

# The Importance of Adipose-Derived Stem Cells and Vascularized Tissue Regeneration in the Field of Tissue Transplantation

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**Abstract:** The importance of stem cells in regenerating or repairing damaged or diseased tissues is well established, but three factors have to be considered in employing stem cells clinically. The first is how to harvest, handle, and multiply them non-invasively, easily, and effectively. From this standpoint, adipose-derived stem cells are considered to be the best to work with among mesenchymal stem cells; since they were first reported in 2001, their pluripotency, proliferative efficiency, and low donor morbidity have been amply confirmed. The second factor is how to differentiate stem cells into the required cells and use them effectively to construct three-dimensional tissues; here, tissue-specific scaffolds and signaling systems are essential. The third factor is how to ensure survival of the differentiated cells and regenerated tissues. Regenerated tissues need to contain vascular systems to allow both the tissues themselves and the differentiated cells to survive. Thus, we believe that the vascularization of regenerated tissues will be an important field of research in the near future. In this paper, we focus on adipose-derived stem cells and vascularized tissue regeneration within the context of tissue transplantation.

## INTRODUCTION

Two ultimate goals of medicine are to develop drugs to treat diseases and to regenerate or repair damaged or diseased tissues. These dreams may come true, because we have recently developed two important tools for research in these fields: “genetic engineering” and “tissue engineering”. These tools are applied clinically as “gene therapy” and “regenerative medicine”, and rapid progress is being made in both areas owing to stem cell research. Stem cells have the potential to deliver exogenous genes and to change into the kinds of cells we need to repair specific injuries.

For transplant surgeons, recent developments in stem cell research are extremely exciting, because stem cells are likely to play a crucial role in regenerating or repairing damaged or diseased tissues. The history of attempts to repair damaged tissues actually extends back thousands of years. For example, ancient Indian texts dating back 2,600 years describe total nasal reconstructions using autologous tissues from the forearms of convicts who had their noses cut off [1]. Details of these techniques have been handed down to latter-day transplant surgeons: gastroenterological surgeons repair the esophagus using tissues from the jejunum, orthopedic surgeons repair bone and cartilage defects with healthy autologous bone and cartilage harvested from other sites, plastic and reconstructive surgeons repair skin and soft tissue defects using skin grafting and flap transfer techniques.

Moreover, the development of immune-suppressing drugs has enabled not only auto transplantation but also allogeneic transplantation to become a reality. Liver and cardiac transplants are performed on a daily basis, and in 1998, allogeneic transplantation of a hand was performed with relatively good results in France, although the

transplanted hand was amputated at the wish of the patient two years and four months later [2]. Since then, more than 15 allogeneic hand transplants have been performed worldwide. There are, however, ethical problems involved in allogeneic transplantation that may be unsolvable [3-5]. Recent developments in stem cell research may change the concept of transplantation and may solve many problems related to donors and recipients.

In this report, we discuss three challenges related to the clinical use of stem cells in engineered-tissue transplantation: 1) how to harvest, handle, and multiply them non-invasively, easily, and effectively; 2) how to differentiate them into the required cells and construct three-dimensional tissues effectively; and 3) how to ensure survival of the differentiated cells and regenerated tissues. While taking these factors into consideration, I will focus on adipose-derived stem cells and vascularized tissue regeneration in this paper.

## 1. Stem Cells

### ES/EG Cells

Biologic tissues consist of cells, extracellular matrices, and signaling systems [6], and each element must be handled precisely in the field of tissue engineering. When it comes to using stem cells to create biologic tissues, there is a choice between embryonic/germ stem cells and adult stem cells.

There are two types of “true” totipotent stem cells, both of which are derived from embryonic sources. One is embryonic stem (ES) cells, which are derived from the inner cell mass of preimplantation embryos [7]. Evans *et al.* first reported deriving ES cells from mouse embryos in 1981 [7], and Thomson *et al.* succeeded in establishing human ES cell lines in 1998 [8]. The other type of totipotent stem cells are embryonic germ (EG) cells, which are derived from the primordial germ cells that migrate to and colonize the

