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# Recent Advances in Stem Cell and Tissue Engineering

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## Abstract

The clinical application of stem cells in tissue engineering and regeneration is becoming more significant. However, its application has been limited by issues like reproducibility of the stem cells, ethical concerns of harvesting some of these stem cells, and controlling the fate of stem cells in vitro and in vivo. The advent of tissue engineering and regeneration has led to the fabrication of advanced biomaterials and scaffolds with enhanced ability to mimic and control the cellular microenvironment similar to that of innate stem cell niche. Combining the use of stem cells with biomaterials and scaffolds especially synthetic hydrogels that have exhibited physicochemical abilities and properties similar to native niche can be the future of tissue engineering in terms of formation of new tissues like bones. Recently, there has been an increase in the use of either endothelial progenitor cells (EPCs), induced pluripotent stem cells (iPSCs), or adult mesenchymal stem cells in preclinical studies; however this is yet to be transferred to clinical setups as there are limitations in terms of regulations and ethical considerations. The purpose of this review is to give comprehensive details about the application of stem cells in tissue engineering.

**Keywords:** endothelial progenitor cells, induced pluripotent stem cells, adult mesenchymal stem, tissue engineering, scaffolds

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## 1. Introduction

Tissue engineering is a multidisciplinary science that applies the principles of bioengineering for the fabrication of new and improved biomaterials capable of maintaining and restoring the functionality of organs and tissues impaired by disease and trauma. This translational approach has been applied to develop and design patient-specific tissue grafts that mimic the functional properties of native tissues. Three important factors have been accredited to the success of tissue engineering: cocultured stem cells, signaling factor, and the bio-fabricated scaffold.

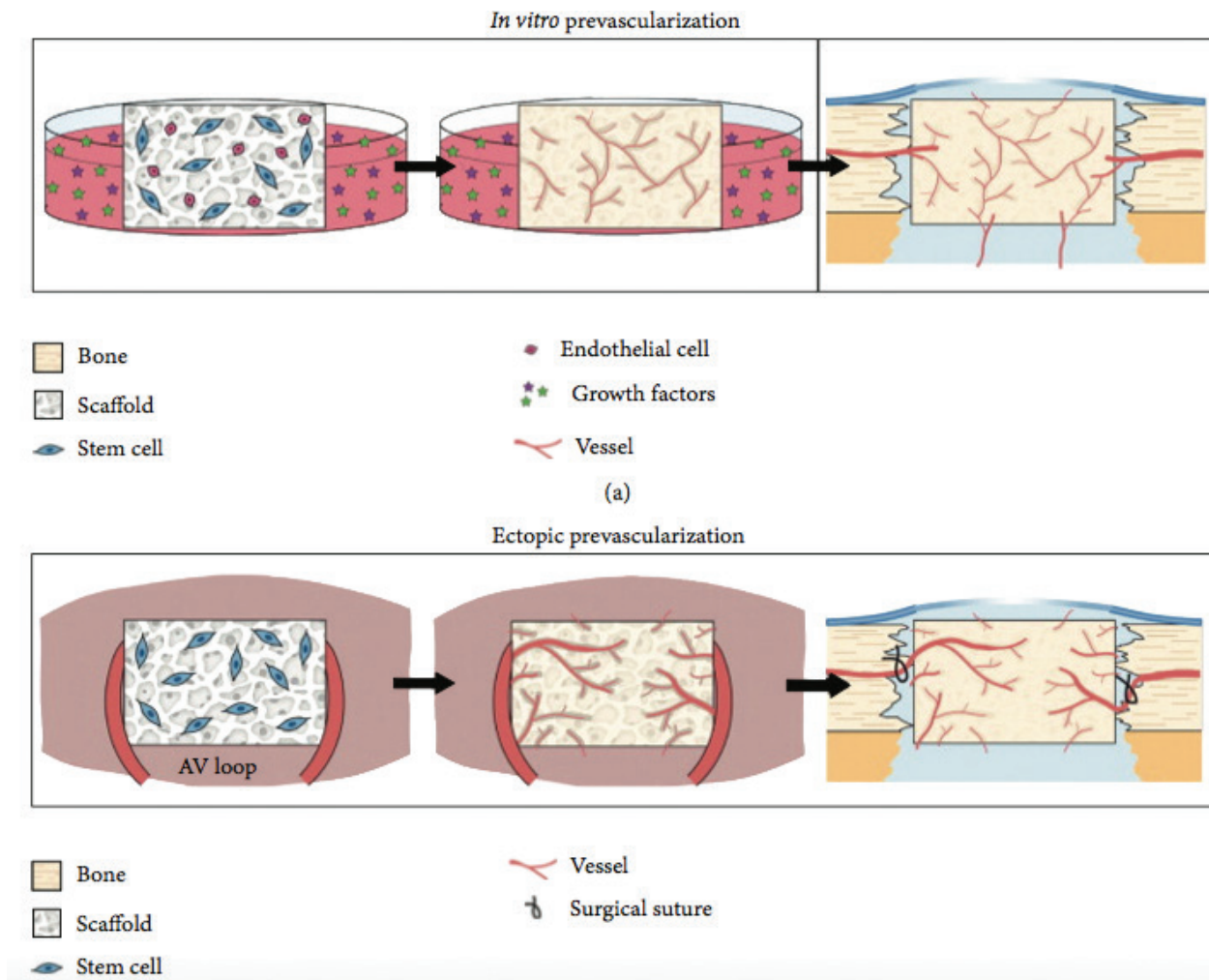
The stem cells are capable of differentiating into several types of tissues and organs, while the bio-fabricated scaffold provides structural support to the seeded stem cells. Signaling factors are responsible for influencing cell phenotype, metabolism, migration, and organization.

