

# Adipose-Derived Stem Cells (ASCs) for Tissue Engineering

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## 1. Introduction

A current challenge in the field of tissue engineering is soft tissue replacement. Techniques for soft tissue reconstruction include use of autologous fat transplantation, alloplastic implants and autologous tissue flaps. However, these approaches have disadvantages, including donor-site morbidity, implant migration, foreign body reaction and immune system rejection. The use of autologous stem cells expanded *in vitro* and combined with novel biomaterials for organ reconstruction offers a potential solution for replacement of tissue or whole organs. Stem cells, first identified in embryonic tissue and later in numerous adult tissues, possess the unique capacity to differentiate into wide range of tissue types. However, although embryonic cells are the most flexible of stem cell lines, they raise the problem of ethical issues. For tissue engineering, candidates of stem cells include embryonic stem cells (Ahn, et al.), induced pluripotent stem cells (iPS) (Crisan, et al.;2008, Parker, et al.;2007) and adult stem cells. The ability of adult stem cells to divide or self-renewal make them attractive source of stem cells for use in tissue engineering. A significant amount of current interest has focused on the possibility that adult human stem cells are the therapeutic alternative to embryonic stem cells because of their plasticity (Aoki, et al.;2010). The presence of self-renewing cells within the bone marrow of mice was reported in 1963 which was later known as hematopoietic stem cells (HSCs) (Becker, et al.;1963, Zhang, et al.;1999). Several years later, HSCs were identified in umbilical cord blood by other investigators (Aust, et al.; 2004, Dellavalle, et al.;2007). Furthermore, several other adult stem cell types such as neural stem cells (Dellavalle, et al.; 2007, Guilak, et al.;2010), were isolated and identified. Moreover, a population of plastic adherent cells were isolated from collagenase digests of adipose tissue.

Adipose tissue derived stem cells were termed as: adipose derived stem/stromal cells (ASCs), adipose-derived adult stem (ADAS) cells, adipose-derived adult stromal cells, adipose-derived stromal cells (ADSCs), adipose stromal cells (ASCs), adipose mesenchymal stem cells (AdMSCs), lipoblast, pericyte, preadipocyte, and processed lipoaspirate (PLA) cells. To prevent the confusion in the literature, the International Fat Applied Technology

Society reached a consensus to adopt the term “adipose-derived stem cells” (ASCs) to identify the isolated, plastic-adherent, multipotent cell population (Gimble, et al.;2007). Adipose tissue derives from the mesodermal layer of the embryo and develops both pre- and postnatally (Gonda, et al.;2008, Kakudo, et al.;2008). Researchers studying the development of adipose tissue have long worked with a fibroblastic cell line, known as preadipocytes, isolated from adipose tissue (Cowherd, et al.;1999, Gregoire, et al.;1998, Kirkland and Hollenberg;1998, Nam and Lobie;2000, Sorisky;1999).

The reason why adipose tissue would contain a stem cell population is not still clear. There is some discussion whether the cells are subpopulation of fibroblasts reside within the fat tissue or are perhaps mesenchymal or peripheral blood stem cells passing through the fat tissue (Crisan, et al.; 2008, Dellavalle, et al.; 2007).

The ASCs represent a readily available source for isolation of potentially useful stem cells (Sterodimas, et al.; 2010). In culture, they have shown to have an impressive developmental plasticity, including the ability to undergo multilineage differentiation and self-renewal (Liu, et al.; 2009). When ASCs are compared with BM-MSCs, further similarities have been demonstrated in regards to their growth kinetics, cell senescence, gene transduction efficiency (De Ugarte, et al.; 2003), as well as CD surface marker expression (Gronthos, et al.; 2001, Katz, et al.; 2005, Zuk, et al.; 2002) and gene transcription (Katz, et al.; 2005). Compared to bone marrow MSCs, ASCs have potential advantages for tissue engineering application, because of the tissue accessibility, multipotency and ease of isolation without painful procedures or donor site injury.

