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# Recent Innovation in Pretreatment for Skin Grafts Using Regenerative Medicine in the East

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## 1. Introduction

Chronic ulcers remain a significant health care concern today, especially in the elderly and immobile population. Pedicled or free flap transfers are usually applied to deep wounds in which bone and/or tendon are exposed. Despite improvements in reconstructive surgery techniques, operative invasion and complications, including flap necrosis and infection, are serious problems in patients whose general condition is unfavorable. For these patients, skin graft provides less invasive coverage of wounds as compared to the flap procedures. However, skin graft cannot survive on deep and poorly vascularized defects. Conversion of such defects to applicable beds to simple skin graft requires technologies to induce high-quality granulation tissue on compromised wounds. Stimulating the repair process after surgical debridement may achieve granulation tissue formation and shorten the period for skin grafts. For this purpose, regenerative medicine has attracted our attention. The characteristics of the methodology include the use of the three main tools of regenerative medicine; biomaterials, cytokines, and cells. This section introduces the technologies of regenerative medicine for wound bed preparation with particular focus on their progress in Asia.

All the patients illustrated in this chapter consented to the treatment. Clinical trials were approved by the Institutional Review Board (IRB) of Saitama Medical University.

## 2. Regenerative medicine for wound bed preparation

As already mentioned, the methodology includes the use of biomaterials, cytokines and cells, regenerative medicine's three main tools.

### 2.1 Biomaterials

Collagen is a natural substratum for various types of animal cells and is contained in tissues in large amounts as compared to other proteins (Linsenmayer, 1985). Advanced purification techniques can feasibly extract biocompatible and biodegenerative collagen matrix from

animal tissues. These properties support the collagen matrix as one of the most suitable components of artificial tissue substitutes for reconstruction of damaged tissues and organs (Chvapil et al., 1973; Doillon & Silver, 1986). Several types of collagen-based artificial skin have been reported since the initial description by Yannas and Burke (1980) (Leipziger et al., 1985; Doillon et al., 1986; Boyce et al., 1988; Bel et al., 1981).

In the West, Integra® (Siad Healthcare, Milano, Italy) has been generally used, and recently approved in Japan, but only for the treatment of burns. On the other hand, clinicians in Japan have widely used two types of artificial collagen matrix substitute dermis composed of an atelocollagen matrix (collagen matrix) with a silicone layer, namely TERUDERMIS (Terumo Corp, Tokyo, Japan) and Pelnac (Smith and Nephew Co., Ltd, Tokyo, Japan). These have been officially approved for the treatment of various skin defects caused by acute wounds as well as chronic wounds (Dantzer et al., 2001; Ichioka et al., 2003).

When these matrix substitutes are applied to a tissue defect, sprouting capillaries and fibroblasts migrate into the collagen, which acts as a scaffold for regeneration, resulting in induction of angiogenesis and fibroplasia. The autogenous regenerating tissue then gradually replaces the atelocollagen, and poorly vascularized deep defects are resurfaced by high-quality granulation tissue that can be easily covered with a simple skin graft (Ichioka et al., 2003). Collagen matrices have been reported to achieve less invasive reconstruction of severe defects with bone and/or tendon exposure that formerly required invasive tissue transfer (Braden & Bergstrom, 1989; Dantzer & Braye, 2001).

## 2.2 Cytokines

Cohen (1962) noticed that the purification of submaxillary gland extracts led to earlier eyelid separation and eruption of the incisor in mice, which eventually led to the isolation of the first growth factor as epidermal growth factor (EGF) as part of his Nobel Prize winning work. Since Cohen's discovery, it has been revealed that many growth factors are implicated in the processes of angiogenesis and wound healing (Greenhalgh, 1996; Stadelmann et al., 1998). In the chronic wound, the balance between stimulation and inhibition is destroyed (Stadelmann et al., 1998; Doughty & Sparks-Defriese, 2007) and fibroblasts have been reported to be less responsive to growth factors (Harding et al., 2002). The analysis of the supernatant from chronic pressure ulcers has shown decreased levels of growth factors, compared with the values in acute wound supernatant (Cooper et al., 1994). Deficiencies of growth factors in chronic ulcers suggest that the supplement of these factors might accelerate tissue repair processes. Therefore, growth factors have been proposed as therapeutic agents.

### 2.2.1 Cytokines for critical limb ischemia

Peripheral artery disease (PAD) is a major cause of the most difficult chronic limb ulcers. The occlusion of large limb arteries leads to ischemia, and can progress to critical limb ischemia (CLI). The treatment for ischemia is given priority in wound care. The main treatment strategy for severe, limb-threatening ischemia is either surgical or endovascular revascularization. If revascularization has failed or is not possible, major amputation is often inevitable. This relates to about 30% of all cases of severe limb ischemia (Adam et al., 2005). Regenerative medicine has been spotted as a new therapeutic option to induce angiogenesis. Recently gene therapies using cytokines have been developed as novel treatment strategies. The first in-human studies of gene therapy for the treatment of PAD and coronary artery

disease(CAD) were reported in the late 1990s (Isner et al., 1996; Schumacher et al., 1998; Laitinen et al., 1998). Since these initial reports, several gene therapies have been reported using growth factors, including vascular endothelial growth factor (VEGF) (Isner et al., 1996), fibroblast growth factor (FGF) (Nikol et al., 2008), hypoxia-inducible factor (HIF) (Rajagopalan et al., 2007), developmentally regulated endothelial locus (Del-1) (Grossman et al., 2007), and hepatocyte growth factor (HGF) (Powell et al., 2008). Among these studies, VEGF has been the most commonly employed approach. The beneficial effects of therapeutic angiogenesis using VEGF gene transfer have been reported in human patients with CLI and CAD (Isner et al., 1998; Baumgartner et al., 1998; Baumgartner et al., 2000; Losordo et al., 1998; Vale et al., 1999; Vale et al., 2000; Rosengart et al., 1999).