Stem cells are undifferentiated cells of embryonic, fetal origin, and they possess the ability to give rise to differentiated cells and then finally develop into organs. Stem cell characteristics include the ability to self-replicate and renew, clonage forming, and high potency ability [1]. In terms of the potency ability of stem cells, stem cells can be totipotent, could differentiate into any cell types (pluripotent) [2], and could differentiate into cells that arise from the three germ layers—ectoderm, endoderm, and mesoderm—from which organs develop [3].

Stem cells can be categorized broadly into embryonic and adult stem cells and are efficient cell sources for tissue regenerative applications. They have also been reported to have the abilities to promote tissue homeostasis, growth, and repair, thereby contributing importantly to tissue and organ regeneration [4]. Bio-fabricated scaffolds consist of decellularized biomaterials to provide structural and anatomical functions to the seeded stem cells, thereby resulting into successful formation of specific tissue. In support of the above report, Kang and colleagues demonstrated that decellularized scaffolds loaded with autologous adipose-derived stem cells (ADSCs) were efficient to repair cartilage defect in an animal model [5]. They concluded that decellularized scaffolds loaded with ADSC induced significant and improved cartilage tissue repair compared to native cartilage.

## 2. Mesenchymal stem cells seeded for bone tissue engineering

MSCs are stromal stem cells that are heterogeneous and are derived from several tissue sources that include adipose tissue [6], periodontal ligaments [7], bone marrow (**Figure 1**) [8], umbilical cord (UC) [9], placenta [10], and lungs [11]. MSCs express surface markers like CD73, CD44, CD90, and CD105. The most widely known and used MSCs are bone marrow MSCs and adipose tissue-derived MSCs isolated and purified from the bone marrow and adipose tissue, respectively. Briefly, the anatomy of the bone marrow is made up of the parenchyma and the stroma part. The parenchyma houses the hematopoietic stem cells, and the stroma part consists of the bone marrow stromal cells (MSCs) that have the capability to differentiate into several cell lines like osteoblasts, chondrocytes, adipocytes, etc. The clinical use of both bone-derived mesenchymal stem cells and adipose stem cells in bone tissue engineering has been reported using various models of bone regeneration such as osteogenesis [12, 13], long bone defects [14, 15], and calvarial defects [16, 17]. Furthermore, co-administration of stem cells with cytokines has been reported to be efficient in bone repair as cytokines and growth factors like stromal derived factor-1 (SDF-1) can lead to increased migration and homing of stem cells to the defected site [18]. In a similar report by Ho et al., they demonstrated that co-administration of stromal-derived factor-1 with BM-MSCs would indirectly enhance bone repair by improving migration of innate cells to the site of bone fracture. They concluded that BM-MSCs overexpressing SDF-1 were efficient in improving the new bone formation during the early stage of fracture healing compared to BM-MSC treatment alone [19]. Genes implicated in fracture healing such as osterix [20], hypoxia-inducible factor-1 [21], and BMP-7 [22] have all been reported to be efficient in bone formation when transfected with MSCs.



