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REVIEW

Adipose stem cells in the clinic

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Abstract— Adipose-derived stem cells (ADSCs) are the most commonly used type of mesenchymal stem cell (MSC) in the clinic. ADSCs have some advantages in transplantation compared with MSCs from bone marrow and umbilical cord blood. ADSCs produce important growth factors for wound healing, modulate the immune system, decrease inflammation, and home to injured tissues. In particular, ADSC extraction from adipose tissue is a simple procedure with minimum invasiveness. Therefore, ADSCs have been evaluated in clinical trials and used in the treatment of many diseases. To date, ADSC transplantation has been approved in some countries to treat medical complications such as perianal pistula and osteoarthritis. This review provides an overview of the applications and future challenges of the use of ADSCs in clinical settings.

Keywords— Adipose-derived stem cells; Stem cells; Stem cell transplantation; Cytotherapy; Regenerative medicine.

INTRODUCTION

Adipose-derived stem cells (ADSCs) were first identified by Zuk and colleagues at the David Geffen School of Medicine at UCLA in 2001. They termed these cells as processed lipoaspirate cells or "PLA" cells (Zuk et al., 2001). Zuk et al. used an enzyme to isolate PLA cells from adipose tissue. PLA cells were also named stromal vascular fraction (SVF) cells that consist of various cell types, including red blood cells, fibroblasts, endothelial cells, smooth muscle cells, pericytes, and preadipocytes (Poznanski et al., 1973). However, most of these cell types cannot adhere to the flask surface and are thus eliminated during culture. These adherent cells exhibit stem cell characteristics such as a multilineage differentiation potential (Zuk et al., 2001). Subsequently, PLA cells have been isolated by many researchers. PLA cells have been called various names such as ADSCs, adipose-derived adult stem (ADAS) cells, adipose-derived mesenchymal stem cells (AD-MSCs), adipose MSCs (AMSCs), and adipose stromal/stem cells (ASCs).

At the IFAT conference, plastic-adherent cells derived from the SVF were termed ASCs or ADSCs. In recent studies of ADSCs, it has been demonstrated that ADSCs possess the characteristics of MSCs that are isolated from the bone marrow or umbilical cord blood. Therefore, ADSCs are considered as a type of MSC. MSCs were first isolated from the bone marrow by Friedenstein et al. in 1968 (Friedenstein et al., 1968). Bone marrow MSCs are considered as the gold standard for MSCs. To unify the classification of MSCs, Dominici et al. (2006) suggested a minimum standard for MSCs. This standard states that MSCs must be plastic adherent when maintained under standard culture conditions; they must express CD105, CD73, and CD90, and lack expression of CD45, CD34, CD14, or CD11b, CD79alpha or CD19, and HLA-DR surface molecules; MSCs must differentiate to osteoblasts, adipocytes, and chondroblasts in vitro (Dominici et al., 2006). Although ADSCs satisfy these standards, some authors have argued that ADSCs are different from MSCs.

Studies have shown that adipose tissue is the richest source of MSCs. There are only 0.001–0.01% mononuclear cells in bone marrow (Pittenger et al., 1999), while adipose tissue contains up to 10% stem cells in the SVF. Recent studies have documented that 1 g of adipose tissue contains approximately 1–2 × 10^6 SVF cells, and 10% of these cells are thought to be ADSCs (Aust et al., 2004; Oedayrajsingh-Varma et al., 2006; Zhu et al., 2008). By comparing colony-forming units (CFUs) between umbilical cord blood, bone marrow, liposuctioned fat, and sliced fat, it has been shown that sliced fat contains the most CFUs (28,000 CFUs/g), whereas liposuc-

tioned fat has 3600–10,700 CFUs/g, umbilical cord blood has 200–20,000 CFUs/mL, and bone marrow has 100–1,000 CFUs/mL. Therefore, ADSCs have become a promising candidate for stem cell therapy.

ADSC PROPERTIES

ADSCs are generally considered as MSCs in the literature. They possess MSC properties, including a fibroblast-like shape when cultured under adherent conditions, differentiation potential for mesenchymal cell lineages such as osteoblasts, chondroblasts, and adipocytes, strong expression of some MSC markers such as CD44, CD73, CD90, and CD105, and negativity for CD14 (monocytes), CD34 (HSCs), CD45 (white blood cells), and HLA-DR (mature cells). However, some studies also show that ADSCs express markers other than those expressed by MSCs (**Table 1)**. ADSCs also express hematopoietic cell markers, pericyte markers, and muscle cell markers. These differences are related to culture conditions and adipose tissue collection. In fact, adipose tissue is usually contaminated with muscular or skin tissue (Basu et al., 2011; Tallone et al., 2011).