In this chapter we will discuss the potential use of adipose-derived stem cells in the field of tissue engineering.

## 2. Isolation and expansion of ASCs

The initial methods to isolate cells from adipose tissue were pioneered by Rodbell and colleagues in the 1960s (Rodbell; 1966, Rodbell; 1966, Rodbell and Jones; 1966) using rat fat tissue. These methods were further adapted for human tissues by several other groups (Deslex, et al.; 1987, Engfeldt, et al.; 1980, Ho, et al.; 2010). The current methods for isolating ASCs rely on a collagenase digestion followed by centrifugal separation to isolate the stromal/vascular cells from primary adipocytes. The pellet is resuspended with a basal medium containing 10% foetal bovine serum (Estes, et al.; 2008). The cell suspension is filtered through 100 µm cell strainer and the cells are plated and incubated at 37°C in the presence of 5% CO<sub>2</sub>. The medium is changed every second day until the cells reach 80-90% confluence. A large number of ASCs can be harvested in this manner, with yields of approximately 250,000 cells per gram of tissue (Aust, et al.; 2004, Guilak, et al.; 2010). In order to remove the use of animal products in human ASC cultures, a very low human serum expansion medium and a completely serum-free medium have been recently reported (Parker, et al.; 2007). Furthermore it was reported that use of platelet- rich plasma can enhance the proliferation of human ASCs. These results can support the clinical application of platelet-rich plasma for cell based, soft-tissue engineering and wound healing (Kakudo, et al.; 2008).

ASCs should be harvested at 80% confluence for freezing. Cryopreservation medium consists of 80% fetal bovine serum, 10% dimethylsulfoxide (DMSO) and 10% DMEM/Ham’s F-12. The cells should be stored in a final concentration of 1-2 million viable cells per milliliter of cryopreservation medium. Aliquoted vials are first frozen in an alcohol freezing

container and store and are stored at  $-80^{\circ}\text{C}$  overnight. On the next day, the frozen vials can be transferred to a liquid nitrogen container for long-term storage. Successful storage of ASCs more than 6 months has been shown. This ensures the availability of autologous banked ASCs for clinical applications in the future (De Rosa, et al.;2009, Gonda, et al.;2008).

## 2.1 Characterization of ASCs

In order to characterize the undifferentiated animal or human ASC cells cultured *in vitro* flow cytometric and immunohistochemical methods are widely used (Gronthos, et al.; 2001, Zuk, et al.; 2001). The cell surface phenotype of ASC is quite similar to MSCs (mesenchymal stem cells). Both ASC and MSC cells express CD29, CD44, CD71, CD90, and CD105 (Zuk, et al.; 2002). In contrast, no expression of the hematopoietic lineage markers CD31, CD34 and CD45 was observed in either of the cultures. In addition the ASC cells express the neutral endopeptidase (CD10 or common acute lymphocytic leukemia antigen CALLA), aminopeptidase (CD13), and ecto nucleotidase (CD73). Furthermore, ASC cells produce Type I and Type III collagens, osteopontin, osteonectin, Thy-1 (CD90), and MUC-18 (CD146) (Gimble and Guilak; 2003).

Different investigator have reported different pattern of expression. For example, while Gronthos et al. (Gronthos, et al.;2001) detected CD34 and VCAM (CD106) on ASC cells, Zuk et al. (Zuk, et al.;2002) did not. Likewise, while Zuk et al. (Zuk, et al.;2002) detected Stro-1, Gronthos et al. did not. These discrepancies could be due to the differences in cell isolation methods, how long the cells were cultured prior to analysis and sensitivity differences between immunohistochemical and flow cytometric detection methods (Zuk, et al.;2002, Zuk, et al.;2001).