**Figure 1.** Showing in vivo and in vitro stem cell application in engineered tissue (a) *In vitro* prevascularization methods induce cell-seeded scaffolds to form vasculature (b) *In vivo* ectopic prevascularization involves implantation of a cell-seeded scaffold into a highly vascularized bed. Adapted from [26] with copyright permission.

### 3. Advances in MSCs and tissue engineering technology

Recently, bone tissue engineering in combination with novel stem cell-based technologies is yielding promising results as reported by Syed-Picard and colleagues in their experimental study that BM-MSC-derived cell sheets could be used to fabricate functional periosteal tissue [23]. Briefly, culturing BM-MSCs to hyperconfluence to produce abundant extracellular matrix to form robust cell sheets generated the BM-MSC-derived cell sheets. The authors reported that the generated cell sheets supported with calcium phosphate pellets were transplanted subcutaneously into mice for 8 weeks. They concluded that there was significant bone-like tissue formation by the BM-MSC-calcium phosphate pellet structure compared to the non-seeded calcium phosphate scaffold.

In another similar study by [24], BM-MSC cell sheet technology was compared to control cell complex. The authors reported that BM-MSC cell sheet resulted into significant expressed levels of growth factors crucial to bone development like vascular endothelial growth factor and PDGF. In another innovative study of stem cell application in tissue engineering, Ren et al. fabricated

and demonstrated a three-dimensional vascularized stem cell sheet construct, composed of both BM-MSCs and human umbilical vein endothelial cells. The authors concluded that there was significant formation of blood vessel formation compared to the control [25].

#### **4. Clinical reports on stem application of bone tissue engineering**

A clinical study by Centeno and colleagues reported the application of culture-expanded, autologous BM-MSC for osteoarthritis in more than 300 patients. The authors reported the safety and efficacy of its use. Briefly, the autologous BM-MSCs were cultured in monolayer culture flasks and transplanted into the affected peripheral joints. They concluded that a 50% improvement in clinical symptoms was recorded among the osteoarthritis patients [27]. The application of infrapatellar fat pad-derived ASCs was demonstrated by Koh and colleagues when they reported its efficiency in improving and managing knee osteoarthritis through clinical and radiological results [28].

A mixture of stem cells and progenitor cells with CD90- and CD14-expressing cells resident in the bone marrow called tissue repair cells (TRC) has been demonstrated to be efficient for reconstructing craniofacial bone defects in a controlled feasibility trial [29]. Briefly, the clinical trial was carried out using 24 patients in need of localized osseous reconstruction. The patients were randomized to either guided bone regeneration (GBR) or TRC transplantation and were subsequently assessed. They concluded that TRC therapy resulted in an accelerated and improved alveolar bone regeneration compared to GBR therapy.

#### **5. Induced pluripotent stem cells seeded for bone tissue engineering**

Yamanaka's group is one of the pioneers of studies related to induced pluripotent stem cells. Yamanaka et al. studies like [30] where they reported the possibility of reprogramming of somatic cells into a primordial embryonic stem cell-like state, capable of differentiating into all three germ layers. There are several studies demonstrating the application of iPSCs in tissue engineering like [31], where they reported the ability of polyethersulfone scaffolds seeded with iPSCs to regenerate cranial bone. The authors concluded that iPSCs seeded with polyethersulfone scaffolds promoted and stimulated cranial bone formation compared to scaffold alone. In similar scaffold study design, Liu used an Arg-Gly-Asp-grafted calcium phosphate cement scaffold seeded with iPSC-MSCs overexpressing NELL1 that were efficient to improve osteogenic differentiation process [32]. However, this report was challenged by [33] reporting that osteogenic abilities of iPSCs can only be realized by scaffolds fabricated with calcium phosphate alone in an ex vivo model. The use of iPSCs in tissue engineering has been reported using animal model by Lian and colleagues, in their mouse model of limb ischemia study. They reported that iPSC-MSCs were more efficient compared to adult BM-MSCs [34] based on their more efficient survival and engraftment abilities after transplantation to induce tissue regeneration.