Table 1. Marker expression of ADSCs

Author	Positive expression	Negative expression
Gronthos et al. 2001 (Gronthos et al., 2001)	CD9, CD10, CD13, CD29, CD34, CD44, CD49d, CD49e, CD54, CD55, CD59, CD105, CD146, CD166, HLA-ABC	CD11a, CD11b, CD11c, CD31,CD45, CD50, CD56, CD62e, HLA-DR
Zuk et al. 2001 (Zuk et al., 2001)	CD13, CD29, CD44, CD49d, CD71	CD14,CD16, CD31,CD34, CD45
Zuk et al. 2002 (Zuk et al., 2002)	CD90, CD105, STRO-1, SH3	CD56, CD62e, CD104, CD106, SMA
Katz et al. 2005 (Katz et al., 2005)	CD29, CD49b, CD49d, CD49e, CD51, CD61, CD90, CD138, CD140a	CD11a, CD11b, CD11c, CD18, CD41a, CD49f, CD62L, CD62P, CD106, CD117, CD133, HLA-DR, ABCG2
Mitchell et al. 2006 (Mitchell et al., 2006)	CD13, CD29, CD34, CD44, CD49a, CD63, CD73, CD90, CD146, CD166	CD31, CD144
Yoshimura et al. 2006 (Yoshimura et al., 2006)	CD34, CD90	CD31, CD45, CD105, CD146
Oedayrajsingh-Varma et al. 2007 (Varma et al., 2007)	CD34, CD54, CD90, CD105, CD117, HLA-ABC, HLA-DR	CD31, CD45, CD106, CD146, CD166
Zannettino et al. 2008 (Zannettino et al., 2008)	CD44, CD90, CD105, CD106, CD146, CD166, STRO-1, 3G5	CD14, CD31, CD45
Traktuev et al. 2008 (Traktuev et al., 2008)	CD10, CD13, CD34, CD90, CD140a, CD140b, SMA	CD31, CD45, CD144
Lin et al. 2008 (Lin et al., 2008)	CD34	CD31, CD140b, SMA
Zimmerlin et al. 2010 (Zimmerlin et al., 2010)	CD34, CD90	CD31, CD146, SMA
Eom et al., 2011 (Eom et al., 2011)	CD44, CD73, CD90, CD105, and HLA-ABC	CD14, CD31, CD34, CD45, CD117, CD133, and HLA-DR
Zeng et al. 2013 (Zeng et al., 2013)	CD44, CD105, CD29, CD90, and CD13	CD31, CD34, CD45, and CD106
Pham et al.2013 (Van Pham et al., 2013)	CD44, CD73, CD90	CD14, CD34, CD45

ADSCs are multipotent stem cells that can differentiate into specific kinds of mesoderm lineage cells, including osteoblasts, chondroblasts, and adipocytes (**Table 2**). However, many studies also show that ADSCs can transdifferentiate into cell types of other lineages such as the ectoderm or endoderm. Differentiation of ADSCs into specific cells requires specific agents.

Table 2. Multiple-lineages differentiation of ADSCs

Kind of cells	Differentiation conditions	Authtors
Osteoblasts	Dexamethasone induction	(Zuk et al., 2002)
	Vitamin D3 induction	(Leong et al., 2006)
	17 beta-estradiol supplementation	(Hong et al., 2007)
	VEGF supplementation	(Behr et al., 2011)
	BMP2 + vitamin D3 induction	(Song et al., 2011)
	BMP2 + platelet-rich plasma	(Chen et al., 2012)
	PLGA scaffolds	(Hao et al., 2008)
	Tricalcium phosphate scaffolds	(Marino et al., 2010)
	PLA/Bioactive glass scaffolds	(Haimi et al., 2009)

	Micromass culture + TGF beta1	
Chondroblasts	Micromass culture + TGF beta1	(Zuk et al., 2001)
	Micromass culture + TGF beta2-expressing ASCs	(Jin et al., 2007; Lu et al., 2012)
	Micromass culture + TGF 3-expressing ASCs	(Lu et al., 2012)
	PRP	(Van Pham et al., 2013)
Adipocytes	Dexamethasone, isobutyl-methylxanthine, indo-methacin, and insulin	(Gharibi and Hughes, 2012)
	Biotin, pantothenate, insu-lin, dexamethasone, 3-isobutyl-1-methylxanthine (IBMX), 2,3-thiazolidinedione (TZD),	(Schiller et al., 2013)

APPLICATIONS OF ADIPOSE STEM CELLS IN THE CLINIC

Applications of adipose tissue grafts and lipoaspirated fat have been developed for the clinic. Initially, most applications of adipose tissue were related to plastic surgery. Subsequently, some studies used SVFs as concentrated adipose tissue containing mononuclear cells to replace whole adipose tissues. Moreover, transplantation of expanded ADSCs has been applied in the last 5 years.