## 3. ASCs applications

Adipose tissue has proven to serve as an abundant source of adult stem cells with multipotent properties suitable for tissue engineering and regenerative medical applications. ASCs can be differentiated into variety of cell types. Differentiation is commonly induced by insulin, dexamethasone, cyclic AMP agonist,  $\beta$ -glycerophosphate, heparin, ascorbate and different cytokines depending on the lineage type.

ASCs like BM-MSCs, differentiate *in vitro* towards soft tissue such adipocytes, smooth muscle and cardiac myocytes when treated with established lineage-specific factors. In addition they can differentiate toward musculoskeletal tissues such as osteocytes, myocytes and chondrocytes. Furthermore neurogenic differentiation of these cells is reported by several investigators.

### 3.1 ASCs differentiation

#### 3.1.1 Adipogenesis

ASCs in response to inductive compounds including glucocorticoid receptor ligands (dexamethasone), insulin, cyclic AMP agonist (forskolin) and peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) undergo adipogenic differentiation (Farmer; 2006, Hauner, et al.; 1989, Lazar; 2005, Zuk, et al.; 2001). During the differentiation process ASCs reduce their proliferation rate and undergo morphological changes. ASCs are induced in the adipocyte differentiation medium containing biotin, d-pantothenate, dexamethasone, methylisobutylxanthine, insulin and equivalent PPAR $\gamma$  agonist. After induction for 2 weeks in adipogenic medium the human ASC contain vacuoles filled with neutral lipid cells which

can be further stained for intracellular lipid droplets accumulation using an Oil Red O stain (Preece;1972).

In addition, these cells secrete increased amounts of the adipocyte protein leptin, and transcribe adipogenic mRNAs such as the fatty acid binding protein, aP2 and lipoprotein lipase (Halvorsen, et al.; 2001, Hauner, et al.; 1989, Sen, et al.; 2001). Some of these parameters such as leptin, aP2 mRNA levels were quantified and found to be increased by several hundred-fold during the differentiation process (Halvorsen, et al.; 2001, Sen, et al.; 2001). It is reported that ASCs harvested from female mice differentiate more efficiently into adipocytes than those from male mice (Ogawa, et al.; 2004).

One of the most important uses of ASCs is for the replacement of adipose tissue itself. Large soft tissue defects are a common problem following trauma, burns and oncological resections. Several studies demonstrated the *in vitro* differentiation of ASCs along adipogenic lineages, including the accumulation of intracellular lipid droplets, and the expression of characteristic proteins and enzymes (Ogawa, et al.; 2004, Tchkonina, et al.; 2002, Zuk, et al.; 2002). ASCs were used to seed artificial scaffolds and were further implanted subcutaneously in mice and rats (von Heimburg, et al.; 2001, von Heimburg, et al.; 2001). The cell-seeded grafts showed significant neovascularisation of the implant, as well as penetration of the preadipocytes or ASCs into the scaffolding, and their differentiation into mature lipid-laden adipocytes.

### 3.1.2 Smooth muscle

ASCs can be differentiated to smooth muscle cells (SMCs) and might offer a cell source for hollow organ engineering. For myogenic differentiation ASCs at passages 3 through 5 are cultured in smooth muscle inductive medium consisting of MCDB131 supplemented with 1% FBS and 100u/ml of heparin for up to 6 weeks at 37°C with 5% CO<sub>2</sub>. The media is changed every 3 days and cell splitting is not required (Jack, et al.; 2009).

The cellular changes after differentiation can be investigated by real-time PCR at mRNA level. As reported the expression of muscle actin (SMA), calponin and myosin heavy chain showed an increase after growth in differentiation medium (Jack, et al.; 2009). The same was observed at protein levels, induction media induced differentiation of the ASCs into a smooth muscle phenotype in which the expression of smooth muscle specific proteins SMA, caldesmon, and myosin heavy chain (MHC) was increased (Jack, et al.; 2009).