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gonads, eventually forming eggs and sperm [9]. ES/EG cells have the potential to differentiate into all kinds of cells. However, both types are derived from human embryonic tissues, so that there are problems associated with the clinical use of ES/EG cells. The first and most obvious problem is ethical concerns. The second is immunologic rejection by recipients. To prevent graft rejection, Grusby *et al.* created mouse models without either of the major histocompatibility complexes (MHC) class I and II [10]. Even the grafts derived from these mice were rejected after transplantation, although at a slower rate than in normal controls [10]. Shablott *et al.* hypothesized that the minor histocompatibility antigens, tissue-specific antigens, and hybrid histocompatibility antigens were also capable of causing cell-mediated graft rejections and might require modifications [11]. The third problem with the clinical use of ES/EG cells is the risk of tumor formation, especially teratomas or teratocarcinomas, resulting from contamination of uncontrolled cells. To avoid these potential problems, genetic engineering of human ES cell lines has been proposed [12]. Another option is the use of autologous pluripotent stem cell lines in therapeutic cloning, a technique similar to that used to clone the sheep Dolly [13]. Nevertheless, many difficult problems remain to be solved in the clinical use of ES/EG cells.

### **Mesenchymal Stem Cells**

Compared to ES/EG cells, adult stem cells are much easier to handle. These stem cells do not have the “true” totipotency of ES/EG cells, but the multipotency of one notable type, mesenchymal stem cells (MSCs), has been amply confirmed by many studies since they were first described in 1976 [14]. The great benefit of these cells is that there are few ethical problems associated with their use for auto transplantation. In addition, immunologic problems do not have to be considered in auto transplantation. Therefore, expectations are high for the use of MSCs in regenerating or repairing damaged or diseased tissues, especially for auto transplantation. In 1976, Friedenstein *et al.* extracted a cell population from whole bone marrow cells that could be differentiated into osteoblasts [14]. In the following years, studies of MSCs focused mainly on their application to the field of orthopedic surgery. However, in 1999, Pittenger *et al.* revealed that human MSCs have the potential to differentiate into various mesenchymal tissue lineages, including bone, cartilage, fat, tendons, skeletal muscles, and marrow stroma [15]. This was a groundbreaking study in that it proved that MSCs could be differentiated into paraxial mesoderm cell types. In 2001, Reyes *et al.* reported MSCs that could also differentiate into visceral mesoderm cells, such as heart muscle, smooth muscle, and vascular endothelium [16]. Thus, they used the term “mesodermal progenitor cells (MPCs)”. Jiang *et al.* later demonstrated that MPCs could differentiate not only into paraxial and visceral mesoderm cells but also into neuroectoderm and endoderm cells [17]. In this review, we will refer to both as MSCs to order not to further complicate the nomenclature.

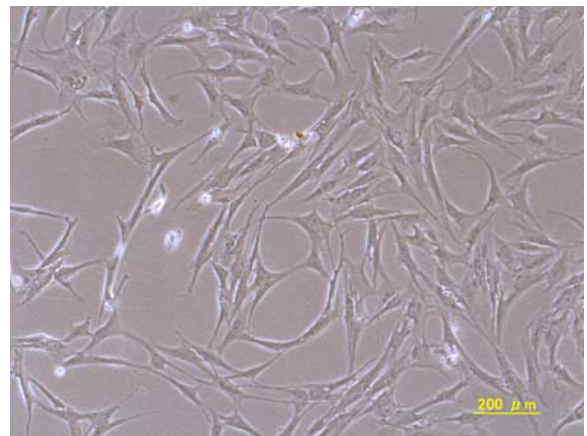
While adult stem cells certainly hold promise for clinical use, questions have been raised about them in recent years. Wurmser *et al.* have claimed that it is actually cell fusion that gives adult stem cells their multipotency [18]. Holden

*et al.* noted that scientists are now taking a more critical look and finding that some apparent reprogramming of adult cells might indeed be cases of cell fusion [19]. This has prompted calls to establish rigorous standards for demonstrating plasticity. These reports have to be taken seriously, and further studies of adult stem cells are necessary to establish their true utility.