The use of transplantation of SVFs and ADSCs has rapidly increased as of 2010. Based on gross calculations according to the clinical trials recorded in clinicaltrial.gov and articles cited in PubMed, at least 3000 patients have been treated with ADSCs or SVFs for more than 10 different diseases. Such treatments are related to plastic surgery, digestive diseases, autoimmune diseases, cardiovascular diseases, skeletal regeneration, neurologic diseases, hematological and immunological disorders, diabetes mellitus, urologic disorders and diseases, and lung disorders and diseases (**Fig. 1**). We found 124 clinical trials registered in clinicaltrial.gov with some clinical trials in phase III (**Table 3**) with a large number of patients (approximately 200 patients). Most clinical trials have been conducted in East Asia, Europe, and North America (**Fig. 2; Supplement 1**).

Studies have shown that ADSC transplantation for the treatment of numerous diseases is safe and effective. To date, there are about 5 clinical trials in Phase III for ADSC transplantation (NCT00475410, NCT01541579, NCT01378390, NCT01803347, andNCT00992147). Four of these clinical trials are related to perianal fistulas treatment. With more than 200 patients, the trial with registration number NCT00475410 showed that perinatal fistula can be effectively treated by ADSC grafts in platelet-rich plasma (PRP) glue with healing rates of approximately 40% at 6 months and more than 50% at the 1-year follow-up (Herreros et al., 2012). ADSC transplantation has also shown good results for treating many other diseases such as knee osteoarthritis (Bui et al., 2014; Koh and Choi, 2012), chronic ulcers (Marino et al., 2013), Crohn's fistula (Cho et al., 2013; de la Portilla et al., 2013; Garcia-Olmo et al., 2009; Lee et al., 2012), limb ischemia (Lee et al., 2012), femoral head necrosis (Pak, 2012), Parry-Romberg disease (Koh et al., 2012), radiotherapy-induced tissue damage (Rigotti et al., 2007), and maxillary and mandibulary bone tissue (Kulakov et al., 2008).

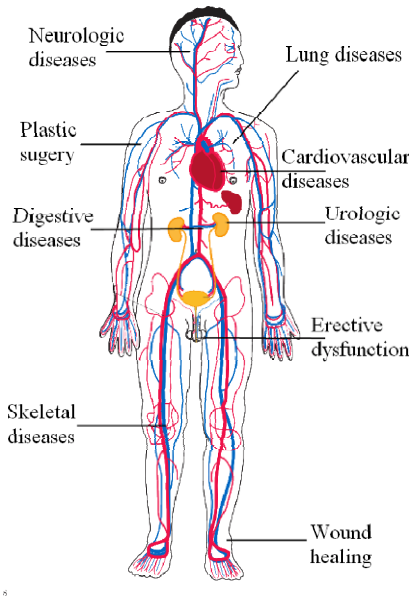

Figure 1. Some diseases were treated by adipose derived stem cells.

Table 3. Regions with ADSC transplantation in clinical trials*

Region Names	Number of Studies	
Central America	2	Panama
East Asia	32	Japan (3), Korea (21), China (3), Taiwan (5)
Europe	38	Austria (2), Belgium (2), Denmark (2), France (5), Germany (3), Italy (2), Netherlands (5), Poland (1), Spain (28), Switzerland (2), United Kingdom (4)
Middle East	3	Iran (1), Israel (2)
North America	38	Mexico (9), United States (29)
North Asia	3	Russian Federation
South America	3	Brazil
South Asia	1	India
Southeast Asia	4	Vietnam (2), Philippine (2)
World	***124***	

**According to http://www.clinicaltrial.gov*

SAFETY OF ADIPOSE STEM CELLS IN THE CLINIC

Similar to any other drug or therapy, ASC transplantation has some limitations and side effects. However, there are different risks for SVFs and ADSCs. SVFs are considered safer than ADSCs. SVFs are directly collected from adipose tissue with enzymes, and the risks of these samples are usually related to adipose tissue processing. In fact, Change et al. (2013) surveyed 100 randomly selected private plastic surgery clinics, 68 plastic surgery departments of general and university hospitals, and 5 biotechnology companies in South Korea that performed ADSC-related procedures using ADSCs they harvested themselves. They found no toxicity resulting from residual collagenase or tumorigenicity associated with the ADSCs (Chang et al., 2013).