Differentiation is a complex process and has a dramatical effect on cell size, shape, membrane potential, metabolic activity and responsiveness to external signals. One of the main characteristic of SMCs is their contractility which plays important roles in angiogenesis, blood vessel maintenance, and mechanical regulation of hollow organs such as bladder.

Differentiated SMCs can show two specific phenotypes, which vary from synthetic and proliferative to contractile and quiescent (Beamish, et al.; 2010). SMCs exhibit a contractile phenotype characterized by high expression of specific contractile proteins including SMA, calponin, SM22, smoothelin, *h*-caldesmon and smooth muscle myosin heavy chain (SM-MHC) (Owens, et al.; 2004, Shanahan, et al.; 1993).

Since differentiated human ASCs express smooth muscle specific proteins they may prove to be of value in the repair of smooth muscle defects in the gastrointestinal and urinary tracts. Juan et al. reported that the ASCs from different sites show different myogenic differentiation abilities *in vitro*. ASCs from the adipose tissues of the nape of the neck and

vicinity of epididymis can be used as ideal seed cells for tissue engineering of lower urinary tract (Yuan, et al.; 2010). Similar study was performed by other group using human subcutaneous and omental adipose tissues. They could show that subcutaneous adipose tissue has higher differentiation capacity than omental adipose tissue which can be a suitable cell source for use in regenerative medicine (Toyoda, et al.; 2009).

### 3.1.3 Osteogenesis. Bone defect repair

In the past decade, several groups isolated cells from the adipose tissue of humans and other species capable of differentiating into osteoblasts *in vitro* (Dragoo, et al.; 2003, Mizuno, et al.; 2002, Zuk, et al.; 2001). ASC cells differentiate into osteoblast-like cells in the presence of ascorbate,  $\beta$ -glycerophosphate, dexamethasone and vitamin D3.

For osteogenic differentiation confluent ASCs cells are incubated for 3 weeks in DMEM containing 10% FBS, 100 nM dexamethasone, 10 mM  $\beta$ -glycerophosphate and 50  $\mu$ M L-ascorbic acid-2-phosphate. After fixation cells are incubated at 37°C for 1 hour with 0.16% naphthol AS-TR phosphate and 0.8% Fast Blue BB dissolved in 0.1 M tris buffer (pH 9.0). For osteogenic differentiation cells were also incubated in 1% alizarin red S for 3 minutes to detect calcium deposition (Sakuma, et al.; 2009).

Over a 2- 4 week period *in vitro*, both human and rat ASC cells deposit calcium phosphate mineral within their extracellular matrix, and express osteogenic genes. Under osteogenic conditions ASCs are observed to express genes and proteins associated with osteoblast phenotypes such as osteopontin, osteonectin, osteocalcin collagen type I, BMP-2 and BMP-4 (Halvorsen, et al.; 2001, Zuk, et al.; 2001). In addition ASCs are able to form mineralized matrix *in vitro* in both long term 2-D or 3-D osteogenic cultures.

*In vivo*, ASC cells embedded in porous cubes of hydroxyapatite/tricalcium phosphate form bone were used as implants in immunodeficient mice (Hicok, et al.; 2004). New osteoid, derived from the human ASC cells, is present within a 6-week incubation period (Hicok, et al.; 2004). This finding indicates that ASCs cells will have therapeutic applications in bone repair. The first case of autologous ASC use for osseous repair has been reported in the treatment of a calvarial defect in a 7-year-old girl (Lendeckel, et al.; 2004). Using different type of scaffolds, human ASC can form bone in immunodeficient mice (Hicok, et al.; 2004, Lee, et al.; 2003).

### 3.1.4 Myogenesis: skeletal muscle repair

There is several line of evidence that ASC cells can differentiate along each of the myocyte lineage pathways when cultured in myogenic induction medium containing 0.1 mM dexamethasone, 50 mM hydrocortisone, 10% FBS and 5% horse serum. ASCs express MyoD and myogenin, transcription factors regulating skeletal muscle differentiation (Pittenger, et al.; 1999, Zuk, et al.; 2001).