### **Adipose-Derived Mesenchymal Stem Cells**

While bone marrow was for a long time the major source of MSCs, recent studies have identified new sources. For example, Zuk *et al.* have found MSCs in adipose tissue [20], Young *et al.* have reported that they can be harvested from skeletal muscles and dermis [21], and Erices *et al.* have demonstrated that they are present in umbilical cord blood [22]. At present, we can not conclude that all of these MSCs are the same, and there is the possibility that each may have characteristics favorable for specific types of differentiation, depending on their source. Further clarification is necessary. However, at this stage, the author is of the opinion that adipose-derived MSCs are the best to work with among mesenchymal stem cells; their pluripotency, proliferative efficiency, and low donor morbidity have been amply confirmed during the last 5 years.

In 2001, a multipotent cell population isolated from fluid drained during liposuction was reported [20] (Fig. 1). At the time, this cell population was named “processed lipoaspirate (PLA) cells”. PLA cells are a pluripotent cell population in adipose tissue, and they have been recognized as MSCs. Traditionally, MSCs referred only to bone marrow-derived cells; however, since we now have other sources for them, it is necessary to make clear the origin of the MSCs used in each study. One proposal is to use the terms “adipose-derived MSCs” and “bone marrow-derived MSCs”. At the 2<sup>nd</sup> annual meeting of the International Fat Applied Technology Society (IFATS, Pittsburgh, 2004), terminology was discussed and it was concluded that the term “ASCs” should be used for pluripotent cells harvested from adipose tissue. However, whether ASCs stood for “adipose-derived stem cells” or “adipose-derived stromal cells” was not clarified. Furthermore, while stromal cells are



**Fig. (1). Adipose-derived MSCs**

Mesenchymal stem cells can be harvested from less than 1.0 g of adipose tissue. Since they were first reported in 2001, the pluripotency, proliferative efficiency, and low donor morbidity of adipose-derived MSCs have been amply confirmed.

a heterogeneous cell population in primary culture, homogeneous cell populations are obtained after several culture passages. Compared to stem cells, the doubling time of mature stromal cells is much longer and their cell adhesion activity is much lower. Thus, stem cell selection occurs naturally after several culture passages. In this sense, it may be acceptable to use the term “stem cells” for cultured stromal cells. We will use the unambiguous term “adipose-derived MSCs” for the remainder of this article.

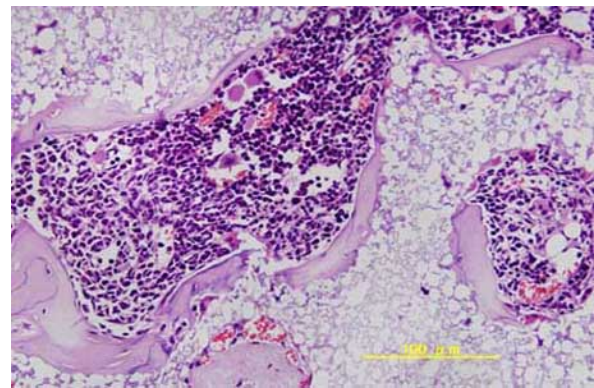
As first reported in 2001 [20], adipose-derived MSCs are ideal in many aspects: they can be harvested, handled, and multiplied non-invasively, easily, and effectively; their pluripotency and proliferative efficiency are not less than those of bone marrow-derived MSCs; and donor morbidity is lower than for MSCs harvested from other sites. Mature adipocytes are particularly easy to remove from adipose tissue, requiring only the use of collagenase treatment and centrifugation, since they are less dense than water. From the clinical point of view, sufficient quantities of MSCs can be harvested and cultured from a mere 1.0 g of fat. Furthermore, only local anesthesia is required, and the wound at the donor site heals within a week. If the donor patients submit to liposuction or lipectomy, enough MSCs can be harvested for immediate auto transplantation without culturing through passages *ex vivo*.

In 2002, Zuk *et al.* reported that human adipose-derived MSCs expressed multiple CD marker antigens similar to those observed on bone marrow-derived MSCs [23]. They studied the cells as they differentiated not only into the mesodermal lineages but also into neural lineages. Adipose-derived MSCs differentiated into putative neurogenic cells, exhibiting a neuronal-like morphology and expressing several proteins consistent with the neuronal phenotype [23]. In addition to human adipose-derived MSC studies, including that of Mizuno *et al.* [24], animal studies using rats or mice have been reported since 2002 [25]. In 2003, Dragoo *et al.* performed both *in vitro* and *in vivo* studies with human adipose-derived MSCs [26]. When they transformed MSCs with the bone morphogenic protein (BMP)-2 gene and implanted them into SCID mice, they

were able to confirm bone formation *in vivo* [26]. Thereafter, Morizono *et al.* suggested the possible use of adipose-derived MSCs as gene delivery vehicles [27]. In 2004, Cowan *et al.* reported the treatment of critical-size mouse calvarial defects using adipose-derived MSCs and a scaffold made of apatite-coated poly(lactic-co-glycolic acid) (PLGA) [28].

