that subcutaneous injections of ASCs enhanced diabetic wound healing via autocrine and paracrine effects [26].

These findings in animal models have begun to undergo clinical translation into practice [54]. Synergistic effects have been reported when combining SVF cells with other forms of therapy such as cell-assisted lipotransfer (CAL), which simultaneously transplants SVF cells with the aspirated fat to improve its survival and volume retention rates [55]. Lipotransfers can be inconsistent, and fat graft resorption rates ranging from 10 to 90% have been reported by independent practitioners [56]. A randomized controlled trial of CAL using autologous ASCs found that ASC-enriched grafts had significantly higher survival rates and residual volumes [57]. Gentile et al. noted that stromal vascular fraction (SVF) cells or platelet-rich plasma (PRP) as a growth factor source led to volume retention outcomes of 63 and 69% in breast reconstruction fat grafting as compared to 39% with the fat graft alone [58]. Likewise, Gentile et al. noted comparable outcomes in a cohort of 20 patients when applying SVF cell or PRP supplementation to fat grafting to repair facial deformities due to trauma or burns [59]. In contrast, a study of $n = 15$ patients by Rigotti et al. did not note any significant improvement in facial fat graft outcomes when using PRP supplementation [60]. Nevertheless, in a clinical study involving 236 subjects, Sasaki clearly documented statistically significant increases in facial fat graft volume retention when supplemented with SVF cells, PRP, or the two in combination [61].

Additional clinical studies have examined the safety and efficacy of adipose-derived cell transplantation to treat critical ischemic limb disease in patients at risk for amputation. Lee et al. were the first to report the safety and efficacy of culture expanded ASC injection therapy in a cohort of 15 critical limb ischemia patients [62]. They observed positive effects on collateral vascularization and limb retention in two/thirds of their subjects. Bura et al. reported confirmatory findings in a cohort of seven subjects treated by intramuscular injection of culture expanded autologous ASC [63]. Likewise, they noted improved vascularization and ulcer healing without complications. In a similar study of ten subjects with peripheral vascular disease, Carstens et al. reported improved vascularization in the majority of patients following intramuscular injection of autologous SVF cells proximal to the extremity. Furthermore, in subjects who also had concomitant chronic lower extremity ulcers, injections of autologous SVF cells beneath and around the ulcer borders within the extremity resulted in complete wound closure after a period of 5 to 9 months [64]. Although these studies were limited to a small number of patients, the preliminary outcomes strongly suggest that larger, randomized controlled clinical trials are warranted to provide clinical evidence for the efficacy of adipose-derived cell therapy in critical limb ischemia and its complications.

Soft Tissue Transplant-Centric Therapies

The use of ASCs in non-injectable forms, such as in cultured sheets or embedded in an artificial skin, allows for the treatment of larger, more complex wounds. Rheinwald and Green reported that the first successfully grown human keratinocytes by serial cultivation in 1975 and experiments using cultured epithelia for wound treatment were underway by 1979 [65, 66]. Advances in tissue engineering have since yielded progressively more advanced artificial skins, which have been used as matrixes for the ASCs to adhere to, such as bacterial cellulose and acellular amniotic membranes [67, 68••]. Kato et al. found that wounds covered with artificial skin layered on an ASC sheet promoted a more effective healing response than artificial skin alone [69•]. Longitudinal studies comparing fat grafting outcomes with respect to volume between patients receiving conventional lipotransfer and CAL will be necessary to fully address this matter.

3D Scaffolds

Three-dimensional scaffolds are structural microenvironments onto which stem cells can be seeded in order to promote a desired effect such as specific differentiation, prolonged survival, promotion of cytokine secretion, or enhanced vascularization [32]. However, achieving the desired seeding of stem cells is far from a straightforward task. Scaffold design includes a multitude of variables that can ultimately affect stem

cell functionality, including pore size, mechanical properties (e.g., Young's modulus and elasticity), chemical properties (e.g., stem cell receptor binding), and temporal properties (e.g., degradation rate). Scaffolds must also be biocompatible without eliciting an immune response. These properties are largely a function of the biomaterial selected, or in some cases even fabricated, to be the scaffold. The most frequently reported biomaterials are either natural polymers (e.g., silk, alginate, collagen, hyaluronic acid) or synthetic polymers (PIPAA, PLA, PLC), or decellularized native tissues [20, 32, 70].