Skeletal myogenesis is characterized by a period of myoblast proliferation, followed by the expression of muscle-specific proteins and fusion to form multinucleated myotubules. Early myogenic differentiation is characterized by the expression of several myogenic regulatory factors including myogenic determination factor MyoD1 (Weintraub, et al.; 1991). Terminally differentiated myoblasts can be characterized by the expression of myosin and the presence of multiple nuclei (Silberstein, et al.; 1986).

In the first *in vivo* report, F Bacou et al injected ASCs into the anterior tibialis muscle of rabbits following cardiotoxin-induced injury. Consistent with prior work using satellite cells

treated muscles were found to be heavier, have an increased fibre area cross-section and exert greater maximal force (Boubaker el Andaloussi, et al.; 2002).

### 3.1.5 Chondrogenesis

ASCs display chondrogenic characteristics following induction with ascorbate, dexamethasone and transforming growth factor- $\beta$  (Awad, et al.; 2003, Huang, et al.; 2004, Zuk, et al.; 2001). Under inductive conditions ASCs express aggrecan, chondroitin sulphate, collagen type II and IV and proteoglycans associated with chondrogenic phenotype. (Awad, et al.; 2004, Erickson, et al.; 2002, Wickham, et al.; 2003, Zuk, et al.; 2001)

For chondrogenic differentiation, ASCs cells are grown to confluency in 30-mm dishes and incubated for 3 weeks in DMEM containing 1% FBS, 50 mM L-ascorbic acid-2-phosphate, 40 mg/ml proline, 100 mg/ml pyruvate, 10 ng/ml transforming growth factor (Harriman, et al.)- $\beta$ 3, and 1x ITS. Induction medium is replaced every 3 days. At the indicated time points, differentiated cells are fixed for 1h with 4% paraformaldehyde and rinsed with PBS. Accumulation of chondrocyte matrix is detected with alcian blue staining (pH 2.5, Wako) (Matsumoto, et al.; 2008).

### 3.1.6 Neuronal differentiation

There is preliminary evidence suggesting that human ASCs can display neuronal and/or oligodendrocytic markers. ADSC at passages 2-5 are seeded in six-well plates at 40%-60% confluence. After three washes with PBS, the cells are induced with NIM (DMEM supplemented with 500 mM IBMX, 200 mM INDO, and 5 mg/ml insulin) for 1 hr. The cells are then examined for the expression of neuronal markers S100, NF70, and nestin followed by hematoxylin-eosin (HE) staining (Ning, et al.; 2006).

The *in vivo* test for the therapeutic potential of ASCs looked at their effects when injected intraventricularly in rats. ASCs survived with increased engraftment at the site of injury compared with controls. Neural lineage markers microtubule-associated protein-2 and glial fibrillary acidic protein were expressed in some engrafted cells. Behavioural tests of the motor and sensory systems showed clear improvements in those treated with ASCs after infarct (Kang, et al.; 2003). It is not clear whether transplanted cells replaced the lost neurons or provided a support role for existing stem cells and injured neurons. Furthermore, in a co-culture model, Kang *et al.* studied the interactions between neural stem cells (NSCs) and ASCs. In comparison to laminin-coated dishes, ASC feeder layers showed ability to support the differentiation and survival of NSCs over 14 days in culture.

## 4. Biomaterials in tissue engineering with ASCs

Currently, autologous and allogenic adipose tissues represent a ubiquitous source of material for fat reconstructive therapies. However, these approaches are limited, and often accompanied by a 40-60% reduction in graft volume following transplantation. A number of factors including a stable scaffold support structure and vascularisation is necessary to support *de novo* adipogenesis and long-term maintenance of adipose tissue formation within adipose tissue engineered constructs (Patrick, et al.; 2002). Recently, cell-based approaches utilizing adipogenic progenitor cells in combination with biomaterial carriers for fat tissue engineering have been developed and were reported to promote both short-term *in vivo* adipogenesis and to repair defect sites (Borges, et al.; 2003, Patrick, et al.; 1999). To date,

however the efficacy of exogenously delivered stem cell populations to support the generation of long-term volume stable adipose tissue *in vivo* is restricted by suboptimal properties of their biomaterial carriers including insufficient biocompatibility and rapid scaffold degradation rates (Patrick, et al.; 2002).