In our study of bone regeneration in mice, we showed that bone matrix can be regenerated subcutaneously from adipose-derived MSCs *in vivo* (Fig. 2). In our experiments, we use green fluorescence protein (GFP) transgenic mice as a source of adipose-derived MSCs as a way to distinguish the transplanted cells from recipient cells [29] (Fig. 3). Transplanted adipose-derived MSCs were proliferated and differentiated into osteoblasts in micropores on the surface of hydroxyapatites (HA), rather than with type I collagen or chitosan scaffolds. This study demonstrated not only bone matrix regeneration but also bone marrow regeneration. We have not yet obtained incontrovertible proof that adipose-derived MSCs differentiated into hematopoietic cells. However, we were able to regenerate subcutaneous microenvironment in which hematopoietic cells survived, and this may lead to new treatments for fibrotic bone marrow diseases such as idiopathic myelofibrosis and osteopetrosis. Bone marrow engineering has great potential in the field of hematopoietic disease therapy, and regeneration of the hematopoietic system using adipose-derived MSCs might be useful in the future for treating hematopoietic stem cell diseases such as leukemia in addition to fibrotic bone marrow diseases. We plan to continue looking for suitable scaffolds and methods for bone and bone marrow regeneration using adipose-derived MSCs.

To confirm the multipotency of adipose-derived MSCs, comparisons between adipose-derived and bone marrow-derived MSCs have been made. De Ugarte *et al.* showed that both human adipose-derived MSCs and bone marrow-derived MSCs express CD13, CD29, CD44, CD90, CD105, SH-3, and STRO-1 [30]. However, differences in expression were noted for the cell adhesion molecules CD49d (Integrin  $\alpha 4$ ), CD54 (ICAM-1), CD34, and CD106 (VCAM-1) [30].

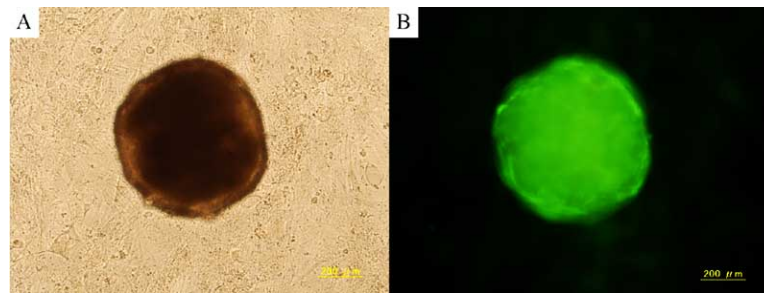


**Fig. (2). Subcutaneous bone regeneration in mice**

**a:** X-ray radiographs of a recipient mouse with scaffolds containing implanted stem cells

**b:** HE staining of regenerated tissue

Adipose-derived stem cells were seeded onto scaffolds made of hydroxyapatites and transplanted subcutaneously into the recipient mice. One month later, after X-ray radiographs were taken (**a**), the tissue was extirpated and examined histopathologically. Bone matrix was clearly observed, and various kinds of blood cells were detected in the micropores (**b**).



**Fig. (3). Cartilage regenerated using adipose-derived MSCs harvested from GFP transgenic mice *in vitro***

After primary culture of GFP(+) adipose-derived MSCs in a control medium (Dulbecco's modified Eagle medium + 10% fetal bovine serum) and expansion to two passages, the cells were incubated in chondrogenic medium (Dulbecco's modified Eagle medium + 1% fetal bovine serum + insulin + ascorbate 2-phosphate + transforming growth factor-beta1) using the micromass technique for four weeks to induce chondrogenesis. Green fluorescent cartilage was regenerated.