However, the use of ADSCs or cultured SVF cells to isolate MSCs can be associated with high risks if applied in the clinic. Expanded ADSCs need to be carefully processed and controlled for application to humans. It is considered that cultured ADSCs should be assessed in terms of stability, toxicity, and tumorigenicity during culture. Some recent studies show that the quality of MSCs significantly decreases after long-term culture. Bonab et al. (2006) showed that MSCs derived from bone marrow underwent senescence after 6 passages, as some properties such as population doubling, telomere length, and differentiation potential decrease after the 6th passage (Bonab et al., 2006). Furthermore, extended culture of bone marrow-derived MSCs alters their ability to differentiate into hematopoietic progenitor cells without concomitant changes in their phenotype or differentiation capacity (Briquet et al., 2010). Another study showed that MSCs can transform into cancer cells (Rubio et al., 2005). However, this study was retracted in 2010. In fact, the researchers were unable to reproduce some of the reported spontaneous transformation events and suspected that the phenomenon had occurred because of cross-contamination artifacts (de la Fuente et al., 2010; Garcia et al., 2010). Rubio et al. also published two studies concerning MSC transformation (Rubio et al., 2008a; Rubio et al., 2008b). However, many other studies show that SVF or ADSC transplantation is safe in animals and humans.

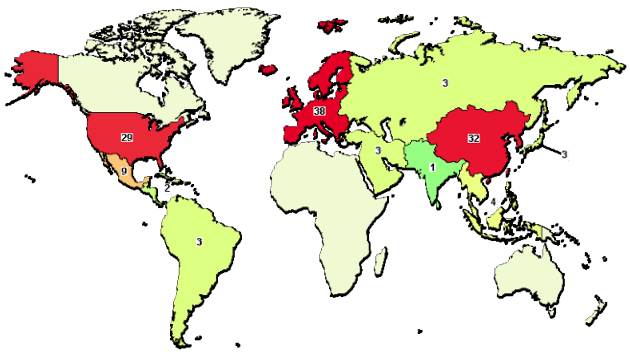

Figure 2. Map of clinical trials about ADSC transplantation in the world. In clinicaltrial.gov, Europe is area with the most clinical trials; and after East Asia, and North America.

In animals, SVF and ADSC transplantation by local injection (Gao et al., 2011; Gimble et al., 2010; Kojima et al., 2011; Kondo et al., 2009; Van Pham et al., 2013) and intravenous transfusion (Lim et al., 2013; Sun et al., 2012; Tajiri et al., 2014; Wang et al., 2013; Yanez et al., 2006) has shown high safety. In a recent long-term tumorigenic assessment of a mouse model, MacIsaas et al. injected expanded ADSCs into mice at high doses and the mice were followed up for 1 year (MacIsaac et al., 2012). They found no difference in the growth/weight and lifespan of cell- and vehicle-treated animals, and no malignancies were detected in the cell-treated animals. Expanded ADSCs have also been injected into the eyes (Rajashekhar et al., 2014). Expanded ADSC transplantation is safe in dogs (Black et al., 2008; Cui et al., 2007; Haghighat et al., 2011; Vilar et al., 2013), rabbits (Toghraie et al., 2011), rats (Tajiri et al., 2014), horses (Nicpon et al., 2013; Ricco et al., 2013), and pigs (Gomez-Mauricio et al., 2013; Niada et al., 2013).

In the clinic, most studies of SVF and ADSC transplantation show that local injection and systemic transfusion of ADSCs are safe. Non-expanded SVF cells have been clinically applied to treat multiple sclerosis (Riordan et al., 2009), knee osteoarthritis (Bui et al., 2014), and femoral head necrosis (Namazi, 2012; Pak, 2012). Autologous expanded ADSCs have been isolated and in vitro-expanded to obtain enough cells for perianal fistula treatment. More than 200 patients were enrolled for intralesional treatment. The results demonstrated that this method is safe and effective (de la Portilla et al., 2013; Garcia-Olmo et al., 2009; Herreros et al., 2012), even after 3 years (Guadalajara et al., 2012). The procedure of expanded ADSC-enriched fat grafting has excellent feasibility and safety (Kolle et al., 2013). Expanded ADSCs have also been injected into the myocardium to treat chronic myocardial ischemia, which showed safety after 3 years (Qayyum et al., 2012).

Lee et al. (2012) showed that intramuscular injection of passage 3 ADSCs into patients with critical limb ischemia is safe, and clinical improvements were observed in 66.7% of patients after 6 months (Lee et al., 2012). Koh and Choi injected ADSCs into patients with knee osteoarthritis. They also recorded a clinical improvement without adverse effects (Koh and Choi, 2012). Ra et al. (2011) also showed that ADSCs could be expanded up to 12 passages while maintaining their MSC properties. These ADSCs were intravenously transfused into SCID mice, Balb/c-nu mice, and 8 male patients. The results showed that none of the mice or humans developed any serious adverse events related to ADSC transplantation during the 3-month follow-up in humans and over 26 weeks in mice. This study used extremely high doses of 2.5 × 10^8 cells/kg in mice and 4 × 10^8 cells in humans (Ra et al., 2011b). Ra et al. also used expanded ADSCs for treating autoimmune disease by intravenous transfusion.