On the other hand, in Japan, Morishita et al (1999, 2002) have focused on HGF. HGF is also a potent angiogenic growth factor (Belle et al. 1998; Hayashi et al., 1999; Taniyama et al., 2001; Aoki et al., 2000), is a potent mitogen for a wide variety of cells and has angiogenic, antiapoptotic, and antifibrotic properties (Azuma et al., 2006; Matsumoto et al., 1996; Bussolino et al., 1992; Morishita et al., 2004). It is suggested that even in high-risk conditions for atherosclerosis, over expression of HGF is enough to stimulate collateral formation to treat ischemic symptoms (Taniyama et al., 2001). Furthermore, the mitogenic activity of HGF has been reported to be more potent than that of VEGF (Belle et al., 1998; Nakamura et al., 1996). Serum levels of HGF, but not VEGF, are elevated in CAD patients with collaterals, and elevated HGF levels are associated with better prognoses in patients with acute coronary syndromes (Lenihan et al., 2003; Heeschen et al., 2003). Morishita et al. (1999; 2004) conducted preclinical investigations and initial human safety studies of HGF gene therapy, which subsequently led to the phase II HGF-STAT trial. Patients with CLI were randomized to treatment with placebo or 1 of 3 doses of HGF plasmid (Powell et al., 2008). TcPO<sub>2</sub> was significantly more improved in patients who received the highest dose of HGF plasmid than in patients in whom a placebo or the lower HGF plasmid doses were administered. The authors concluded that intramuscular injection of HGF plasmid has an acceptable safety profile for the treatment of patients with CLI. Intramuscular injection of HGF plasmid may have a favorable effect on limb perfusion as measured by TcPO<sub>2</sub> in patients with CLI. Based on these findings, the phase III trial is now underway to determine whether HGF has a clinically meaningful effect on wound healing, limb salvage, and survival.

### **2.2.2 Cytokine products for topical application**

Topical application of cytokines might be effective for wound healing. In the West, the growth factor product generally used is recombinant human platelet-derived growth factor (PDGF) (Regranex®). In South Korea, products based on PDGF, epidermal growth factor (EGF) (Easyef®) and basic fibroblast growth factor (bFGF) (Fibrast®) are available. In Japan, a bFGF product has been licensed since 2001 for use on various skin defects such as diabetic foot wounds, pressure ulcers, venous ulcers and trauma. The following subsections introduce EGF and bFGF for wound bed preparation.

#### **2.2.2.1 Epidermal growth factor (EGF)**

Epidermal growth factor (EGF) is a polypeptide of 53 amino acids that was first isolated from the mouse submaxillary gland by Cohen (1962) as previously mentioned. EGF acts by binding with the high affinity to epidermal growth factor receptor (EGFR) which is expressed in almost all types of tissue, triggering an increase in the expression of certain

genes that ultimately lead to DNA synthesis and cell proliferation (Herbst, 2004). EGF has been observed to stimulate the differentiation of epithelial cells, endothelial chemotaxis and angiogenesis, and fibroblast migration and proliferation, and to regulate extracellular matrix turnover (Deasy et al., 2002). Enhanced wound healing has been noted in dermal wounds treated with topical or subcutaneous EGF (Starkey et al., 1975). Franklin & Lynch (1979) recorded quicker epithelial regeneration and less scar contracture in EGF-treated wounds in rabbits.

With the introduction of recombinant human EGF in the 1980s, the range of studies increased to include burn wounds and chronic ulcers (Brown et al., 1989; Falanga et al., 1992). Studies with partial thickness human burn wounds and topical EGF confirmed a decrease in wound healing time (Brown et al., 1989). Although the use of EGF in human impaired wound healing by Falanga et al. (1992) showed a modest improvement in wound healing times and rate of epithelialization, the results were not statistically significant. Some other reports also suggested that the efficacy of EGF in chronic wounds is limited (Franklin & Lynch 1979; Brown et al., 1989). Therefore, no conclusions about the efficacy of EGF for chronic wounds can be made at present.

#### 2.2.2.2 Basic fibroblast growth factor (bFGF)

In 1974, Gospodarowicz isolated a protein that accelerated the proliferation of fibroblasts from bovine pituitary glands and termed it the fibroblast growth factor (FGF) (Gospodarowicz et al., 1987; Gospodarowicz et al., 1988; Greenhalgh et al., 1990). One of the best-known FGF activities includes the stimulation of fibroblast proliferation leading to granulation tissue formation (Floss et al., 1997). FGF also plays a key role in proliferation of endothelial cells and keratinocytes and the mitogenesis of mesenchymal cells (Floss et al., 1997; Menetrey et al., 2000). Experimental studies have demonstrated that bFGF accelerates angiogenesis, granulation, and epithelialization (Gospodarowicz et al., 1988). Some clinical studies have shown the efficacy and safety of bFGF for the treatment of various wounds including diabetic ulcers, pressure ulcers and burns (Ishibashi et al., 1996; Ichioka et al., 2005).