## 6. Endothelial progenitor cells (EPCs) seeded for bone tissue engineering

EPCs are bone marrow-derived precursor cells and express CD34 molecules. They have the ability to differentiate into endothelial cells and ultimately contribute to the process of angiogenesis [35]. They have been reported to be resident cells in the peripheral blood and potentially contribute to the initiation of neovascularization [36]. There have been several studies demonstrating the use of EPCs in tissue engineering. Zigdon-Giladi and co-workers in their nude mouse model study with calvarial defect demonstrated that human EPCs could enhance the processes of vasculogenesis and osteogenesis [37]. They concluded that there was a significant increase in blood vessel density as well as increased extra-cortical bone height and length in the human EPC-transplanted group compared to the control. Furthermore, EPCs seeded on Gelfoam scaffold were reported to be efficient in stimulating cranial bone formation at the site of injury compared to the unseeded scaffold [38].

In a clinical case carried out by Kuroda and colleagues of tibial surgery, the efficacy of EPCs was demonstrated when autologous, granulocyte colony-stimulating factor (GCSF)-mobilized CD34(+) cells were used in successful tibial autologous bone grafting [39].

## 7. Stem cells and decellularized scaffolds

Recently, scaffolds have been designed in the form of decellularized tissues and organs and are commonly used in tissue engineering and regenerative medicine (**Table 1**). Recent and novel advancement in tissue engineering has been the bedrock for the functional replacement of whole organs. Several organs have been bioengineered and implanted into laboratory animal recipients and potentially showing regenerative abilities and functions. Both acellular and decellularized scaffolds have been seeded with stem cells and potentially have exhibited promising clinical results.

Organ/tissue engineered	Decellularized scaffolds	Cells	Type of experiment	References
Skin tissue engineering	MatrACELL-processed human acellular dermal matrix	NA	In vivo and clinical	[40]
Urethral tissue engineering	3D porous urinary bladder acellular matrix	NA	Clinical	[41]
Bone tissue engineering	Decellularized bone cylinders	Human-induced pluripotent stem cells	In vitro and in vivo	[42]
	Decellularized bone scaffolds	Human adipose-derived stem cells	In vitro	[43]
Cardiac tissue engineering	Decellularized porcine pulmonary valves	Autologous bone marrow mesenchymal stem cells	In vivo	[44]

Organ/tissue engineered	Decellularized scaffolds	Cells	Type of experiment	References
Pulmonary tissue engineering	Acellular porcine and human trachea-lung scaffolds	Murine embryonic stem cells; bone marrow-derived mesenchymal stem cells	In vitro	[45]
Renal tissue engineering	Decellularized rat kidneys	Mouse embryonic stem cells	In vitro	[46]
Tracheal tissue engineering	Genipin cross-linked decellularized rat tracheal scaffold	Pluripotent murine embryonic stem cells	In vitro	[47, 48]
	Decellularized leporine tracheal scaffold	Bone marrow-derived mesenchymal stromal cells	Clinical	[49]
Vascular tissue engineering	Decellularized vascular scaffold from rat abdominal arteries	NA	In vivo	[50]
	Decellularized inferior vena cava of rabbits	Adipose-derived mesenchymal stem cells	In vitro	[51]
Neural tissue engineering	Genipin cross-linked gelatin electrospun scaffolds	Rat allogeneic mesenchymal stromal cells	In vitro	[52]
Cartilage tissue engineering	Decellularized stem cell matrix	Human adult synovium-derived stem cells	In vitro	[53]
Hepatic tissue engineering	Acellular whole liver scaffold	Mesenchymal stem cells	In vitro and in vivo	[54]

Adapted from Rana et al. [55] with copyright permission.

