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EDITORIAL

Adipose-derived stromal cells: Their identity and uses in clinical trials, an update

Louis Casteilla, Valérie Planat-Benard, Patrick Laharrague, Béatrice Cousin

Louis Casteilla, Valérie Planat-Benard, Patrick Laharrague, Béatrice Cousin, Université de Toulouse, UPS, UMR 5241 Métabolisme, Plasticité et Mitochondrie, BP 84225, F-31 432 Toulouse Cedex 4, France
Louis Casteilla, Valérie Planat-Benard, Patrick Laharrague, Béatrice Cousin, CNRS, UMR 5241 Métabolisme, Plasticité et Mitochondrie, BP 84 225, F-31 432 Toulouse, France
Patrick Laharrague, Laboratoire d'Hématologie, CHU Toulouse, France
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Correspondence to: Louis Casteilla, PhD, CNRS, University Paul Sabatier, UMR 5241 BP 84225, F-31 432 Toulouse Cedex 4, France. louis.casteilla@inserm.fr
Telephone: +33-5-62170904 Fax: +33-5-62170905
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Abstract

In adults, adipose tissue is abundant and can be easily sampled using liposuction. Largely involved in obesity and associated metabolic disorders, it is now described as a reservoir of immature stromal cells. These cells, called adipose-derived stromal cells (ADSCs) must be distinguished from the crude stromal vascular fraction (SVF) obtained after digestion of adipose tissue. ADSCs share many features with mesenchymal stem cells derived from bone marrow, including paracrine activity, but they also display some specific features, including a greater angiogenic potential. Their angiogenic properties as well as their paracrine activity suggest a putative tumor-promoting role for ADSCs although contradictory data have been published on this issue. Both SVF cells and ADSCs are currently being investigated in clinical trials in several fields (chronic inflammation, ischemic diseases, *etc.*). Apart from a phase Ⅲ trial on the treatment of fistula, most of these are in phase Ⅰ and use autologous cells. In the near future, the end results of these trials should provide a great deal of data on the safety of ADSC use.

Key words: Mesenchymal stem cells; Stroma cells; Cell therapy; White adipose tissue

Peer reviewers: Mikhail G Kolonin, PhD, Centre for Stem Cell Research, Institute of Molecular Medicine, University of Texas Health Science Center at Houston, 1825 Pressler st., Rm. 630-F, Houston, TX 77030, United States; Soo-Hong Lee, PhD, Assistant Professor, College of Life Science, CHA Stem Cell Institute, CHA University, 606-16 Yeoksam 1-dong, Gangnam-gu, Seoul 135-081, South Korea

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INTRODUCTION

The interest in adipose-derived multipotent stroma cells has increased greatly, largely because it is easy to obtain large amounts of these cells *via* the liposuction process, using only local anesthesia. Since many aspects of adipose-derived stromal cells (ADSCs) are fully described in recent reviews[1], we will focus on specific points that are poorly discussed elsewhere and will also comment on the clinical uses of these cells based on our own expertise in the field of ischemia.

WHAT ARE ADSCS AND WHAT THEY DO?

Mesenchymal stem cells (MSC) were first described as

Table 1 Differentiated phenotype given rise from adipose-derived stromal cell and interactive effects of these cells with immune and cancer cells

Phenotype given rise in *in vitro* system	Ref.
Classic mesenchymal phenotype (adipocyte, osteoblast, chondrocyte)	[1]
Hematopoietic supporting cells	[25]
Other phenotypes	Vascular cells (Smooth-muscle cells, Endothelial)[16]
	Neurones[1]
	Cardiomyocyte and skeletal cells in the required presence of 5 azacytidine[16]
Modulation of inflammation and immune suppressive functions	Rheumatoid arthritis[31]
	GVH[30]
	Autoimmune encephalomyelitis[32]
Anti-cancer effect	Tumor progression inhibition[34]
Pro-cancer effects	Tumor progression growth[35,37]