### 2.3 Cell therapies

Stimulation of the microcirculation and enhancement of angiogenesis may promote granulation tissue formation on compromised wounds. For this purpose, several technologies using autologous cells have been developed. Bone marrow firstly attracted our attention as a possible beneficial material for wound healing, because it contains multipotential progenitor cells that can differentiate into endothelial cells and secrete several growth factors. Several reports have illustrated the potential of bone marrow to induce angiogenesis and also that it might contain early stem cells that can differentiate into non-hematopoietic tissues such as the skin (Ichioka et al., 2004; Yamaguchi et al., 2005). Asahara and colleagues (1999; 1997). have shown that vascular endothelial progenitor cells (EPCs), the population of mononuclear cells, from the bone marrow passed through the peripheral circulation and migrated locally to tumors, injured or ischemic regions. Furthermore, it has been suggested experimentally that bone marrow cells contribute to the formation of a matrix (Fathke et al., 2004; Badiavas et al., 2003), vascular formation (Asahara et al., 1999), secretion of angiogenic cytokines (Kamihata et al., 2001; Sanchez-Guijo et al., 2010), and stimulation of muscle cells. (Tateno et al., 2006.)

### 2.3.1 Cell therapies for critical limb ischemia

Several experiments have demonstrated therapeutic relevance of cell therapy for the ischemic limb. *Ex vivo*-expanded human EPCs transplanted into limb ischemia mice models showed a recovery of blood flow, an enhanced collateral density, and a 60% limb salvage (7% in controls) (Kalka et al., 2000). Iba et al. (2002) demonstrated that implantation of Peripheral blood mononuclear cells and platelets into ischemic limbs effectively induced collateral vessel formation using rat models, suggesting that this cell therapy is useful for therapeutic angiogenesis.

Some reports indicated the efficacy and feasibility of the clinical use of cell therapy (Tateishi-Yuyama et al., 2002; Kajiguchi et al., 2007; Matoba et al., 2008; Miyamoto et al., 2004). Therapeutic angiogenesis using cell transplantation (TACT) is a treatment strategy for non-option patients with CLI in Japan. Tateishi-Yuyama et al. (2002) reported the first large clinical study on the use of bone marrow derived mononuclear cells in the treatment of limb ischemia. According to this report, injection of bone marrow derived mononuclear cells into the muscle of the ischemic limb apparently improved the ankle-brachial index (ABI), transcutaneous oxygen pressure (TcPO<sub>2</sub>), rest pain, and the pain free walking distance. The Japanese Ministry of Health, Labour and Welfare has approved this technology, namely "Therapeutic angiogenesis using bone marrow cell transplantation", as advanced medicine for critical limb ischemia. In addition, two other technologies using autologous cells, "Therapeutic angiogenesis using peripheral mononuclear cells" and "Therapeutic angiogenesis using peripheral blood stem cells", have been also approved (Matoba et al., 2008; Kajiguchi et al., 2007; Miyamoto et al., 2004).

### 2.3.2 Topical application of autologous cells

Topical application of bone marrow cells and platelet rich plasma (PRP) have been experimentally and clinically well-reported for their efficacy in the promotion of angiogenesis and wound healing (Wu et al., 2010; Lacci & Dardik, 2010).

#### 2.3.2.1 Bone marrow

Bone marrow has long been known to participate in wound healing by providing inflammatory cells which produce cytokines and orchestrate a cascade of events (Gillitzer & Goebeler, 2001). Recent bodies of evidence suggest that bone marrow might also serve as a resource to provide skin progenitor cells (Krause et al., 2001; Liang & Bickenbach, 2002). Several reports have experimentally illustrated that topically applied bone marrow cells might promote wound healing (Badiavas et al., 2003; Sivan-Loukianova et al., 2003; McFarlin et al., 2006).

Badiavas et al. (2003) indicated that wounding stimulated the engraftment of bone marrow cells to the skin and induced bone marrow-derived cells to be incorporated and differentiate into non-hematopoietic skin structures using mice models. The authors concluded that bone marrow might be a valuable source of stem cells for the skin and possibly other organs. The application of peripheral blood mononuclear cells accelerated the neovascularization and epidermal healing in a model of chronic full-thickness skin wounds in diabetic mice (Sivan-Loukianova et al., 2003). McFarlin et al. (2006) found that local injection of mesenchymal stem cells significantly improved wound healing in an animal wound model. Bone marrow-derived cells have been reported as transit-amplifying cells in injured tissue where they differentiate into keratinocytes, using a mouse wound model (Borue et al., 2004).