Thus adipose-derived MSCs and bone marrow-derived MSCs have similar surface phenotypes, although they are distinct for these several cell adhesion molecules that are implicated in hematopoietic stem cell homing, mobilization, and proliferation [30].

It is very important to try to clarify the origin of adipose-derived MSCs. At present, there are two hypotheses. The first proposes that adipose-derived MSCs originate from bone marrow MSCs, based on the concept that MSCs flow out of the bone marrow and drift to all of the mesenchymal tissues to support regeneration or fixation of those tissues. The second hypothesis is that MSCs already exist in the ontogenetic stage, and that some of them form bone and bone marrow, while others form adipose tissue and remain in the mesenchymal tissues. Further study is required to determine which hypothesis is correct.

In 2004, Lendeckel *et al.* reported the first clinical application of adipose-derived MSCs [31]. Now, in addition to bone fractures and defects, myocardial infarction, cerebral infarction, and spinal cord injuries are considered to be targets of clinical therapy with adipose-derived MSCs. Thus, adipose-derived MSCs are considered to have great potential for tissue engineering.

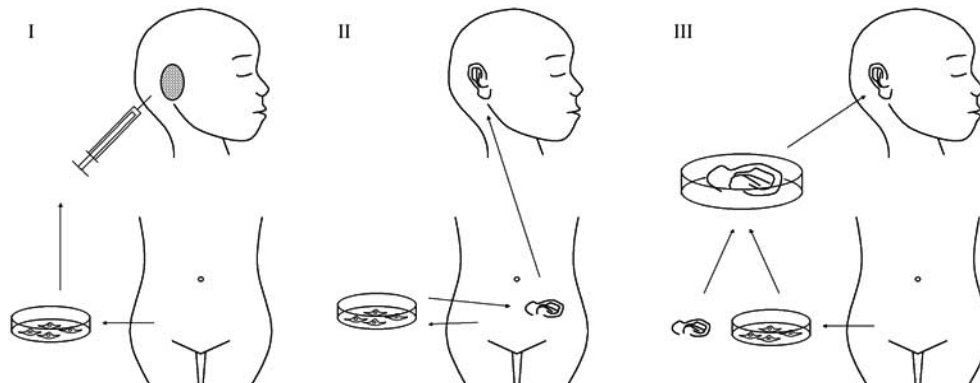
## 2. Tissue Engineering

### *Construction of Three-Dimensional Tissue*

To regenerate or repair damaged or diseased tissues, it is possible to conceive of three different types of procedures (Fig. 4). In the first (Type I), tissue is regenerated directly in the tissue defect. In Type II, tissue is first regenerated elsewhere in the body and then transplanted with other tissues such as vascular systems into the tissue defect. In Type III, tissue is regenerated *ex vivo* and then transplanted into the body.

The Type III method presents a variety of very practical problems. As mentioned above, biologic tissues consist of three elements: cells, extracellular matrices, and signaling systems [6]. It is difficult to maintain the extracellular matrix and signaling systems outside the body, because precise regulation of pH, oxygen pressures, seeding density, growth factors, and nutrients is required [32]. As we do not yet have the ability to regulate all of these factors, Type III regeneration is not yet feasible.

In Type I tissue regeneration, the signaling systems basically take care of themselves, because endogenous



**Fig. (4). The schemas for regenerating or repairing damaged or diseased tissues**

In Type I, tissue is regenerated directly in the tissue defect. This method is useful for minor defects of bone, cartilage, and adipose tissue, among others, but there are many cases in which it does not work. For example, the ear has a complex three-dimensional geometric structure so that it has to be regenerated initially elsewhere in the body. In Type II, tissue is first regenerated elsewhere in the body and then transplanted with other tissues such as vascular systems into the tissue defect. In Type III, tissue is regenerated completely *ex vivo* and then transplanted into the body. The problem with this method is that it is difficult to maintain the extracellular matrix and signaling systems outside the body.

signaling systems already exist around the tissue defect. If there is enough extracellular matrix in the tissue defect region, stem cells alone can be seeded into the region. If there is not enough, scaffolds containing stem cells need to be transplanted. It is not necessarily essential to differentiate the stem cells into the specific cell types that are needed, because it is possible that stem cells work just as a carrier of signals like cytokines in this setting. If the signals reach the cells around the defect, tissues may be regenerated from the surrounding area. In fact, we can consider this to be a cell therapy rather than tissue regeneration, and as such could be modified using genetic engineering techniques.