immature cells in adult bone marrow, able to give rise to mesenchymal lineages such as osteoblasts, chondrocytes and adipocytes[2]. These cells are selected by adhesion onto Petri dish before expansion. Under low culture density, distinct colonies are formed, each one deriving from a single precursor cell, the CFU-F. It has been estimated that MSCs represent a very low proportion (0.01%-0.0001%) of the nucleated cells in adult human bone marrow[3]. In 2005, the International Society for Cellular Therapy established the minimal criteria for MSC definition. Three criteria were proposed: adherence to plastic, specific surface antigen (CD73+, CD90+, CD105+, CD45-, CD34-, CD14 or CD11b-, CD79- or CD19-, HLA-DR) and *in vitro* capability to give rise to adipocytes, osteoblasts and chondrocytes[4]. A clarification published later proposed the term "multipotent mesenchymal stromal cells," since only a cell subset seems able to display self-renewal properties[5,6]. It is also necessary to add to this definition the supporting effect of these cells, particularly on hematopoietic stem cells[7].

For a long time, as first described in the 1960s, a protocol similar to that used to purify MSCs from bone marrow was used to purify adherent immature cells called preadipocytes[1]. To obtain these cells, fat pads should be minced and incubated with collagenase in order to dissociate the extracellular matrix. Afterwards, floating mature adipocytes are separated from the pelleted stromal vascular fraction (SVF). Since the SVF comprises a heterogeneous cell population, the final isolation step consists in plating these cells in order to select the adherent population by successive washings. With the appropriate cocktail of differentiating agents, these cells can give rise adipocytes, demonstrating *a posteriori*, the existence of adipose progenitors in the stromal fraction of adipose tissues, irrespective of the age of the patient. These preadipocytes were later demonstrated to be multipotent and were named ADSCs[8]. However, since their self-renewal has not been definitively established and, in agreement with the statement of International Society for Cellular Therapy[5], we prefer to use the term "stromal" instead of "stem". In contrast to MSCs, when freshly prepared and during the first rounds of proliferation, these cells express the CD34 antigen[9]. The frequency of these cells is much higher in adipose tissue (100 to 500 fold higher) than that of MSCs in bone marrow. Although numerous authors use the same term, MSC, both for cells derived from bone marrow and for those derived from adipose tissue, several differences have been described at genomic, proteomic and functional levels[10-12], suggesting that MSCs and ADSCs are different and that MSCs are probably more committed towards osteoblastic and chondrogenic lineages than ADSCs[1].

A confusing point is that the term ADSCs or adipose-derived stem/stroma cells is also used for crude SVF. This fraction is highly heterogeneous and contains many cell subsets including native ADSC, mature endothelial and hematopoietic cells, the latter representing a large portion of this fraction (up to 20%)[9]. In this context, these cells cannot be named stem or mesenchymal cells. In our opinion, the term ADSCs should be restricted only to the cells described below, although a more precise classification depending on cell potential may exist.

The functional properties of mesenchymal stromal cells can be summarized as: multipotency, functional cell support that could be termed stromagenesis, modulation of immuno-inflammatory functions. These last two properties may be connected. Most of these effects are believed to be mediated *via* paracrine activity[13,14]. In this context, it is noteworthy that fat is considered as a true endocrine tissue and that adipose lineage cells display a strong secretory activity[15]. Many reviews focus on these features in bone marrow and adipose-tissue-derived cells[1,7,15,16]. With the exception of the classic mesenchymal phenotype (adipocyte, osteoblast, chondrocyte), no study has clearly demonstrated a complete and functional differentiation of mesenchymal-like cells. Most often, the phenotype is only established by the detection of some markers of differentiated phenotypes. A recent study suggested that MSCs could give rise to "intermediate biphenotypic cells" which co-express cell-specific markers whilst maintaining the stromal phenotype but without truly becoming functional[17]. Such findings strongly support the use of the term "differentiated phenotype-like cells" to define these cells after differentiation, as they only mimic true differentiated cells without displaying all the features of them.