Decellularized tissue, which is tissue that has been processed such that only the structural component of the extra cellular matrix remains, has particularly strong benefits for its use as a clinically applicable biomaterial. Such materials have the major advantage of being human derived, greatly reducing the probability of an immune reaction or zoonotic disease transmission after transplantation in clinical applications. Decellularized tissue scaffolds can also be easily stored for off-the-shelf usage in clinical practice. Of note, the use of acellular dermal and adipose tissue seeded with ASCs has resulted in particularly promising results. Findings by Huang et al., one of the first groups to utilize acellular dermal matrices (ADMs) with ASCs, found that ADM + ASC treatment resulted in faster wound epithelialization [71]. These results are corroborated in more recent research performed by Nie et al. in a diabetic rat model, wherein ADM + ASCs resulted in significantly faster wound closer than both untreated wounds as well as wounds treated with ASCs alone [72]. Both studies report that wounds treated with ASCs seeded onto acellular dermal matrix resulted in increased granulation tissue formation as well as capillary density.

Scaffold technology has garnered attention and acceptance in minor plastic surgery applications where esthetic outcome is a predominant concern of patients. In particular, scaffold technology has been employed as a potential method of reducing adipose graft resorption and imparting a specific shape to the resulting soft tissue [73, 74]. Despite such common place use of scaffolds, their combination with stem cells is still on the horizon from clinical translational and regulatory perspective. Nevertheless, there is potential for combined ASC seeded scaffolds in major plastic surgery procedures, as indicated by promising preclinical results by Jin et al., who found that the combination of ASCs with a decellularized dermal tissue scaffold improved wound healing in a rabbit breast reconstruction model [75].

In wound healing applications, ASC seeding onto scaffolding materials has resulted in increased vascularization, prolonged ASC survival, suppression of inflammation, and increased healing rates in animal models, even when compared to ASC implantation without scaffolding. Minjuan et al. also found that the use of ASCs seeded onto human amniotic membranes led to hair follicle development during the healing process in a murine full-thickness wound model [68••]. (Table 2) summarizes 3D scaffold materials and their uses as discussed in this section.

Limitations and Safety Considerations

While the therapeutic potential of ASCs is strong, results from studies of their efficacy and safety have been inconsistent. For example, Fuentes-Julián et al. found that local injections of ASCs into the graft junction resulted in greater inflammation and neovascularization in a rabbit corneal allograft model [87]. The efficacy of ASC-based therapies is affected by the source from which they were harvested and the conditions under which they were harvested. Cells collected from older donors exhibited reduced differentiation capabilities, especially in angiogenic lineages [88, 89]. Results from Duscher et al. suggest that the impaired wound healing and angiogenic potential of aged ASCs is a result of increased homogeneity of the stem cell population in older individuals [90]. Cronk et al. found that ASCs from diabetic mice have decreased proliferation and increased apoptosis in vitro relative to cells from healthy mice. In vivo, they found that the vasoprotective effects of injected autologous ASCs taken from diabetic mice are similarly impaired compared to allogeneic injections collected from healthy counterparts [91].

The multipotency and immunosuppressive effects of ASCs necessitate consideration of the oncological safety of ASC-based treatments. The addition of ASC-derived conditioned medium enhances the survival of tongue cancer cells exposed to the chemotherapeutic drug cisplatin in vitro [92]. Additionally, Harris et al. found that the regenerative potential of human ASCs was diminished in the presence of the chemotherapy drug paclitaxel in a rat model [93]. The vulnerability exhibited by ASCs to their local environment is also potentially problematic when the pathology underlying the wound alters the environment to inhibit them. Gong et al. found that differentiation of ASCs towards an endothelial lineage was inhibited in vitro by glycation end products, which can be found in high concentrations in the diabetic microenvironment [94].