They also showed that there were no side effects in the 10 enrolled patients (Ra et al., 2011a). Intravenous infusion of autologous expanded ADSCs has been approved as a safe method in the treatment of progressive supranuclear palsy (Choi et al., 2014). Intravenous infusion of allogeneic expanded ADSCs is also safe for the treatment of acute respiratory distress syndrome (Zheng et al., 2014),

In addition to the risks related to mutations and transformation of ADSC during long-term culture, adverse effects of ADSC transplantation also depend on the culture conditions. In general, GMP-compliant culture is considered to be essential to ensure ADSC quality. One of the concerns of ADSC culture relates to supplementation of fetal bovine serum (FBS) in the culture medium. FBS not only contains xenogeneic proteins that cause immune reactions, but can also transmit viruses. However, some studies have clinically used ADSCs expanded in FBS culture medium.

SVFs and ADSCs in the clinic

SVFs are a mixture of mononuclear cells including more than 5 kinds of cells, whereas ADSCs are a heterogeneous cell population of the SVF. This cell population is purified by adherent culture. It is easy to understand when there are a comparable mean between adipose tissue and bone marrow, SVFs and mononuclear cells (MNCs). Some studies have considered SVF cells as ADSCs; however, these cells are in reality different. Similar to MNCs and MSCs from bone marrow, there are few studies that have compared transplantation efficiencies between SVFs and ADSCs. Compared with MSCs, MNCs from bone marrow have some advantages in certain cases (Karlupia et al., 2014).

Further investigations need to be performed, but it is likely that leukocytes and red blood cells contaminate SVFs or MNCs, resulting in adverse effects. Recent studies in animal models show that MNCs or SVF with leukocyte or red blood cell contamination cause graft-versus-host disease or autoimmune diseases. However, some studies demonstrate that various kinds of stem cells are included in MNCs or SVFs, which contribute to their regeneration (Lv et al., 2013).

Future of ADSC transplantion

ADSCs have become the main type of adult stem cell that is approved for use in humans. ADSC transplantation has been gradually developed in many countries for the treatment of chronic and degenerative diseases. Although ADSC transplantation has some clinical benefits, the specific mechanisms of ADSC-based treatment are unclear. For successful ADSC application, ADSC migration should be controlled in the human body. Moreover, there should be verification of the in vivo differentiation of ADSCs.

Some recent clinical studies have shown that ADSC transplantation shows better results when used in combination with certain therapies. In fact, a new strategy is the use of adjuvants in ADSC transplantation. Adjuvants are considered as stimulators and differentiating factors that can improve the patient's condition. The most commonly used adjuvant is PRP. In combination with ADSCs, PRP has been successfully applied in the treatment of osteoarthritis (Bui et al., 2014). Furthermore, some cytokines or vitamins may improve the quality or viability of ADSCs in the human body.

For other approaches, studies have focused on the in vitro differentiation of ADSCs into specific cell types. These specific types of cells can be used in stem cell therapy and tissue engineering to create tissues for transplantation.

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Abbreviations

AMSCs: Adipose MSCs; Adipose-derived adult stem: ADAS; ADSC: Adipose-derived stem cells; CFUs: colony-forming units; FBS: fetal bovine serum; GMP: Good manufacturing practice; IFAT: International Fat Applied Technology Society; PLA: Lipoaspirate cells; MSC: Mesenchymal stem cell; MNC: Mononuclear cells; PRP: Platelet rich plasma, SVF: stromal vascular fraction

Competing interests

The authors declare that they have no competing interests.

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Supplement 1. Some clinical trials classified based on kinds of disease used ADSC transplantation