For functional tissue replacement such as bone, Silk-based biomaterials have previously been demonstrated to offer exceptional benefits over conventional synthetic (e.g. polyglycolic and lactic acid copolymers) and natural (e.g. collagen type I) biomaterials (Meinel, et al.; 2004). The slow degradation and mechanical integrity of silk scaffolds in comparison with other conventional biomaterials such as collagen and PLA, above all for long-term *in vivo* studies, suggest that silk fibroin-based scaffolds would be an optimal biomaterial for long-term adipose tissue growth and function (Mauney, et al.; 2007). Also, previous studies have demonstrated the ability of adipocytes to secrete various paracrine factors which can positively influence both the migration and differentiation of preadipocytes (Shillabeer, et al.; 1989). Mauney et al. studied biomaterials derived from silk fibroin prepared by aqueous (AB) and organic (HFIP) solvent-based processes, along with collagen (COL) and poly-lactic acid (PLA)-based scaffolds *in vitro* and *in vivo* for their utility in adipose tissue engineering strategies (Mauney, et al.; 2007).

For *in vitro* studies, they used adipose-derived mesenchymal stem cells (hASCs) and seeded them on the various biomaterials and cultured them for 21 days in the presence of adipogenic stimulants (AD). In their study, hASCs (and hMSCs) cultured on all biomaterials in the presence of AD showed significant upregulation of adipogenic mRNA transcript levels (e.g. GLUT4) to similar extents when compared to noninduced controls (Mauney, et al.; 2007). Also, oil-red O analysis of hASC-seeded scaffold displayed substantial amounts of lipid accumulating adipocytes following cultivation with AD. Following a 4-week implantation period in a rat muscle pouch defect model, both AB and HFIP scaffolds supported *in vivo* adipogenesis either alone or seeded with hASCs (Mauney, et al.; 2007). On the other hand, COL and PLA scaffolds underwent rapid scaffold degradation and were irretrievable following the implantation period. The authors concluded that macroporous 3D AB and HFIP silk fibroin scaffolds offer an important platform for cell-based adipose tissue engineering applications, and in particular, provide longer-term structural integrity to promote the maintenance of soft tissue *in vivo* (Mauney, et al.; 2007).

Tissue-specific scaffolds and signalling systems are essential to differentiate stem cells into the required cells and use them effectively to construct three-dimensional (3D) tissues (Sterodimas, et al.; 2010). It has also been proved that adipose tissues engineered with ASCs and type I collagen scaffolds can serve *in vivo* for the replacement of damaged tissue (Lu, et al.; 2006). This has been confirmed by Zhang et al., where collagen I scaffold exhibited excellent cellular compatibility and can be used as a vehicle for adipose tissue engineering (Zhang, et al.; 2007).

Porous collagenous microbeads can be useful as injectable cell delivery vehicles for adipose-derived stem cells, allowing *ex vivo* proliferation and differentiation on particles that are small enough to be injected into a defect and molded into the desired shape without migration of the cells. The cell-seeded microbeads can be injected through a needle into the wound site, and agglomeration of the microbeads can retain the cells and microbeads in the site (Rubin, et al.; 2007). Furthermore, the use of natural material hold promises in tissues engineering.