**Table 1.** Applications of tissue-engineered scaffolds recellularized with stem cells.

## 8. Decellularized cardiac tissues and stem cells

There are reports of fabricated decellularized cardiac tissue used as potential scaffolds. For example, human cardiac extracellular cell matrix sheets have been reported to be seeded with mesenchymal stem cells and cardiomyocytes by [56]. The authors concluded that the MSC-cardiomyocyte-derived scaffold efficiently improved and stimulates cardiac tissue regeneration. In another report by [57], decellularized engineered heart valve was successfully implanted for reconstruction of the right ventricular outflow tract. The authors concluded that via echocardiography, the implanted heart valve demonstrated normal physiological pressure gradient after 10 years, with no record of calcification and, in addition, it exhibited an excellent hemodynamic performance.

## 9. Decellularized respiratory tissues and stem cells

There are reports of fabricated decellularized tissue used as potential scaffolds for respiratory tissue because of their simplified anatomical structure. One of the earliest reports on the fabrication of scaffold for tracheal tissue regeneration is [49] where the authors compared the efficiency of decellularized leporine tracheal scaffold seeded with amniotic-derived mesenchymal stem

cells and non-seeded decellularized scaffolds. The authors concluded that MSC-seeded scaffold exhibited a high level of survival of the cells and epithelialization as well as a high level of elastin.

In another study on decellularized tissue, Nichols and colleagues fabricated acellular pig scaffolds using decellularized scaffold seeded with murine embryonic stem cells, pig bone marrow-derived mesenchymal stem cells, and primary human alveolar epithelial type II cells [45]. They concluded that there were recorded changes in type I collagen levels and evidences of cell attachment and viability.

## **10. Clinical application of tissue-engineered trachea and stem cells**

There have been some reports on the successful implantation of bioengineered tissues like tracheal seeded with stem cells clinically. Macchiarini and colleagues first reported the fabrication of human tissue-engineered trachea seeded with autologous epithelial cells and mesenchymal stem cell-derived chondrocytes. They reported that the engineered scaffold was later transplanted into a bronchomalacia patient to replace her left main bronchus. They concluded that there were evidences of functional airway activities and improved mechanical properties of the scaffold within 4 months [58].

In another clinical report by Otti and co-workers following a 5-year study, transplanted tracheal graft exhibited excellent vascularization and recellularization with respiratory epithelium and normal ciliary functions [59]. However, the authors also reported that because of longer production period of the tracheal graft, it might not be suitable for patients in need of urgent transplantation. In a quest to produce a tracheal graft with reduced production time, Baiguera and colleagues designed a human tracheal graft with production period of 3 weeks. The authors reported that the fabricated graft still possess structural and mechanical properties similar to native trachea [47].

In another innovative clinical study carried out by [60], the authors replaced an adult airway with a stem cell-seeded decellularized tracheal scaffold in a patient suffering from congenital tracheal stenosis. They concluded that the graft scaffold showed accelerated revascularization followed by epithelialization after 12 months. Recently, human-derived decellularized trachea seeded with stem cells was demonstrated to be efficient in terms of stability, epithelialization, neovascularization, and chondrocytes formation in a patient suffering from tracheal stenosis [61].

## **11. ASCs and breast tissue regeneration**

Adipose tissue is an important constituent of soft tissues in the body that offers protection to underlying structures. Tissue flap procedures are said to be more efficient in producing a more natural reconstruction; however it is very invasive, while breast implants have been associated with complications like extrusion and lack of contraction of the breast capsule. Adipose-derived stem cells (ASCs) have been identified to be the leading candidate for breast reconstruction, although ASC supplementation has been studied in clinical trials for wound healing therapies [62].



## 12. Fat graft and ADSC application for breast tissue regeneration

Masuda and colleagues [63] in their report demonstrated that transplanted omental tissue both in the presence and absence of pre-adipocytes isolated from epididymal adipose tissues under the dorsal skin of Wistar rats after 12 weeks efficiently produced high levels of triacylglycerol content, capillary density, and VEGF. They concluded that co-transplantation with pre-adipocytes significantly accelerated adipose tissue formation. In another study by Matsumoto and co-workers [64], they reported that cell-assisted lipotransfer (CAL) fat had an increased survival rate than non-CAL fat, and there were early signs of microvasculature in CAL fat. Moseley and colleagues [65] using a nude mice showed that fat supplemented with ASCs sustained its adipocyte-rich appearance and weighed 2.5× greater compared to non-ASC supplemented grafted fat. Furthermore, Zhu and co-workers reported comparable findings that fat grafts treated with ASCs increase capillary density and neovascularization [66]. Several studies have also reported that cultured human ASCs produce and release several angiogenic growth factors under hypoxia condition [67, 68] and have been associated with increased fat graft microvasculature.