Clinical trial	Phase	Clinical trial number	Protocol	Location
Plastic surgery				
Study of autologous adipose-derived stem cell transplantation in patients with lipodystrophy	I	NCT00715546	Autologous transplantation of liposuction material enriched with adipose-derived stem cells	Brazil
Effect of human adipose tissue–derived MSCs in Romberg disease	II	NCT01309061	Intramuscular infusion of autologous ASCs (10^7 cells/500 ul)	Korea
Safety and efficacy of autologous cultured adipocytes in patients with depressed scar (AdipoCell)	II/III	NCT00992147	From 0.11–4.63 x 10^7 autologous ASCs into each scar	Korea
Study to demonstrate the effectiveness of Antria cell preparation process in extraction of SVF from adipose tissue	I	NCT01399307		United States
Digestive diseases				
Study AdipoPlus: efficacy and safety of autologous ASCs for Crohn fistula	I	NCT01011244	Local injection of autologous ASCs	Korea
Study ALOREVA: efficacy and safety of allogenic ASCs for treatment of recto-vaginal fistulas in Crohn disease	I-IIa	NCT00999115	Intralesional injection of 20–40 x 10^6 allogenic ASCs	Spain
Safety and Efficacy Study of Autologous Cultured Adipose -Derived Stem Cells for the Crohn's Fistula	II	NCT01011244	Local injection of 10^7 autologous ASCs	Korea
Follow-up Study of Autologous Cultured Adipose-derived Stem Cells for the Crohn's Fistula (ANTG-ASC-203)	II	NCT01314079		Korea
Safety and Efficacy of Adipose-Derived Stem Cells to Treat Complex Perianal Fistulas Patients With Crohn's Disease (FATT)	III	NCT01378390	Intralesional injection of 20–40 x 10^6 autologous ASCs	Austria, Spain, The Netherlands
Efficacy and Safety of Adipose Stem Cells to Treat Complex Perianal Fistulas Not Associated to Crohn´s Disease (FATT1)	III	NCT00475410	Intralesional injection of 20–40.10^6	Spain, Germany, United Kingdom
Autoimmune diseases				
Safety and Effects of Autologous Adipose-Derived Stromal Cells Delivered in Patients With Type II Diabetes	I/II	NCT01453751	Intravenous injection of SVF cells from 100 ml of fat	Philippines
Safety and efficacy of autologous Adipose-Derived Stem Cell Transplantation in Patients With type 1 diabetes	I/II	NCT00703599	Intravenous injection of SVF cells from 100 ml of fat	Philippines
Treatment of Patients With Newly Onset of type 1 diabetes With Mesenchymal Stem Cells	I/II	NCT01068951	Autologous transplantation of the patients own mesenchymal stem cells (approximately 2 x 10^6 cells/kg body weight) intravenously.	Sweden
Safety and effects of autologous adipose-derived stromal cells delivered in patients with type II diabetes	I/II	NCT01453751	Intravenous administration of the ASCs	United states
Autologous adipose tissue derived mesenchymal stem cells transplantation in patient with Buerger's disease	I/II	NCT01302015	Intramuscular injection of 5 x 10^6 cells/kg	Korea
Multicenter Clinical Trial for the Evaluation of Mesenchymal stem cells From adipose Tissue in Patients With Chronic	I/II	NCT01222039	Conventional treatment plus intravenous infusion of allogenic mesenchymal stem cells from adipose tissue.	Spain

Cardiovascular diseases				
A Randomized Clinical trial of Adipose-derived Stem Cells in Treatment of Non Revascularizable Ischemic myocardium	I	NCT00426868	Direct injection of ADRCs into the Left Ventricle	Spain
Clinical Trial of Autologous adipose tissue Derived Stromal Cell Therapy for Ischemic Heart Failure	I	NCT01709279	Intra-coronary administration of autologous adipose tissue derived stroma cells	Japan
Randomized Clinical trial of Adipose-Derived Stem Cells in the treatment of Pts With STelevation myocaridal Infarction	I	NCT00442806	Injection of ADRC's	Netherlands, Spain
Human adipose Derived Mesenchymal stem cells for Critical Limb ishcemia in Diabetic Patients	I/II	NCT01257776	Intra-arterial administration through a selective cannulation of target common femoral artery	Spain
Autologous adipose -Derived Stromal Cell Delivered Via Intramuscular Injections for the Treatment of Critical Limb Ischemia	I/II	NCT02099500	Stem cell implantation will be performed using intramuscular injection into the affected ischemic site of interest	United States
Safety and Effect of adipose Tissue Derived Mesenchymal Stem cells Implantation in Patients With Critical Limb Ishcemia	I/II	NCT01663376	To evaluate the change of treated critical limb ischemia before cell implantation and at 3, 6, 12 months post injection of MSCs	Korea
Application of cell Regeneration Therapy With Mesenchymal stem cells From adipose Tissue in Critical Chronic ischemic Syndrome of Lower limbs in Nondiabetic Patients	I/II	NCT01745744	Infusion of mesenchymal stem cells from adipose tissue administered intraarterially: $0.5x10^6$ cells / kg of patient weight and $1x10^6$ cells/ kg of patient weight	Spain
Treatment CLI Nonrevascularizable Lower Limb With Cell Therapy (HULPVAS)	I/II	NCT01824069	Intramuscular injection of a suspension of adult mesenchymal stem cells derived from adipose tissue at doses of 1 million per kilo of weight	Spain
Feasibility Study of the TGI adipose - derived Stromal Cell (ASC)-Coated ePTFE Vascular Graft	I/II	NCT01305863	An ePTFE vascular graft in which the lumen of the graft has been coated with an autologous coating of adipose - derived stromal cells (ASC)	United States
ACELLDream (patients with peripheral vascular disease not amenable to bypass or angioplasty)	I/II	NCT01211028	Intramuscular injection of 100 x 10^6 autologous ASCs; Adverse events	France
Treatment of diabetic lower extremity wounds and venous stasis ulcers with lipoaspirate injection	I/II	NCT00815217	Local injection of adipose tissue containing ASCs; Wound healing	United States
Skeletal regeneration				
Autologous Mesenchymal Stem Cells vs. Chondrocytes for the Repair of Chondral Knee Defects	I/II	NCT01399749	Local implantation of 106 autologous ASCs/ cm^2 lesion	Spain
Autologous Adipose-Derived Stromal Cells Delivered Intra-articularly in patients with osteoarthiris	I/II	NCT01739504	Liposuction and intra-articular injection	United States
ADIPOA - Clinical Study	I	NCT01585857	Autologous adipose derived stem cells administrated for intra-articular use	France
Autologous Adipose Stem Cells and Platelet Rich Plasma Therapy for Patients With Knee Osteoarthritis	I/II	NCT02142842	Autologous stromal vascular fraction (SVF) and platelet rich plasma (PRP) will be injected into joints	Vietnam