Based on the results of the experimental studies, bone marrow-derived stem cells have been clinically used in the treatment of chronic wounds (Badiavas & Falanga, 2003; Ramsey et al.,

1999; Metcalfe & Ferguson, 2007). Badiavas & Falanga (2003) showed that topically applied autologous bone marrow-derived cells can bring about closure of long-standing and hard-to-heal wounds. These authors reported that bone marrow-derived cultured mesenchymal stem cells accelerated the healing of cutaneous wounds (Falanga et al., 2007). A similar clinical approach has been performed by Rogers et al (2008) and reported that topical application and injection into the wound periphery of bone marrow can be a useful and a potentially safe adjunct to wound simplification and ultimate closure (Rogers et al., 2008). It was reported that locally applied mononuclear bone marrow cells restored angiogenesis and promoted wound healing of an ulcer of the lower leg in a type 2 diabetic patient (Humpert et al., 2005).

In Japan, several methods of applying bone marrow derived cells for wound have also been tried. Mizuno et al. (2010) employed the combination of mononuclear bone marrow cells and allogeneic cultured dermal substitute for the treatment of intractable ulcers in critical limb ischemia. The authors injected mononuclear cells intramuscularly into the lower leg and around the wound area and applied allogeneic cultured dermal substitute on the wound surface (Mizuno et al., 2010). In our strategy, we impregnated autologous bone marrow cells into a collagen matrix (Terdermis): bone marrow-impregnated collagen matrix, (Fig.1) that has been utilized for the treatment of chronic wounds.

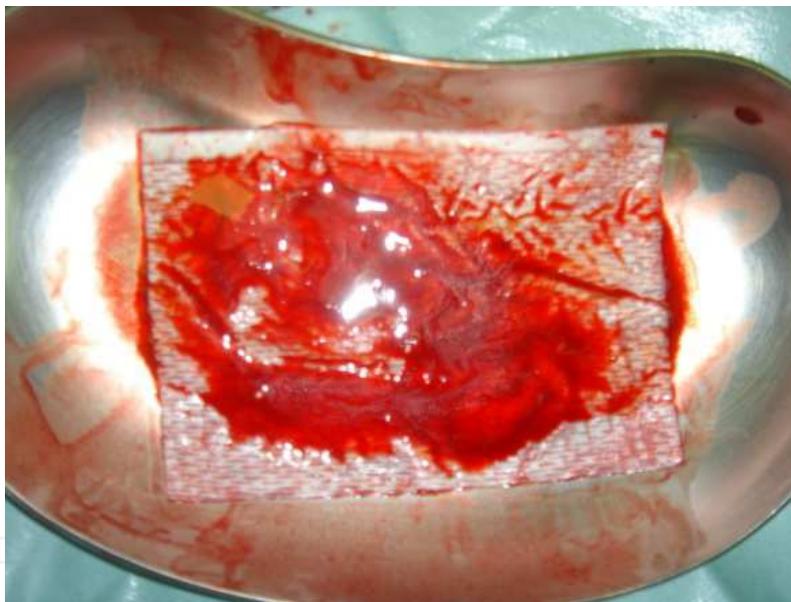


Fig. 1. The macroscopic finding of a bone marrow-impregnated collagen matrix

We have experimentally and clinically suggested the efficacy of this procedure for chronic ulcer treatment (Ichioka et al., 2005, 2009). One typical case is presented to illustrate the outcomes.

[patient 1] A 48-year-old woman suffered from a venous leg ulcer that had not healed despite seven years of standard conventional wound therapy (Fig. 2. A). Surgical debridement followed by bone marrow-impregnated collagen matrix application was undertaken under lumbar anesthesia (Fig. 2. B, C). Twenty-two days later, well-vascularized healthy granulation tissue had developed (Fig. 2. D), split-thickness skin graft was performed. The patient has remained free of complications for 29 months since treatment (Fig. 2. E).



Fig. 2. (A) Nonhealing ulcer on the left lower limb before wound debridement. (B) Application of the bone marrow-impregnated collagen matrix after debridement. (C) Robust granulation tissue 3 weeks after PRP collagen application. (D) Split-thickness mesh skin grafting was performed. (E) Healed wound.

#### 2.3.2.2 Platelet-rich plasma (PRP)

Besides the fundamental role in hemostasis at the injured site, platelets initiate and enhance wound healing by releasing numerous plasma proteins and various growth factors (Everts et al., 2006; Knighton et al., 1986; Knighton et al., 1988). Platelets stimulate angiogenesis, proliferation and migration, and collagen synthesis. The main growth factors produced by platelets include platelet-derived growth factor (PDGF) (Bennett et al., 2003), transforming growth factor beta ( $TGF-\beta$ ) (Assoian & Sporn., 1986), insulin-like growth factor (IGF-I)