Coleman and colleagues in a retrospective study of 17 breast procedures done from 1995 to 2000 reported that all patients had a significant enhancement in their breast size and shape postoperatively [69]. Coleman and colleagues stated that most patients in their study underwent mammography a year after breast surgery without any known screening complications. Yoshimura and colleagues [70] in their clinical study did CAL on six patients with facial lipoatrophy. The authors concluded that the CAL group had a better clinical improvement score compared to the non-CAL patients. In another related study by Yoshimura and colleagues [71], they conducted two clinical trials, using CAL for breast reconstruction. Yoshimura et al. concluded that after treatment of 55 patients, there was advancement in the clinical results with evidences of graft retention. In addition, reconstruction and retention outcomes were demonstrated by Kitamura and co-workers [72] after CAL treatment in five patients.

In a more recent clinical study by Tissiani and Alonso [73], they investigated the effectiveness of autologous fat grafts supplemented with stromal vascular fraction (SVF) in secondary breast reconstruction surgery. The authors concluded that after 3 years of follow-up of the patients they proved volumetric persistence of this type of fat tissue grafts without any significant clinical complications recorded. In another clinical study by Claro and colleagues, it was reported that the complication rate after autologous fat tissue grafting was low compared to the complication rate after breast reconstruction surgery procedures done with breast implants and/or myocutaneous flaps [74].

## 13. ASCs and skin tissue engineering

Böttcher-Haberzeth and colleagues have extensively reported the development of a skin substitute known as tissue-engineered dermo-epidermal skin substitutes (DESS). It is made of the two basic native skin layers, epidermal and dermal layers, and it can potentially serve as a

near replacement for the natural skin for clinical application [75]. Adipose-derived stem cells are attractive and valuable tools for regenerative skin engineering as they can differentiate into different skin cell lineages as well as secrete paracrine factors responsible for initiating skin tissue repair and regeneration.

Trottier and colleagues demonstrated the endogenous production of the extracellular cell matrix components by various skin cells known as IFATS collection. The authors reported that through this method there was formation of strong multiple layers of cell sheet that lead to increase in the skin graft thickness. The authors recorded satisfactory epidermal thickness and stratification [76]. In another study by [77], the authors seeded ASCs onto different scaffolds to determine the differentiation fate of the respective cells. The ASCs seeded on collagen type 1-based matrix and PEGylated fibrin-based scaffold differentiated into fibroblast-like dermal cells and blood capillary network, respectively. Recently, tropoelastin-based scaffold for skin substitutes was developed by [78]. Briefly, biomimetic scaffold was seeded in vitro with ASCs and transplanted onto the SCID mice. The authors concluded that ASCs grew rapidly and colonized the scaffold that resulted in increased epidermal thickness in vivo.

## 14. Conclusion

Scaffold-based tissue engineering using stem cells has improved the field of tissue regeneration in medicine; however, it is still at the infancy level. An extensive in-depth scientific knowledge and study of different stem cells will go a long way to translate them to clinical application. In addition, more extensive studies are needed to be done on different scaffold designs because the success of tissue engineering depends on these scaffolds and provides a niche to transplanted cells. Furthermore, most of the use of stem cells in tissue regeneration has been directed toward small tissue defect as such efforts to develop bioengineered grafts to repair larger tissue defects (bone defects) should be made. Several stem cells like induced pluripotent stem cell, mesenchymal stem cells, and ASCs are promising source of patient-specific stem cells with great regenerative potential. However, few or no clinical translation is available as they are potential teratoma and carcinogenic causative agents, and isolation of some of these cells is deemed unethical. Stem cells seeded on decellularized scaffolds have been reported to demonstrate promising and excellent results over the years. However, more clinical evaluations are needed to be properly sure they are safe clinically.

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