Neurologic diseases				
AutologousMesenchymal Stem Cells From Adipose Tissue in patiens with secondary progressive multiple Sclerosis	I/II	NCT01056471	Intravenous infusion of autologous mesenchymal stem cells. Dose: 10^6 cells/Kg	Spain
Safety and Clinical Outcomes Study: SVF Deployment for Orthopedic, neurologic, Urologic, and Cardiopulmonary conditions	I/II	NCT01953523	Administration of autologous adipose derived SVF Intra-venous, intra-articular, and soft tissue injection delivery of SVF	United States
Intrathecal Transplantation Of Autologous Adipose Tissue Derived MSC in the Patients With Spinal Cord Injury	I	NCT01624779	Autologous adipose tissue derived mesenchymal stem cells	South Korea
Treatment of Sequelae Caused by Severe Brain Injury With Autologous adipose derived Mesenchymal stem cells	I/II	NCT01649700	Patients will receive five infusions, one month apart, each comprising 5-7x10^7 cells of autologous adipose derived mesenchymal stem cells	Taiwan
Treatment of Cerebellar Ataxia With Mesenchymal stem cells	I/II	NCT01649687	Patients will receive intravenously one dose of 5-7.10^7 cells of allogeneic adipose -derived mesenchymal stem cell	Taiwan
Safety and Effect of adipose Tissue Derived Mesenchymal stem cell Implantation in Patients With Spinal Cord injury	I/II	NCT01769872	Intravenous injection of Autologous adipose Derived Mesenchymal stem cell. Dose : 2x10^8 cells/ 20mL Intrathecal injection of Autologous adipose Derived Mesenchymal stem cell. Dose : 5x10^7 cells / 2mL Into a spinal cord injection of Autologous adipose Derived Mesenchymal stem cell. Dose : 2x10^7 cells / 1mL	Korea
Reparative Therapy in Acute Ischemic Stroke With Allogenic Mesenchymal stem cells From adipose Tissue, Safety Assessment, a Randomised, Double Blind Placebo Controlled Single Center Pilot Clinical Trial	II	NCT01678534	A single intravenous dose within the first two weeks after the onset of stroke symptoms. Dose: 1 million units/kg	Spain
Autologous adipose Derived MSCs Transplantation in Patient With Spinal Cord	I	NCT01274975	Intravenous infusion of Autologous adipose Derived Mesenchymal stem cells. Dose : 4.10^8 cells	Korea
Transplantation of Autologous adipose Derived stem cells (ADSCs) in Spinal Cord Injury treatment	I/II	NCT02034669	Device: Laminectomy Device: Intradural space Device: Intrathecal Device: Intravenous	Vietnam
The Effect of Human adipose Tissue-derived MSCs in Romberg's disease	II	NCT01309061	Intramuscular infusion of Autologous adipose Tissue derived MSCs with autologous microlipoinjection. Dose: 1x10^7 cells/500ul/lipoinjection 20ml	Korea
Study to Assess the Safety and Effects of Autologous adipose -Derived Stromal in Patients With Parkinson's disease	I/II	NCT01453803	The adipose tissue is transferred to the laboratory for separation of the adipose tissue-derived stem cells, which are then transferred for catheter injection	Mexico
Safety and Effects of Autologous adipose -Derived Stromal cells in Patients With Diffuse Lesions in the brain	I/II	NCT01453777	The cells will be delivered MMvia catheter into the internal carotid artery and intravenously	Mexico
Study to Assess the Safety and Effects of Autologous adipose Derived Stromal cells in Patients After stroke	I/II	NCT01453829	The cells will be implanted into the Internal Carotid Artery and intravenously	Mexico
Autologous adipose Tissue Derived Mesenchymal stem	I/II	NCT01643681	Into lumbar intervertebral disc infusion. Autologous adipose Derived Mesen-	Korea