(Hock et al., 1988), endothelial growth factor (EGF), vascular endothelial growth factor (VEGF) (Mohle et al., 1997), fibroblast growth factor (FGF) (Brunner et al., 1993). Platelet-rich plasma (PRP) is defined as a portion of the plasma fraction of autologous blood having a platelet concentration above baseline (Mehta & Watson, 2008; Marx, 2001). PRP can be supplied with a simple centrifugation procedure using solely autologous blood, suggesting that it is a minimally invasive method (Shashikiran et al., 2006; Bhanot & Alex, 2002). Roberts and Sporn (1993) and Marx (1998; 2001) have contributed a wealth of knowledge for the topical application of PRP in dentistry. In wound treatments, several investigations have reported the beneficial effects of PRP since its first report in 1985 (Driver et al., 2006). Margolis et al. (2001) reported a retrospective cohort study devised to estimate the effectiveness of platelet releasate (PR) in the treatment of diabetic neuropathic foot ulcers. The wounds of the 26,599 patients enrolled in this study, 43.1% of patients healed within 32 weeks, including 50% of patients treated with PRP and 41% of patients not treated with PR treatment. The investigators concluded that PRP was more effective than the standard care (Margolis et al., 2001). Driver et al. (2006) carried out the first prospective, randomized, controlled multicenter trial in the United States regarding the use of autologous PRP for the treatment of diabetic foot ulcers. The authors found the PRP treatment group attained significantly better outcomes as compared with the control group. (Driver et al., 2006). In our strategy, PRP is adapted with a collagen matrix to prepare the wound bed for skin graft or spontaneous closure (Fig. 3), and is applied to the debrided wound.



Fig. 3. Collagen matrix impregnated with PRP

Some recent studies have examined the clinical application of PRP using a drug delivery system (DDS). O'Connell et al. (2008) reported that a newly developed material containing PRP, which they named platelet-rich fibrin matrix membrane (PRFM), exhibited a gradual steady-state release of platelet-derived growth factors for as long as 7 days and potentially provided a fibrin scaffold to further facilitate the tissue repair process (O'Connell, et al. 2008). In Japan, Yazawa et al. (2003) reported that when a platelet concentrate was used in conjunction with fibrin glue as a carrier, the contents were released over a period of about 1 week. We have also reported that platelet-protein film (PPF) as an autologous fibrin clot which PRP and plasma proteins, might continuously release growth factors to the wound bed (Fig. 4) (Tanaka et al., 2007).

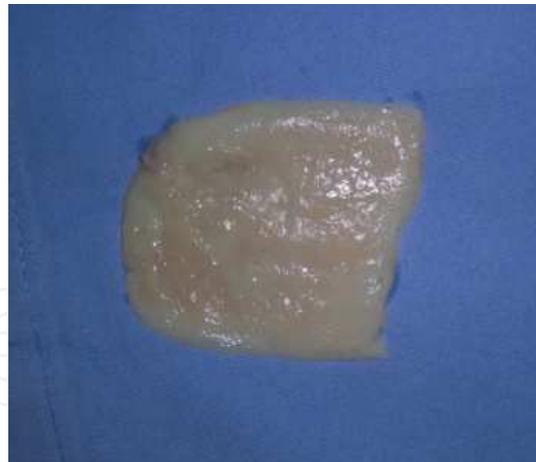


Fig. 4. The macroscopic finding of PRP

One successful case is presented to illustrate the possible outcome of treatment using PRP.  
[Patient 1]

A 89-year-old female developed a pressure ulcer over the left lower limb; the ulcer had not healed despite three months of standard conventional wound therapy (Fig. 5 A). Surgical debridement followed by PRP collagen application was performed under general anesthesia (Fig. 5 B). Three weeks later, well-vascularized, healthy granulation tissue had developed (Fig. 5 C), and a split-thickness skin graft was performed to completely close the wound (Fig. 5 D). The patient has remained free of complications for 4 months since treatment (Fig. 5 E).



Fig. 5. (A) Nonhealing ulcer on the left lower limb before wound debridement.(B) Application of PRP collagen after debridement.(C) Good granulation tissue 3 weeks after PRP collagen application.(D) Split-thickness mesh skin graft was performed.(E) Healed wound.

### 3. Conclusion

Advanced regenerative medicine-based technologies currently provide successful and less invasive wound closure with spontaneous healing or can be used in combination with skin

grafting instead of invasive surgical tissue transfer. Recent developments in physical therapies including negative pressure wound therapy (NPWT) reinforce the efficacy of conservative wound treatment. However, we should always bear in mind that topical therapeutic management strategies work effectively only on adequately perfused wound beds under a moist environment without devitalized tissue or a critical bacterial burden.