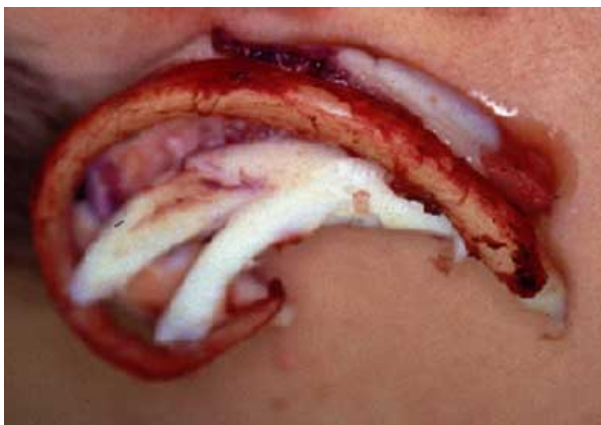
Type II will be a very important method in the future, because there are many situations in which direct regeneration (Type I) is difficult. For example, a human ear has a complex three-dimensional geometric structure so that it needs to be initially regenerated elsewhere in the recipient body before transfer. In fact, this is not so different from what we actually do on a regular basis in plastic and reconstructive surgery for total ear reconstruction (Fig. 5). In 1997, Cao *et al.* published an impressive report [33] in which they described how they seeded chondrocytes onto polymers to produce tissue-engineered cartilage in the shape of a human ear on the backs of mice.

Unlike in Type I tissue regeneration, the signaling systems are extremely important in Type II, because endogenous signaling systems do not always exist in the regions used for regeneration, which are distant from the defect. Let's take the repair of a bone defect as an example. If the bone were to be regenerated in the abdominal subcutaneous region, which would be the easiest site for such purposes, all kinds of difficulties would have to be overcome. First, stem cells would have to be differentiated into osteoblasts, and three-dimensional tissues would have to be constructed. The difficulty of doing this is quite familiar to plastic surgeons, because free bone grafts do not survive in recipient sites without surrounding bone; transplanted bone that is not in contact with any other bone

is quickly absorbed. This probably occurs because of the lack of bone formation signals, supporting the importance of signaling systems in Type II tissue regeneration. Moreover, it is critical for optimal bone induction to establish delivery systems such as scaffolds and inductive signals [34]. We know from many studies in the field of bone regeneration that hydroxyapatite alone appears to be osteoinductive in some species [35]. According to a report by Cowan CM *et al.*, scaffolds made of apatite-coated PLGA are more appropriate than any other scaffolds [28]. If inductive signals such as BMP are present, osteoinduction will be much faster. BMP gene transfer to stem cells using genetic engineering techniques is useful for this purpose. In the case of bone formation, we should be able to regenerate bone ectopically with the selection of appropriate scaffolds made of biomimetic biomaterials such as hydroxyapatite. Of course, we also have to devise appropriate scaffolds for regenerating other tissues, such as cartilage, fat, and so on. Further studies of signaling systems and scaffolds will be required to make progress here.

### Vascularized Tissue Regeneration

In planning three-dimensional tissue regeneration, both signals and vascularization are essential for maintaining function and shape. As the regenerated tissue expands, greater blood flow into the tissue is required. It is obvious that cells and tissues need blood flow to survive, but there are actually three main reasons why vascularization is needed during tissue regeneration: 1) to carry oxygen and nutrients into the tissue; 2) to prevent decomposition or absorption of the cells or tissue; and 3) to allow tissue to be transplanted with a vascular pedicle. Once blood flow stops, small tissues can survive for several days on extracellular fluid until blood capillaries infiltrate the tissue. However, large tissues can not survive without large blood vessels, and central necrosis may occur. The importance of vascularization for the prevention of decomposition is demonstrated by the clear difference in the survival rate between simple cell transplantation and tissue