cells Transplantation in Patient With Lumbar Intervertebral Disc degeneration			chymal stem cells. Dose : 4.10^7 cells/1ml	
Pulmonary diseases				
Evaluate Safety and Efficacy of Intravenous Autologous ADMSc for Treatment of Idiopathic Pulmonary fibrosis	I/II	NCT02135380	Ex-vivo expanded Mesenchymal stem cells (MSC) intravenously each. All the three doses will be given at weekly intervals	India
Safety and Efficacy of adipose Derived stem cells for Chronic Obstructive Pulmonary diseases	I/II	NCT01559051	Patients undergo a liposuction where 120 cc of fat are extracted. The ADSCs are then isolated and injected intravenously	United States
Adipose Derived cells for Chronic Obstructive Pulmonary diseases	I/II	NCT02041000		United States
Adipose derived Mesenchymal stem cells in Acute Respiratory Distress Syndrome	I	NCT01902082	Patients received one dose of 10^6 allogeneic adipose derived mesenchymal stem cells/kg body weight intravenously within 48 hours of enrollment	China
Liver diseases				
Liver Regeneration Therapy Using Autologous adipose Tissue Derived Stromal cells	I	NCT00913289		Japan
Liver Regeneration Therapy by Intrahepatic Arterial Administration of Autologous adipose Tissue Derived Stromal cells	I	NCT01062750	Adipose tissue derived stromal cells dosage single administration of autologous adipose tissue derived stroma cells via intrahepatic arterial catheterization	Japan
Stem Cells Treatment for the Local Urinary Incontinence After a Radical Prostate Cancer Surgery	II	NCT01799694	Inject in muscle of autologous adipose derived stem cells	Spain
Stem Cells Treatment for the Local Feminine Stress Urinary Incontinence Treatment	I/II	NCT01804153	Intralesional application ASC	Spain
Study to Assess the Safety and Effects of Autologous Adipose Derived Stromal Cells Delivered in Patients With Renal Failure	I/II	NCT01453816	The cells will be delivered via catheter into the renal artery and intravenously	Mexico
Effectiveness and Safety of Autologous adipose Derived Regenerative cells for the Treatment of Urethral Strictures	I/II	NCT01889888	Lipoaspirate will be processed to isolate and concentrate ADRCs. Patients will undergo mechanical dilation followed by submucosal periurethral ADRC injections circle-wise into stricture site under endoscopic vision	Russian
Effectiveness and Safety of cells Assisted Lipotransfer for the Treatment of Stress Urinary incontinence	I/II	NCT01850342	Autologous fat micrograft enriched with ADRC will be injected at the bulbomembranous region of urethra circle-wise under endoscopic vision	Russian
MSC for Occlusive Disease of the kidney	I	NCT01840540		United States
Diabetes mellitus				
Safety and Efficacy of Autologous Adipose Derived Stem Transplantation in Patients With Type 1	I/II	NCT00703599	Intravenous administration of autologous activated stromal vascular fraction derived from 100-120 ml lipoaspirate	Phillipines
Safety and Efficacy of Autologous Adipose Derived Stem cells Transplantation in Type 2 diabetics	I/II	NCT00703612	Intravenous administration of autologous activated stromal vascular fraction derived from 100-120 ml lipoaspirate following mini-liposuction of abdominal adipose tissue	Philippines

Safety and Effects of Autologous adipose -Derived Stromal Cells Delivered in Patients With Type II diabetes	I/II	NCT01453751		United States
Wound healing				
Adipose Derived Regenerative Cellular Therapy of Chronic wounds	II	NCT02092870	Patients will receive a single treatment with ASCs. Cells will be delivered using a 1 cc syringe with an appropriate gauge and length needle.	United States
Others				
Stem cell for the Improvement of erectile and Cardiac Function in Aging men	I	NCT02107118	Cells are returned to the study doctor for installation into the subject every 2 weeks for 3 months	United States
Autologous adipose Derived Stromal cells Delivered Into the Corpus Cavernous in Patients With erectile dysfunction	I/II	NCT02087397	Stem cells implantation will be performed using direct injection into the Corpus	United States