Conclusions

The past 5 years have witnessed considerable advances regarding the pre-clinical science of adipose-derived cells in regenerative medicine. Basic scientists have placed greater attention to evaluation of the secretome of the adipose-derived cells. This has led to a better understanding of the role of cytokines, exosomes, and microRNAs play in directing

Table 2 List of scaffolds utilized with ASCs

List of scaffolds utilized with ASCs

Reference	Scaffold material	Model ASC Source Use	Treatment effects	Notes
Mclaughlin et al. Lin et al. (Marra Group) [37, 76]	Poly N-isopropylacrylamide (PIPAAm) used to grow cell sheets	Mouse Mouse ASCs Wound Healing	Increased healing of wounds at earlier time points compared to control.	Temperature sensitive properties allow to dis/attachment of ASC cell sheets
Kim et al. [77]	Hyaluronic acid/Alginate hydrogel	Rabbit Human ASCs Vocal Fold Healing	Vocal folds exhibited a more favorable ECM, without excessive collagen deposition and improved viscoelastic properties.	Human ASCs remained largely undifferentiated and viable after 1 month, suggesting a paracrine effect.
Xu et al. (Han Group) [78]	Hyaluronic acid	Rabbits Rabbit ASCs Vocal Fold Healing	ASCs+Scaffolds had superior collagen arrangement compared to ASCs alone.	
Hu et al. (Han Group) [79]	Hyaluronic acid	Dogs Dog ASCs Vocal Fold Healing	ASCs differentiated to a fibroblast phenotype had increased elastin secretion compared to undifferentiated ASCs or fibroblasts. ASCs and differentiated ASCs exhibited reduced inflammation and favorable collagen formation.	
Garg et al. [80]	5% Collagen-Pullulan hydrogel	Mouse Human ASCs Wound Healing	Wounds healed significantly faster, showed increased vascularity, and closed 2.3 days early than control groups. ASCs showed increased survival when embedded within hydrogel.	Pullulan is a biodegradable polysaccharide produced by the fungus *Aureobasidium pullulans*.
Zonari et al. [81]	Poly(3-hydroxybutyrate-c-o-hydroxyvaler- ate) (PHBV)	Rat Rat ASCs Wound Healing	The PHBV scaffold triggered an immune response, causing degradation of the scaffold by day 28. ASCs + Scaffold treated wounds showed increased vascularity.	
Nie et al. [72]	Acellular Dermal Matrix	Diabetic Rat Rat ASCs Wound Healing	Wounds healed significantly faster and showed increased granulation tissue, capillary density, and epithelial regeneration.	ASC/Dermal matrix complexes had significant growth factor secretion and promoted dermal fibroblast migration in-vitro through paracrine signaling
Lam et al. [82]	Porcine small intestine submucosa	Mouse Mouse ASCs Wound Healing	ASC survival and proliferation increased. Wound healing rates were modestly increased. Scarring was markedly reduced.	Scaffold material is suturable, pliable, and non-immunogenic
Wang et al. [83]	Decellularized human adipose tissue extracellular matrix	Rat Human ASCs Subcutaneous implantation/Adipose tissue Regeneration	Implanted fat grafts maintained volume over an 8 week period without inflammation.Compared with normal fat grafts, the ASC + scaffold treatment resulted in worse long-term vascularization and adipose tissue formation.	
Bayati et al. [84]		Rat		

Table 2 (continued)