In Table 1 we have summarized the differentiated phenotypes arising from ADSCs and the interactive ef-

fects of these cells with immune and cancer cells. We would like to focus our comments on some specific or neglected aspects. For ADSCs, it is noteworthy that among the various potentials of these cells, many reports concern the cardiovascular field, including both *in vivo* and functional evaluations[9,18-20]. In this context, we successively demonstrated strong angiogenic features in ischemic hindlimb, myocardial infarction and wound-healing situations, associated or not with irradiation[9,21,22]. It appears that ADSCs are more efficient in this field than their bone marrow counterparts, and a direct comparison in the same set of experiments indicated a better angiogenic effect of ADSCs than MSCs[23]. Another functional characteristic initially attributed to MSCs is their ability to support hematopoiesis[6,24]. ADSCs also appear to posess this property, although they appear less efficient in supporting immature hematopoietic cells[25]. Another key feature of bone marrow MSCs is their ability to modulate immune and inflammatory functions[26]. This property has been clearly demonstrated and is currently being investigated in a clinical trial, although the exact underlying mechanisms and the molecules involved are still being discussed and could be species-dependent[27,28]. Based on the complexity of the effects, it is reasonable to suggest that they are due to a combination of numerous molecules, and that these could display some redundancy. Such redundant factors could explain the discrepancies between the different studies. Immunosuppressive capacity and modulation of inflammation are shared with ADSCs, which seem very efficient both *in vitro* and in different *in vivo* situations[29-32]. This immunosuppressive effect associated with the angiogenic properties of ADSC raises questions about the interactions between these cells and cancer cells. This is crucial as a positive relationship between obesity and cancer is well-known[33]. We recently demonstrated that ADSCs strongly inhibit pancreatic cancer cell line proliferation, both *in vitro* and *in vivo,* and induce tumor cell death by altering cell cycle progression[34]. These data appear to be contradictory to the description of angiogenic properties of these cells in ischemic situations and to four recent reports demonstrating that ADSCs could promote tumor growth[35-38]. Among these reports, the work published by Donnerberg' s group is particularly interesting as it is the only report on the effect of ADSCs on primary cancer cells rather than cell lines, and also because it describes an investigation of the interactions between ADSCs and dormant or active cancer cells that were purified using different stem cell markers[35]. The authors concluded that ADSCs could trigger the growth of tumors from active cancer cells but not from dormant cells. Furthermore, when all reports are compared it appears that a positive effect of ADSCs on tumor cells is observed when these cells are co-injected with cancer cells or transplanted at the beginning of the tumor process. In contrast, a negative effect can be observed when ADSCs are implanted in pre-existing tumors[34]. Thus, we can suggest that, partner dependent, reactive cross-talk can take place between ADSCs and other cell types in order to maintain proper development of the tissue and a correct balance between proliferation and differentiation.

The possible difference between native and cultured cells remains an open question. Indeed, as it now appears that extensive proliferation can achieve reprogramming, it is not possible to exclude the possibility that the features attributed to mesenchymal cells, defined after a large number of doublings in classic culture conditions, could be more related to the culture process than to the intrinsic properties of native mesenchymal cells.

WHERE DO ADSCs COME FROM?

To better understand the physiological importance and role of a cell, it is vital to know and understand their development. Nearly all animal species have developed strategies to handle energy stores, in the form of white adipose tissue (WAT), according to their particular needs. Most mammals have both intra-abdominal and subcutaneous fat pads[39]. In humans, WAT development mainly occurs during the last trimester of intra-uterine life. At birth, fat represents around 16% of body weight. In adult humans, this tissue is dispersed throughout the body with major intra-abdominal (around the omentum, intestines, and perirenal areas) and subcutaneous depots (buttocks, thighs, and abdomen). Additionally, WAT is found in many other areas: the retro-orbital space, face, extremities, bone marrow. It is noteworthy that major differences in the metabolic properties and patterns of gene expression within different fat depots have been described and could be related to different pathogenic states[39]. Although adipose tissue development is often associated with an increase in the risk of metabolic diseases and morbidity, Tran *et al*[40] neatly demonstrated that subcutaneous fat is intrinsically different from visceral fat and protects against metabolic disorders. Endocrine and paracrine activity would explain a large part of these differences. It is clear that all deposits are not equivalent and this must be kept in mind when analyzing precursors present in tissue and particularly in ADSCs. Indeed, at least in mice, the potential of ADSC differ according to the location of adipose tissue from which they are purified[41].