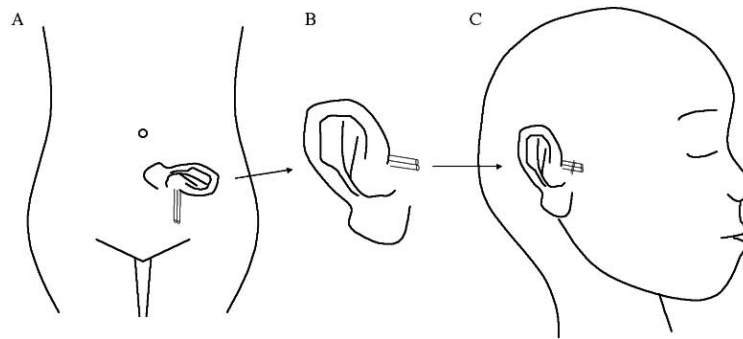


**Fig. (5). Total human ear reconstruction**

**a:** Ear frame made with autologous costal cartilage

**b:** The frame is transplanted under the skin of the forearm

In the field of plastic and reconstructive surgery, total ear reconstruction is performed using autologous costal cartilage. In the example shown here, the ear frame was first transplanted subcutaneously in the forearm. Later, the ear frame covered with skin was transplanted to the head together with the radial forearm artery and veins. These vessels were anastomosed with a superficial temporary artery and veins (unpublished data from professor Hiko Hyakusoku of Nippon Medical School).



**Fig. (6). Prefabricated regenerated tissue transplantation**

If there are large vessels attached to the regenerated tissue, microvascular surgeons can transplant them everywhere using a process of microvascular anastomosis under a microscope. This procedure is very similar to that used with “prefabricated flaps” in the field of plastic and reconstructive surgery.

transplantation as flaps. For example, simple fat injection is inefficient in breast reconstruction (the adipocytes do not survive), while adipose tissues survive completely when they are transferred as flaps containing vascular systems. It is clear, therefore, that not only extracellular matrix but also vascular systems are important for the maintenance of regenerated tissues. The importance of transplanting a vascular pedicle is that if large vessels are attached to the regenerated tissue, microvascular surgeons, such as plastic and reconstructive surgeons, can transplant them anywhere using microvascular anastomosis under a microscope; that is, regenerated tissue can be transplanted freely if there is a vascular pedicle (Fig. 6). This procedure is described in the next section. For the three reasons listed above, we believe that the vascularization of regenerated tissues will be an important field of research in the near future.

#### ***Transplantation of Regenerated Tissue - The Concept of Prefabricated Flaps***

The next step is to transplant the regenerated tissue into the recipient site. Type I regeneration is easy but its

application is limited, and Type III is very problematic; therefore Type II is the best way. The concept of Type II is actually very similar to that of the “prefabricated flap” used in the field of plastic and reconstructive surgery.

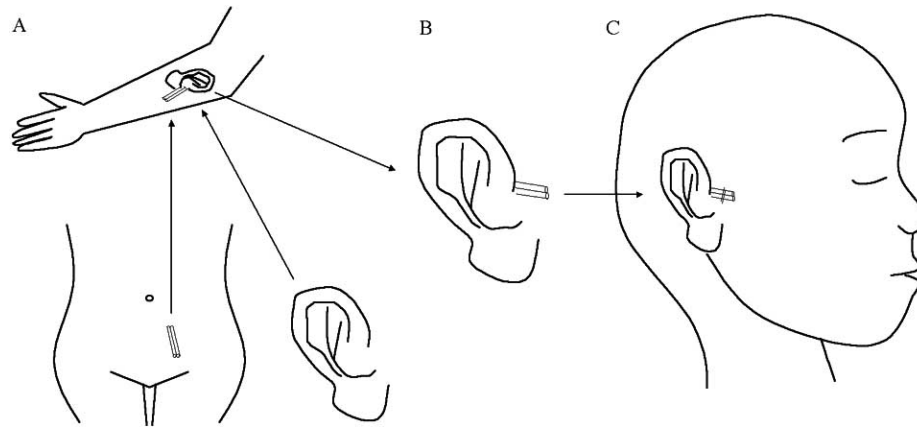
Plastic and reconstructive surgeons use reconstructed tissues in the form of flaps. Flaps are vascularized tissues, which make them different from free skin grafts, free bone grafts, and free fat injections. The flaps have improved since Daniel and Harii carried out the first free flap transfer by the process of microvascular anastomosis in the early 1970s, and it is now possible to transfer flaps everywhere where recipient vessels exist [36, 37]. As demonstrated in Orticochea’s seminal report [38], plastic and reconstructive surgeons have also fabricated flaps to suit their purposes before transplanting them; these fabricated flaps were later named “prefabricated flaps” [39-41]. Many attempts have been made to build vessels, bones, cartilage, mucosa, and other structural features into conventional flaps. It is logical to build regenerated tissue as prefabricated flaps because they can be vascularized easily.