#### 4. References

- Adam, DJ., Beard, JD., Cleveland, T et al. (2005). Bypass versus angioplasty in severe ischemia of the leg (BASIL): multicentre, randomized controlled trial. *Lancet*, 366, pp. 1925–1934, ISSN 0140-6736.
- Aoki, M., Morishita, R. Taniyama, Y et al. (2000). Angiogenesis induced by hepatocyte growth factor in non-infarcted myocardium and infarcted myocardium: up-regulation of essential transcription factor for angiogenesis, ets. *Gene Ther.* 7, pp. 417–427, ISSN 0969-7128
- Asahara, T., Masuda, H., Takahashi, T et al. (1999). Bone marrow origin of endothelial progenitor cells responsible for postnatal vasculogenesis in physiological and pathological neovascularization. *Circ Res* 85, pp. 221-228, ISSN 0009-7330
- Asahara, T., Murohara, T., Sullivan, A et al. (1997). Isolation of putative progenitor endothelial cells for angiogenesis. *Science* 275, pp. 964-967, ISSN 0036-8075
- Assoian, RK. & Sporn, MB. (1986). Type beta transforming growth factor in human platelets: release during platelet degranulation and action on vascular smooth muscle cells. *J Cell Biol*, 102, pp. 1217–1223, ISSN 0021-9525
- Azuma, J., Taniyama, Y., Takeya, Y et al. (2006). Angiogenic and antifibrotic actions of hepatocyte growth factor improve cardiac dysfunction in porcine ischemic cardiomyopathy. *Gene Ther*, 13, pp. 1206–1213, ISSN 0969-7128
- Baumgartner, I., Pieczek, A., Manor, O et al. (1998). Constitutive expression of phVEGF165 after intramuscular gene transfer promotes collateral vessel development in patients with critical limb ischemia. *Circulation*, 97, pp. 1114–1123, ISSN 0009-7322
- Baumgartner, I., Rauh, G., Pieczek, A et al. (2000). Lower-extremity edema associated with gene transfer of naked DNA encoding vascular endothelial growth factor. *Ann Intern Med*, 132, pp.880–884, ISSN 0003-4819
- Badiavas, EV., & Falanga, V. (2003). Treatment of chronic wounds with bone marrow-derived cells. *Arch Dermatol*, 139, pp. 510–516. ISSN 0003-987X
- Badiavas, EV., Abedi, M., Butmarc, J et al. (2003). Participation of bone marrow derived cells in cutaneous wound healing. *J Cell Physiol*, 196(2), pp. 245-50, ISSN 0021-9541
- Bel, E., Ehrlich, HP., Buttle, DJ et al. (1981). A living tissue formed in vitro and accepted as a full thickness skin equivalent. *Science*, 211, pp. 1042-1054, ISSN 0036-8075
- Belle, EV., Witzenbichler, B., Chen, D et al. (1998). Potentiated angiogenic effect of scatter factor/hepatocyte growth factor via induction of vascular endothelial growth factor: the case for paracrine amplification of angiogenesis. *Circulation*, 97, pp. 381–390, ISSN 0009-7322
- Bennett, SP., Griffiths, GD., Schor, AM et al. (2003). Growth factors in the treatment of diabetic foot ulcers. *Br J Surg*, 90, pp. 133–146, ISSN 0007-1323
- Bhanot, S. & Alex, JC. (2002). Current applications of platelet gels in facial plastic surgery. *Facial Plast Surg.* 18(1), pp. 27-33, ISSN 1521-2491

- Borue, X., Lee, S., Grove, J et al. (2004). Bone marrow-derived cells contribute to epithelial engraftment during wound healing. *Am J Pathol*, 165, pp. 1767-1772, ISSN 0002-9440
- Boyce, ST., Christian, DJ. & Hansbrough, JF. (1988). Structure of collagen-GAG dermal skin substitute optimized for cultured human epidermal keratinocyte. *J Biomed Mater Res*, 22, pp. 939-957, ISSN 1552-4973
- Braden, BJ. & Bergstrom, N. (1989). Clinical utility of the Braden scale for predicting pressure sore risk. *Decubitus*, 2, pp. 44-46, 50-51, ISSN 0898-1655
- Brown, G., Nanney, L., Griffen, J et al. (1989). Enhancement of wound healing by topical treatment with epidermal growth factor. *N Eng J Med*, 321, pp. 76-89, ISSN 0028-4793
- Brunner, G., Nguyen, H., Gabrilove, J et al. (1993). Basic fibroblast growth factor expression in human bone marrow and peripheral blood cells. *Blood*, 81, pp.631-638, ISSN 0006-4971
- Bussolino, F., DiRenzo, MF., Ziche, M et al. (1992). Hepatocyte growth factor is a potent angiogenic factor which stimulates endothelial cell mobility and growth. *J Cell Biol*, 119, pp. 629-641, ISSN 0021-9525
- Chvapil, M., Kronenthal, RL. & Winkle, WV. Jr. (1973 ). *Medical and surgical applications of collagen. International Review of Connective Tissue Research*, vol. 6, Hall D.A.and Jackson D. S. (eds), Academic Press, New York, pp. 1-61, ISBN 9780123637109
- Cooper, DM., Yu, EZ., Hennessey, P et al. (1994). Determination of endogenous cytokines in chronic wounds. *Ann Surg*, 219, pp. 688-692, ISSN 0003-4932
- Cohen, S. (1962). Isolation of a mouse submaxillary gland protein accelerating incisor eruption and eyelid opening in the new-born animal. *J Biol Chem*, 237, pp. 1555-1562. ISSN 0021-9258
- Dantzer, E. & Braye, FM. (2001). Reconstructive surgery using an artificial dermis (Integra): results with 39 grafts. *Br J plast Surg*, 54, pp.659-664, ISSN 0007-1226.
- Deasy, BM., Qu-Peterson, Z., Greenberger, JS et al. (2002). Mechanisms of muscle stem cell expansion with cytokines. *Stem Cells*, 20, pp. 50-60, ISSN 1066-5099
- Doillon, CJ. & Silver, FH. (1986). Collagen-based wound dressing: Effects of hyaluonic acid and fibronectin on wound healing. *Biomaterials*, 7, pp. 3-8, ISSN 0142-9612
- Doillon, CJ., Whyne, CF., Brandwein, S. et al. (1986). Collagen-based wound dressing: Control of the pore structure and morphology. *J Biomed Mater Res*, 20, pp. 1219-1228, ISSN 1552-4973
- Doughty, D. & Sparks-Defriese, B. (2007). Wound healing physiology. In: Bryant RA, Nix DP, eds. *Acute&Chronic Wounds: Current Management Concepts*. 3rd ed. St. Louis: Mosby/Elsevier, 56-81, ISBN 9780323030748
- Driver, VR., Hanft, J., Fylling, CP et al. (2006). Autologel Diabetic Foot Ulcer Study Group. A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. *Ostomy Wound Manage*. 52(6), pp. 68-70, 72, 74 passim, ISSN 0889-5899
- Everts, PA., BrownMahoney, C., Hoffmann, JJ et al. (2006). Platelet-rich plasma preparation using three devices: implications for platelet activation and platelet growth factor release. *Growth Factors*. 24(3), pp. 165-71, ISSN 0897-7194
- Falanga, V., Iwamoto, S. & Chartier M. (2007). Autologous bone marrow-derived cultured mesenchymal stem cells delivered in a fibrin spray accelerate healing in murine and human cutaneous wounds. *Tissue Eng*, 13, pp. 1299-1312, ISSN 1076-3279