Like muscle and bone, adipose tissue is generally regarded as having a mesodermal origin, even though no studies have been performed tracing the precise lineage. However, as with the bones and muscles of the skull, it was recently reported that adipose cell lineages originate from the neural crest during development[42]. So, both neuroectoderm and mesoderm could give rise to local adipose tissue. This dual origin (ectoderm and mesoderm) could be also true during development, as was proposed for MSCs[43]. Indeed, during development neuroepithelial cells supply an Initial and transient wave of MSC differentiation[43].

Very few data are available on the early development of adipose tissue in humans. In 1965, Wassermann was the first to study the development of WAT in compari-

son with other organs in humans. Through a careful histological study he demonstrated that adipose depots develop from primitive organs[44]. Within these primitive organs, clusters of adipocytes emerge from a bulk of mesenchymal cells related to the development of the vascular network, giving rise to fatty lobules. The most differentiated cells are far-distant from capillaries. Vascularization therefore plays a major role in the development of adipose tissues. Angiogenesis and adipogenesis appear coordinated in time and space. In evaluating the particular relationship between adipose lineage cells and endothelial cells, we have established that many adipose precursors express the surface marker CD34, a protein also present at the surface of immature cells and endothelial cells[9]. Since we have also provided evidence of a true angiogenic potential *in vitro* and *in vivo*, we hypothesized that these adipose precursors could commit to the endothelial lineage under appropriate conditions. Bouloumié's group drew similar conclusions from *in vivo* studies[19]. The precise location of native ADSCs inside adipose tissue has not been determined. Indeed, one set of experiments suggests that ADSCs display pericyte properties, as proposed for all MSCs[45,46]. This conclusion is not consistent with one of our recent reports[47] in which immunohistological analysis revealed that native ASCs exhibited specific morphological features with long protrusions. Moreover, native ASCs were found scattered in AT stroma and did not express *in vivo* pericytic markers such as NG2, CD140b or alpha-smooth muscle actin, which appeared during the culture process. More recently, employing a non-invasive assay to follow fat mass reconstitution *in vivo*, Rodeheffer *et al*[48] identified a subpopulation of early adipocyte progenitor cells (Lin^-, $CD29^+$, $CD34^+$, $Sca\text{-}1^+$, $CD24^+$) resident in adult WAT. Using genetically marked mice, Tang *et al*[49] found that most adipocytes descend from a pool of proliferating progenitors that are already committed, either prenatally or early in postnatal life. These progenitors reside at least in part in the mural cell compartment of the adipose vasculature, but not in the vasculature of other tissues. These data could be related to the hypothesis that naïve MSCs originate from a subset of human perivascular cells that express both pericyte and MSCs markers *in situ* (CD146, NG2, PDGF-Rβ)[45,46]. Therefore, adipose-derived stroma cells could differentiate from various types of vascular cell types, probably located within the WAT itself. However, it appears that the developmental origin of white preadipocytes differs according to the location[50] and this opens up the question of possible differences in the potential of preadipocytes/ADSC.

TOWARDS CLINICAL TRIALS

Table 2 showed the different steps for a clinical trial. There is great interest in adipose tissue as a source of therapeutic cells as the cells are obtained from adults, thereby avoiding ethical concerns, and use tissue which is abundant and easy to obtain, even when compared with bone marrow where sampling requires general anesthesia. Another advantage is that, as the frequency of ADSC is much higher in adipose tissue than those of MSC in bone marrow, a large number of cells can be obtained without a large number of passages. In this way, the risk of culture-induced chromosomal abnormality senescence is greatly decreased[51].

From the point of view of safety and adverse-side effects,two other key issues are the possibility of undesirable differentiation and the possibility of interaction between ADSCs and resident cancer cells. Concerning the first point, undesirable calcifications have been observed after the transplantation of BN-MNC cells in the heart after infarction[52]. More recently, cysts and microcalcifications were detected in 4 out of 70 patients after breast reconstruction using lipoaspirate associated with crude SVF[53]. To our knowledge, no other cases of undesirable differentiation have been described, suggesting either that such events are rare or have not been fully and systematically evaluated. However, this issue has been discussed and analyzed in recent pre-clinical papers[54]. No definitive conclusion can be reached on the possible interaction between ADSCs and cancer cells as contradictory reports have been published,as discussed previously. We can merely stress that a risk cannot be excluded in the context of pathologies associated with cancer.