Placental decellular matrix (PDM) holds potential as a scaffold for adipose tissue engineering applications. The placenta is a rich source of human extracellular matrix (ECM)

components that can be harvested without harm to the donor. Constructs derived from the ECM may mimic the native environment of the body, promoting normal cellular organization and behavior. Natural materials also have advantages in terms of ease of processing, biodegradability and biocompatibility (Schmidt and Baier; 2000). Cell-adhesive placental decellular matrix scaffolds facilitate proliferation and viability, while differentiation is augmented when the cells are encapsulated in non-adhesive cross-linked hyaluronan (XLHA) scaffolds (Flynn, et al.; 2008). Incorporation of XLHA into the PDM scaffolds may improve the construct bulking properties and may influence cellular infiltration, differentiation and wound healing (Shu XZ; 2004).

Other candidate for suitable scaffolds is non-woven polyglycolic acid (PGA) and hyaluronic acid gel. In a recent study it has been shown that more adipose-tissue-like construct is regenerated when using type I collagen sponge than when the non-woven polyglycolic acid or hyaluronic acid gel are used (Itoi, et al.; 2010). In addition, significant evidence has been shown that ASCs and PLGA spheres can be used in a clinical setting to generate adipose tissue as a noninvasive soft tissue filler (Choi, et al.; 2006).

Altman et al. could show that human adipose-derived stem cells seeded on a silk fibroin-chitosan scaffold enhance wound healing and show differentiation into fibrovascular, endothelial, and epithelial components of restored tissue (Altman, et al.; 2009). In addition, it has been shown that transfection of human ASCs with liposome- enveloped xenogenic protein from a neonatal rat tissue preparation can induce differentiation of stem cells along the directed lineage (Gaustad, et al.; 2004). These observations support the hypothesis that the inductive biochemical and structural cues of the microenvironment are conserved across species and that a silk fibroin-chitosan delivery vehicle can provide a beneficial niche in supporting migration, proliferation, and differentiation of the applied cells (Altman, et al.; 2009).

Another complex biomolecule which has sparked great interest for tissue engineering is Hyaluronic acid which has been stated to support the growth and development of progenitor cells (Brun, et al.; 1999, Solchaga, et al.; 1999). The material has a progressive rate of biodegradation, lacks cytotoxicity and does not induce a systemic immune response or chronic inflammation in a human *in vivo* model (Stillaert, et al.; 2008). Hyaluronic acid-based (HA) scaffolds were demonstrated to be suitable materials for soft-tissue regeneration; they maintain volume when seeded with preadipocytes. Hemmrich et al. evaluated, *in vitro* and *in vivo*, human preadipocytes seeded onto plain hyaluronan benzyl ester (HYAFF®11) or HYAFF®11 coated with the extracellular matrix glycosaminoglycan hyaluronic acid and they found extensive formation of new vessels throughout the construct but with only minor adipose tissue (Hemmrich, et al.; 2005).

Long-standing, 3D predefined-shape adipose tissue from hAD-MSCs of human adipose tissue remains a challenge. Lin et al. cultured scaffolds (Gelatin sponges, monofilament polypropylene and polyglycolic acid meshes) with hAD-MSCs in adipogenic medium for 2 weeks before implantation, and implanted scaffolds were harvested after 2, 4, and 6 months *in vivo*. All of the successfully harvested scaffolds were filled with newly formed adipose tissue and had retained their predefined shape and dimensions (Lin, et al.; 2008). It has been shown that hAD-MSCs are not successful soft tissue filler if used alone (Lin, et al.; 2008, Moseley, et al.; 2006).

There are numerous adipose tissue engineering culture strategies in which the core tissue engineering principles comprising appropriate cells, scaffold, and microenvironment are optimized (Patrick; 2001). Specifically, there are static versus dynamic culture, co-

cultivation, and addition of growth factors, vascularization, and long-term sustainability of engineered constructs. The advantage of dynamic culture includes increased nutrient and oxygen delivery to cells within a 3D construct (Frye and Patrick; 2006). Improved bioreactor designs to address direct perfusion conditions are necessary to advance dynamic culture techniques (Choi, et al.; 2010).