- Fathke, C., Wilson, L., Hutter, J et al. (2004). Contribution of bone marrow-derived cells to skin: collagen deposition and wound repair. *Stem Cells*, 22(5), pp. 812-22, ISSN 1066-5099
- Franklin, J. & Lynch, J. (1979). Effects of topical applications of epidermal growth factor on wound healing. *Plast Reconstr Surg*, 64, pp. 766-70, ISSN 0032-1052
- Floss, T., Arnold, HH. & Braun, T. (1997). A role for FGF-6 in skeletal muscle regeneration. *Genes Dev*, 11, pp. 2040-5, ISSN 0969-7128
- Gillitzer, R. & Goebeler, M. (2001). Chemokines in cutaneous wound healing. *J Leukoc Biol*, 69, pp. 513-521, ISSN 0741-5400
- Greenhalgh, DG., Sprugel, KH., Murray, MJ et al. (1990). PDGF and FGF stimulate wound healing in the genetically diabetic mouse. *Am J Pathol*. 136, pp. 1235-46, ISSN 0002-9440
- Greenhalgh, D. (1996). The role of growth factors in wound healing. *J Trauma*, 41, pp. 159-67, ISSN 0022-5282.
- Gospodarowicz, D. (1988). Molecular and developmental biology aspects of fibroblast growth factor. *Adv Exp Med Biol*, 234, pp. 23-39, ISSN 0065-2598
- Gospodarowicz, D., Ferrara, N., Schweigerer, L et al. (1987). Structural characterization and biological functions of fibroblast growth factor. *Endocr Rev*, 8, pp. 95-114, ISSN 0163-769X
- Grossman, PM., Mendelsohn, F., Henry TD et al. (2007). Results from a phase II multicenter, double-blind placebo-controlled study of Del-1 (VLTS-589) for intermittent claudication in subjects with peripheral arterial disease. *Am Heart J*, 153, pp. 874-880, ISSN 0002-8703
- Humpert, PM., Bartsch, U., Konrade, I et al. (2005). Locally applied mononuclear bone marrow cells restore angiogenesis and promote wound healing in a type 2 diabetic patient. *Exp Clin Endocrinol Diabetes*, 113, pp. 538-540, ISSN 0947-7349
- Harding, KG., Morris, HL. & Patel GK. (2002). Science, medicine and the future: Healing chronic wounds. *BMJ*, 324, 160-163
- Hayashi, S., Morishita, R. & Nakamura, S. (1999). Potential role of hepatocyte growth factor, a novel angiogenic growth factor, in peripheral arterial disease: down-regulation of HGF in response to hypoxia in vascular cells. *Circulation*. 100, pp. II301-II308, ISSN 0009-7322
- Heeschen, C., Dimmeler, S. & Hamm, CW. (2003). Prognostic significance of angiogenic growth factor serum levels in patients with acute coronary syndromes. *Circulation*, 107, pp. 524-530, ISSN 0009-7322
- Herbst, RS. (2004). Review of epidermal growth factor receptor biology. *Int J Radiat Oncol Bio Phys*, 59(Suppl 2), pp.21-6, ISSN 0360-3016
- Hock, JM., Gentrella, M. & Canalis, E. (1988). Insulin-like growth factor I has independent effects on bone matrix formation and cell replication. *Endocrinology*, 122, pp. 254-60, ISSN 0013-7227
- Iba, O., Matsubara, H. & Nozawa, Y. (2002). Angiogenesis by Implantation of Peripheral Blood Mononuclear Cells and Platelets Into Ischemic Limbs. *Circulation*. 106, 2019-2025, ISSN 0009-7322
- Ichioka, S., Ohura, N., Sekiya, N et al. (2003). Regenerative surgery for sacral pressure ulcers using collagen matrix substitute dermis (artificial dermis). *Ann Plast Surg*, 51(4), pp. 383-9, ISSN 0148-7043