In Tables 3 and 4, we have indexed all the clinical trials that we found using adipose, derived and stem as keywords on the "clinicaltrial" and "pubmed" websites. As discussed previously, there is some confusion about the use of the term adipose-derived stroma/stem cells either for ADSCs or crude SVF. All trials using crude SVF and ADSC are presented in Tables 3 and 4 respectively. Based on the ease of obtaining crude SVF, it is not surprising to find the first published clinical application describing the use of this cell fraction in a case report concerning a massive defect of the calvaria after injury[55]. In this report, crude SVF was mixed with fibrin glue. Three months after the reconstruction, CT-scans showed new bone formation and near complete calvarial continuity around the site of the damage. Unfortunately, no another related papers have been published since this seminal report. It is surprising not to find more reported trials particularly in the context of breast reconstruction. This could be due to the peculiar status for SVF cells which can be extemporaneously obtained in the operating room and thus escape the classic legislation on cell therapy. This might be considered regrettable since, as stated above, one trial described undesirable events (cysts and microcalcification)[53] and the possible risk of a cancer promoting effect of any cells derived from adipose tissue is questionable. Moreover, it is noteworthy that two clinical trials dedicated to the treatment of cirrhosis with autologous SVF were suspended although no reason was disclosed. Other trials are investigating the effect of SVF in the cardiovascular field, including acute myocardial infarction. This is an ideal situation for testing SVF effects as, in a clinical setting, it is not possible to use expanded cells which

Table 2 The different steps for a clinical trialand cancer cells

Steps of clinical trial	Elements of discussion
Design	Autologous
	Immunocompatibility
	Lag of time between fat sampling and delivery
	Amount of cells
	Allogenic
	Histocompability issue
	If bank, ready to use treatment
	Inclusion criteria
	Too broad: leads to wrong conclusions associated with great variability and independent parameters,
	Too restricted: enrolment difficulties associated with non relevant and inadequate parameters
	Exclusion criteria
	Too broad: enrolment difficulties associated with non relevant and inadequate parameters
	Too restricted: risks of adverse side effects associated with interactions between transplanted cells and undesirable context
	Number of patients: statistically defined
	Objective and well-established criteria of safety and efficacy
	Uni or multicenter analysis
	Standardization of procedures between centers
	Efficiency of enrolment
Sampling	Liposuction:
	Local anesthesia
	Fat depot
	Technique (no ultra-sound)
	Anti-coagulant
Culture	Opened or closed system
	Bovine or human-derived products
	Number of passages
	Quality and Safety control
	Release criteria
Injection	iv
	Poorly invasive but large distribution and mostly trapped in lung
	im or intra tissue
	More invasive
	More restricted localization
	Pressure challenge for adipose-derived stromal cells
Monitoring of the tolerance and the safety	Criteria: pain, wound healing, inflammation, immunology, tumor
	Kinetics for analysis
	Short and long term safety
Monitoring of the results	Objective criteria, standardisation of procedures
Analysis of the results	Adequate statisitic
	Stick to primary and secondary aims

require a delay for cultivation unless the therapeutic cells are allogenic and already frozen. This would require the existence of a cell bank, which is not yet the case for these cells. For these applications, a positive outcome may be unlikely as similar protocols have already been tested with bone marrow mono-nuclear cells (BM-MNC and not MSC) with negative results in most cases[56]. By the same reasoning, there may be some optimism for the use of SVF in the treatment of critical ischemia hindlimb as the injection of BM-MNC was relatively successful even after 2 years[57,58].