List of scaffolds utilized with ASCs

Reference	Scaffold material	Model ASC Source Use	Treatment effects	Notes
	Electrospun Polycaprolactone (PCL)	Rat ASCs Wound Healing	ASCs seeded onto the PCL scaffold increased levels of kertinocyte differentiation markers. Wounds treated with ASCs on PCL Scaffolds showed increased epithelization with accompanying skin appendages, as well as increased wound healing rates.	PCL is commonly used in sutures, contraceptives, wound dressings.
Wang et al. [85]	Injectable decellularized human adipose tissue & Injectable decellularized porcine small intestine	Mice Human ASCs Adipogenic differentiation and functionality	Human ASCs seeded onto decellularized adipose tissue exhibited greater adipogenic differentiation and adopted a more similar morphology to native adipose tissue than ASCs seeded onto decellularized porcine intestine. Angiogenesis was only seen with ASCs + decellularized adipose tissue.	Differentiated ASCs seeded onto porcine small intestine lacked normal adipocyte functionality
Minjuan et al. [68]	Human Acellular Amniotic membrane	Mice Human ASCs Wound healing	Mice treated with ASCs seeded onto Acellular Amniotic membrane showed increased wound healing rates, growth of more epidermal layers, and hair follicle development.	
Kato et al. [69, 86]	Poly N-isopropylacrylamide (PIPAAm) used to grow cell sheets	Diabetic rat Rat ASCs Wound Healing	Rats treated with ASC cell sheets had improved wound healing time. Wounds treated with cell sheets exhibited increased angiogenesis as well as VEGF and HGF secretion ASCs were found up to 14 days after transplantation in perivascular spaces.	Cell sheets were prone to drying and require regular maintenance to ensure hydration.

down-stream biochemical pathways of target cell populations. This body of data has begun to explain the mechanism by which adipose-derived cells exert their reparative and regenerative actions. As a consequence, there has been a growing confidence in advancing adipose-derived cells to early phase clinical trials. A number of evidence-based clinical studies, albeit with small numbers of patients, have demonstrated both the safety and efficacy of adipose-derived cell therapies for conditions such as critical limb ischemia, soft tissue reconstruction, and cosmetics.

Wound healing and its complications remain a pressing societal burden due to their cost to the health care economy and patient well-being and quality of life. Despite years of research, treatments that can heal chronic or complex wounds are limited primarily to preventive measures and conventional surgical interventions. Adipose-derived cell therapies present promise as a novel approach to this medical condition and, as such, merit further investigation. This will require continuing studies exploring the fundamental mechanisms of SVF cell and ASC actions in the context of angiogenesis, vascularization, immunomodulation, and related regulatory functions. Furthermore, additional pre-clinical studies will be required in not only rodent but large animal models. Studies will be necessary to determine the impact of donor age, gender, and underlying health conditions on the functionality, quality, and yield of adipose-derived cells in subcutaneous and other adipose depots. For example, would it make more sense to isolate SVF cells from a 75-year-old, obese diabetic smoker with critical limb ischemia for autologous use at point of care rather than to manufacture allogeneic culture-expanded ASC isolated from adipose tissue obtained following elective liposuction donated by a non-smoking, healthy, normal weight 20-year old? The answer to this question will profoundly influence the field at a practical level. Preclinical animal studies support the feasibility and efficacy of allogeneic ASC transplantion, and further work is necessary to develop this paradigm in humans [95, 96]. Should there be a focus on developing improved devices for the cost-effective harvest of autologous SVF cells at point of care and/or the large scale efficient expansion of allogeneic ASC under cGMP guidelines? While these questions will not have immediate answers, the design of future studies and experiments should incorporate these issues into their outcomes. Ultimately, the basic and clinical translational science should be conducted in a manner that simultaneously advances and simplifies the regulatory process with respect to the broader safety and efficacy of adipose-derived cell therapies.

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Author's contributions M.E.M., T.A.B., and J.M.G. researched data for the article and wrote the article. M.E.M., T.A.B., J.B., T.F., X.W., B.A.B, and J.M.G. made substantial contributions to discussions of the content and final revision of the manuscript. All authors reviewed and/or edited the manuscript before submission.

Compliance with Ethical Standards

Conflict of Interest J.M.G. and X.W. are co-founders, co-owners and Chief Scientific Officer and Vice President for Research and Development, respectively, of LaCell LLC, a biotechnology company focusing on the clinical translation of stromal-cell and stem-cell science. J.M.G., X.W., and T.F. are the co-founders and co-owners of Obatala Sciences Inc., a biotechnology company focusing on humanized "fat on a chip" as a product for drug discovery where T.F. serves as the President and Chief Executive Officer.

J.M.G. is an inventor on multiple patents relating to adipose cells and products. X.W is about to submit a patent application from LaCell LLC on the use of adipose cells in therapy.

The other authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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