**Fig. (7). Free vascular bundle transfer**

- a:** The inferior epigastric artery and veins
- b:** Flap prefabrication after vascular bundle transfer
- c:** Prefabricated flap harvesting
- d:** 3 months after operation

It was an important development for the history of the prefabricated flaps that Hyakusoku *et al.* invented a technique known as free vascular bundle transfer. In the example shown here, the inferior epigastric artery and veins were harvested in a preliminary operation. These vascular bundles were anastomosed with superficial temporal vessels and buried in the hairy region of the scalp. After 3 weeks, a neovascularized (prefabricated) scalp flap with hair was elevated and transferred to the eyebrow. The eyebrow was reconstructed with scalp and hair. In combination with tissue regeneration, this technique should allow us to create regenerated tissue that can be easily transferred everywhere (unpublished data from professor Hiko Hyakusoku of Nippon Medical School).



**Fig. (8). Free vascular bundle transfer**

If we can combine tissue engineering with prefabricated flap transfer, especially vascular bundle transfer, we will be able to regenerate tissues anywhere in the body we wish, and it will be possible to transfer these vascularized tissues to any desired location.

In an important development for the history of prefabricated flaps, Hyakusoku *et al.* invented a technique known as free vascular bundle transfer [39, 42] (Fig. 7). In 1996, they also demonstrated allogeneic vascular bundle transfer in experimental studies [43]. This technique allows flaps to be harvested from almost any locations, even if no vascular pedicle exists anatomically. For example, the lack of large vessels in the scalp used to mean it was impossible to harvest flaps from that region, even though it would have been an ideal source for reconstruction of other hairy parts of the body such as the eyebrows or the upper lip. Hyakusoku *et al.* solved the problem as follows. The inferior epigastric artery and veins were harvested in a preliminary operation. These vascular bundles were anastomosed with superficial temporal vessels and buried under the scalp. After 3 weeks, a neovascularized (prefabricated) scalp flap with hair was elevated with the vascular pedicle and transferred to the eyebrows [42]. In the near future, this technique in combination with tissue regeneration should allow us to create vascularized regenerated tissue that can be easily transferred everywhere (Fig. 8).

### 3. Future Prospects for Stem Cell Therapy

If stem cells could be harvested with one syringe and injected directly into the tissue defect, this would clearly be the best way to regenerate or repair damaged or diseased tissues. Unfortunately, it is not so easy, and studies of stem cell injection in animals tell us that many cells fail to survive without scaffolds and signaling systems, even in auto transplantation (unpublished results). Therefore, vascularized three-dimensional tissue reconstruction is the only truly practical way to accomplish regeneration. The burden on patients is enormously reduced if we use adipose-derived stem cells, rather than cells from other sources. In this review, therefore, the importance of adipose-derived stem cells and vascularized tissue regeneration has been emphasized. Thanks to the efforts of specialists in this field, the free transplantation of regenerated tissues is likely to be a reality soon. We will focus particularly on the use of adipose-derived stem cells to create prefabricated regenerated tissue for transplantation (Fig. 8).

### ACKNOWLEDGEMENTS

This review could not have been written without the guidance of Hiko Hyakusoku, Head and Professor, and Hiroshi Mizuno, Assistant Professor, Department of Plastic and Reconstructive Surgery, and Takashi Shimada, Head and Professor, Department of Biochemistry and Molecular Biology, Nippon Medical School. I would also like to thank Tomoharu Kiyosawa, Department of Plastic and Reconstructive Surgery, National Defense Medical College, for his valuable suggestions and Juri Fujimura, my wife and co-worker, for her important advices. Thanks are also due to my colleagues at Nippon Medical School, and apologies to the many scientists whose work has not been cited due to space limitations.

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