Only the clinical trials described in Table 3 correspond to the use of ADSCs after purification and expansion. ADSC were systematically evaluated for their ability to rebuild volume in depressed scars following the subcutaneous injection of ADSC which differentiated towards adipocytes. This trial of 36 patients was completed in 2007 but has not, to our knowledge, yet been documented in any peer-reviewed international journal. Only one report relates to a field in which ADSCs have been evaluated for their reconstructive properties based on their classic mesenchymal differentiation potentials, specifically in the field of bone or cartilage reconstruction when the osteogenic or chondrogenic potentials of ADSC are well-established and widely investigated[59]. In this case report with 36 mo of follow-up, the defect was successfully reconstructed with a microvascular flap using beta-tricalcium phosphate, autologous ADSCs and bone morphogenetic protein-2 to trigger their osteogenesis. Although this result is encouraging, a case report cannot give prove a general effect and no conclusions can be definitively drawn until phase Ⅰ and Ⅱ trials have been conducted. Most other ADSC trials concern fistula complications that result from tissue degeneration following an uncontrolled inflammatory process. In a noteworthy case report, Garcia-Olmo *et al*[60] found that expanded ADSCs are more efficient than the freshly-prepared in treating Crohn's disease. The trials on fistula indicate that ADSCs are very efficient in controlling inflammation and improving the healing process[22,61,62]. Garcia-Olmo *et al*[61,62]

Table 3 Clincial trials using stromal vascular fraction

Clinical trials with SVF	Design	Results	Ref
Traumatic calvaria defect	Autologous SVF + fibrin glue: case report	Success	{Lendeckel, 2004 #483}
Breast reconstruction after lumpectomy	Autologous fat + autologous SVF. No arm control	Cysts and Microcalcifications (4/70 patients)	{Yoshimura, 2008 #481}
	Autologous fat + autologous SVF, phase Ⅳ		{Yoshimura, 2008 #481} NCT00616135*
Lipodystrophy Ⅰ	Autologous SVF + fat Phase Ⅰ	recruiting	NCT00715546*
Non revascularizable myocardium	Autologous SVF Injection into the left ventricle	ongoing	NCT00426868*
Treatment of Pts With ST-Elevation Myocardial Infarction	Autologous SVF, Phase Ⅰ Injection into the left ventricle	Ongoing	NCT00442806*
	Autologous SVF, 2 doses against placebo, Phase Ⅱ, Ⅲ, Intracoronary injection	Not yet open	NCT01216995*
Diabetes Ⅰ	"Activated" autologous SVF, phase Ⅰ / Ⅱ iv administration	recruiting	NCT00703599*
Diabetes Ⅱ	"Activated" autologous SVF, phase Ⅰ / Ⅱ	recruiting	NCT00703612*
Liver cirrhosis	Autologous SVF Intrahepatic arterial administration	Suspended suspended	NCT00913289* NCT01062750

The clinical trials that are indexed in this table were retrieved using adipose, derived and stem in clinicaltrial and PubMed websites. As discussed in the text, there is some confusion about the use of the term adipose-derived stroma/stem cells. This term should be restricted to cultured mesenchymal stem cells. In fact, it can recover the use of the crude and strongly heterogeneous stroma fraction just after its recovery after fat digestion. The trials listed in this table correspond to the use of such fraction (*identifier on Clinicaltrials website: *http://clinicaltrials.gov/ct2/results?term=adipose+derived+cells). SVF: Stromal vascular fraction.

Table 4 Clincial trials using adipose-derived stromal cell

Clinical trials with ADSC	Design	Results	Ref
Maxillary reconstruction	Autologous ADSC case report	Success	{Mesimaki, 2009 #480}
Cryptoglandular origin fistula with or without Crohn's disease	Autologous ADSC phase Ⅰ / Ⅱ intra-tissue	ADSCs more effective (P = 0.001). Recurrence rate with ADSC = 17.6%	{Garcia-Olmo, 2008 #451; Garcia-Olmo, 2009 #449}
	Autologous ADSC Phase Ⅱ, 2 arms (fibrin glue, fibrin glue + ADSC)	Ongoing, not recruiting	NCT00115466*
Crohn's disease fistula	Autologous ADSC, phase Ⅰ and Ⅱ	Phase Ⅰ, complete Phase Ⅱ recruiting	NCT00992485* NCT01011244*
	Autologous ADSC, phase Ⅰ	Phase Ⅰ / Ⅱ recruiting	NCT01157650*
	Allogenic ADSC: phase Ⅰ / Ⅱ 20×10^6 then 40×10^6	recruiting	NCT00999115*
Complex Perianal Fistulas not associated to Crohn's disease	Autologous ADSC, phase Ⅲ three arms (fibrine, ADSC, fibrin glue + ADSC; 20×10^6 then 40×10^6 when no effect)	Completed (214 enrolled patients)	NCT00475410*
	Long term safety	Recruiting	NCT01020825*
Depressed Scar	Autologous ADSC predifferentiated towards adipocyte, phase Ⅱ, Ⅲ	Complete	NCT00992147*
Chronic critical limb Ischemia	Autologous ADSC, phase Ⅰ im 100×10^6	Recruiting	NCT01211028*
Chronic critical limb Ischemia in diabetic patients	Autologous ADSC, phase Ⅰ / Ⅱ iv administration	Recruiting	NCT01079403*
Fecal incontinence	Autologous ADSC, phase Ⅰ	Recruiting	NCT01011686*
GVHD	Autologous ADSC iv 10^6/kg	4/5 alive (after a median follow-up of 40 mo)	{Fang, 2007 #469}
	Autologous ADSC Three arms no administration, iv 10^6/kg or 3×10^6/kg	Recruiting	NCT01222039
Secondary Progressive Multiple Sclerosis	Autologous ADSC phase Ⅰ / Ⅱ 3 arms (iv 10^6 and 4×10^6/kg against no intervention)	Recruiting	NCT01056471*