It has been shown that hASCs express pericyte lineage markers *in vivo* and *in vitro*, exhibit increased migration in response to PDGF-BB *in vitro*, exhibit perivascular morphology when injected *in vivo*, and contribute to increases in microvascular density during angiogenesis by migrating toward vessels (Amos, et al.; 2008). In cell-assisted lipotransfer (CAL), autologous ASCs are used in combination with lipoinjection (e.g. Parry-Romberg syndrome). A stromal vascular fraction (SVF) containing ASCs is freshly isolated from half of the aspirated fat and recombined with the other half. The preliminary results suggest that CAL is effective and safe for soft-tissue augmentation and superior to conventional lipoinjection and microvasculature can be detected more prominently in CAL fat (Yoshimura, et al.; 2008). Recently, adipose stem cells have proved to selectively induce neovascularisation and increase the viability of random-pattern skin flaps. This mechanism might be both due to the direct differentiation of ASCs into endothelial cells and the indirect effect of angiogenic growth factors released from ASCs (Lu, et al.; 2008).

## 5. Conclusion

ASCs provide an abundant and readily accessible source of multipotent stem cells. The use of autologous stem cells expanded *in vitro* and combined with novel selected biomaterials for organ reconstruction offers a potential solution for replacement of tissue or whole organs. ASC does have one important advantage over the other sources of stem cells namely easy availability. There is no human tissue as expendable as adipose tissue, making it relatively easy to isolate adequate numbers of ASCs for possible human therapies. Human ASCs can be ideal cell source for tissue engineering. They are available in large quantities of cells per individual, multipotent, are transplantable in an autologous setting. However, further studies are needed before ASCs can be used clinically. In particular, investigators need to demonstrate the safety and efficacy of ASCs cells in animal models, either alone or in combination with novel biomaterial scaffolds.

## 6. Acknowledgment

Both the authors Dr. Mathias Treppe and Dr. Souzan Salemi contributed equivalently in writing this chapter.

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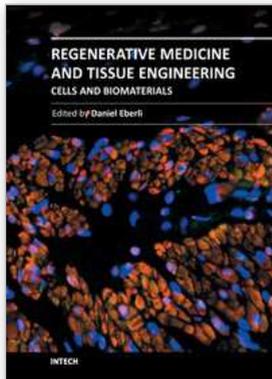
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## **Regenerative Medicine and Tissue Engineering - Cells and Biomaterials**

Edited by Prof. Daniel Eberli

ISBN 978-953-307-663-8

Hard cover, 588 pages

**Publisher** InTech

**Published online** 29, August, 2011

**Published in print edition** August, 2011

Tissue Engineering may offer new treatment alternatives for organ replacement or repair deteriorated organs. Among the clinical applications of Tissue Engineering are the production of artificial skin for burn patients, tissue engineered trachea, cartilage for knee-replacement procedures, urinary bladder replacement, urethra substitutes and cellular therapies for the treatment of urinary incontinence. The Tissue Engineering approach has major advantages over traditional organ transplantation and circumvents the problem of organ shortage. Tissues reconstructed from readily available biopsy material induce only minimal or no immunogenicity when reimplanted in the patient. This book is aimed at anyone interested in the application of Tissue Engineering in different organ systems. It offers insights into a wide variety of strategies applying the principles of Tissue Engineering to tissue and organ regeneration.

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Mathias Tresp, Souzan Salemi, Rita Gobet, Tullio Sulser and Daniel Eberli (2011). Adipose-Derived Stem Cells (ASCs) for Tissue Engineering, *Regenerative Medicine and Tissue Engineering - Cells and Biomaterials*, Prof. Daniel Eberli (Ed.), ISBN: 978-953-307-663-8, InTech, Available from:  
<http://www.intechopen.com/books/regenerative-medicine-and-tissue-engineering-cells-and-biomaterials/adipose-derived-stem-cells-ascs-for-tissue-engineering>

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