The clinical trials that are indexed in this table were retrieved using adipose, derived and stem in clinicaltrial and Pubmed websites. As discussed in the text, there is some confusion about the use of the term adipose-derived stroma/stem cells that can be used for crude SVF. This term should be restricted to cultured adipose derived mesenchymal stem cells and the table lists the trials using such cells (*identifier on Clinicaltrials website: *http://clinicaltrials.gov/ct2/results?term=adipose+derived+cells). ADSC: Adipose-derived stromal cell; GVHD: Graft-versus-host disease.

published the conclusions of randomized phase I and Ⅱ trials in which they compared injection of ADSC into rectal mucosa with fibrin glue to fibrin glue alone on 25 patients with complex perianal fistulas associated or not with Crohn's disease. Following a first dose of 20 million ADSCs, a second dose of 40 million was administered 8 wk later in cases where there was no initial healing. Patients were considered healed when a total epithelialization of the external opening was evident after 8 wk. Seventy one percent of patients treated with ADSC and fibrin glue displayed fistula healing compared to 16% observed in patients treated with fibrin glue alone ($P < 0.001$). This positive effect on healing is all the more remarkable as it is otherwise poorly documented, even in rodent models[22]. Two further clinical trials have focused on Graft *versus* Host disease,.an application which is not surprising given the efficiency of MSCs at the clinical level[63] and the similarity in immunomodulation properties between MSCs and ADSCs[29,30]. Multiple sclerosis can be also included in the field of the modulation of inflammation/immune response. In a rodent model, it was demonstrated that intravenously injected ADSCs can home to the lymph nodes and brain and that they act by suppressing the autoimmune response in early phases of disease as well as by inducing local neuroregeneration by endogenous progenitors in animals with established disease[32]. The strong immunosuppressive effects of ADSC reported by various independent groups naturally led to investigation the effect of ADSC on MS. Based on the positive and well-documented positive effects of intravenous administration of MSCs, positive effects of ADSCs[63] are also expected in this field. Only two trials have investigated the effect of ADSCs on chronic critical limb ischemia, one after intra-muscular injections, the second with intravenous injections in diabetic patients. A futher planned trial also intends to use allogenic ADSCs in the context of fistula. This trial is important as it could open up the field of ADSC-associated regenerative medicine.

CONCLUSION

The various clinical trials demonstrate that fat-derived therapy is not a dream, but is becoming a reality. Surprisingly, results so far suggest that the efficiency of ADSCs in regenerative medicine could be related more to their capacity to modulate immunity and/or inflammation than to their differentiation potentials. The physiological relevance of this phenomenon needs to be better documented, as this could lead to improved efficiency and perhaps new therapeutic possibilities for these cells. However, it is reasonable to speculate that one type of cells will not be able to cover all therapeutic applications and that it will be necessary to fully delineate the respective applications for the various types of cells. In this context, it is reasonable to suggest that, each time ADSCs display effects more or less similar to other cell types, the inherent advantages of adipose tissue.will favour its use over cells from other sources.

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