- Ichioka, S., Kudo, S., Shibata, M et al. (2004) Bone marrow cell implantation improves flap viability after ischemia-reperfusion injury. *Ann Plast Surg*, 52(4), pp. 414-8, ISSN 0148-7043
- Ichioka, S., Ohura, N., Nakatsuka, T et al. (2005). The positive experience using a growth factor product on deep wounds with bone exposure. *Journal of Wound Care*. 14(3), pp. 105-109. ISSN 0969-0700
- Ichioka, S., Kouraba, S., Sekiya, N et al. (2005). Bone marrow-impregnated collagen matrix for wound healing: experimental evaluation in a microcirculatory model of angiogenesis, and clinical experience. *Br J Plast Surg*, 58, pp. 1124-30. ISSN 0007-1226
- Ichioka, S., Yokogawa, H., Sekiya, N et al. (2009). Determinants of Wound Healing in Bone Marrow impregnated Collagen Matrix Treatment: Impact of Microcirculatory Response to Surgical Debridement. *Wound Repair Regen*, 17(4), pp. 492-7, ISSN 1067-1927
- Ishibashi, Y., Harada, S., Takemura, T et al. (1996). Clinical effectiveness of KCB-1(bFGF) on patients with skin ulcerations clinical trial for 12 weeks. *J Clin Therapeut Med*, 12, pp. 2117-29, ISSN 0910-8211
- Isner, JM., Pieczek, A., Schainfeld, R et al. (1996). Clinical evidence of angiogenesis after arterial gene transfer of phVEGF165 in patient with ischaemic limb. *Lancet*. 348, pp. 370 -374, ISSN 0140-6736
- Isner, JM., Baumgartner, I., Rauh, G et al. (1998). Treatment of thromboangiitis obliterans (Buerger's disease) by intramuscular gene transfer of vascular endothelial growth factor: preliminary clinical results. *J Vasc Surg*, 28, pp. 964-973, ISSN 0741-5214
- Kajiguchi, M., Kondo, T., Izawa H et al. (2007). Safety and Efficacy of Autologous Progenitor Cell Transplantation for Therapeutic Angiogenesis in Patients With Critical Limb Ischemia, *Circ J*, 71, pp. 196 -201, ISSN 1346-9843
- Kalka, C., Masuda, H., Takahashi, T et al. (2000). Transplantation of ex vivo expanded endothelial progenitor cells for therapeutic neovascularization. *Proc Natl Acad Sci USA*, 97, pp. 3422-3427, ISSN 0027-8424
- Kamihata, H., Matsubara, H., Nishiue, T et al. (2001). Implantation of bone marrow mononuclear cells into ischemic myocardium enhances collateral perfusion and regional function via side supply of angioblasts, angiogenic ligands, and cytokines. *Circulation*, 104(9), pp. 1046-1052, ISSN 0009-7322
- Knighton, DR., Ciresi, KF., Fiegel, VD et al. (1986). Classification and treatment of chronic nonhealing wounds. Successful treatment with autologous platelet-derived wound healing factors (PDWHF). *Ann Surg*, 204(3), pp. 322-30, ISSN 0148-7043
- Knighton, DR., Doucette, M., Fiegel, VD et al. (1988). The use of platelet derived wound healing formula in human clinical trials. *Prog Clin Biol Res*, 266, pp. 319-29, ISSN 0361-7742
- Krause, DS., Theise, ND., Collector, MI et al. (2001). Multi-organ, multilineage engraftment by a single bone marrow-derived stem cell. *Cell*, 105, pp. 369-377, ISSN 0092-8674
- Lacci, KM. & Dardik A. (2010) Platelet-rich plasma: support for its use in wound healing. *Yale J Biol Med*. 83(1), pp 1-9, ISSN 0044-0086
- Laitinen, M., Makinen, K., Manninen, H et al. (1998). Adenovirus-mediated gene transfer to lower limb artery of patients with chronic critical leg ischaemia. *Hum Gene Ther*, 9, pp. 1481-1486, ISSN 1043-0342

- Leipzig, LY., Gllushko, V., Dibernardo, B et al. (1985). Dermal wound repair: Role of collagen matrix implants and synthetic polymer dressing, *J Am Acad Dermatol*, 12, pp. 409-419, ISSN 0190-9622
- Lenihan, DJ., Osman, A., Sriram, V et al. (2003). Evidence for association of coronary sinus levels of hepatocyte growth factor and collateralization in human coronary disease. *Am J Physiol Heart Circ Physiol*, 284, pp. H1507-H1512, ISSN 0363-6135
- Liang, L., & Bickenbach, JR. (2002). Somatic epidermal stem cells can produce multiple cell lineages during development. *Stem Cells*, 20, pp. 21-31, ISSN 1066-5099
- Linsenmayer, TF. (1985). collagen," in *Cell biology of extracellular matrix*, E.D. Hay(ed.), Plenum Press, New York, pp.5-37, ISBN 9780306439513
- Losordo, DW., Vale, PR., Symes, JF et.al. (1998). Gene therapy for myocardial angiogenesis: initial clinical results with direct myocardial injection of phVEGF165 as sole therapy for myocardial ischemia. *Circulation*, 98, pp. 2800-2804, ISSN 0009-7322
- Margolis, DJ., Kantor, J., Santanna, J et al. (2001). Effectiveness of platelet releasate for the treatment of diabetic neuropathic foot ulcers. *Diabetes Care*, 24(3), pp. 483-488, ISSN 0149-5992
- Marx, RE. (2001). Platelet-rich plasma (PRP): what is PRP and what is not PRP? *Implant Dent*, 10(4), pp. 225-228, ISSN 1056-6163
- Marx, RE., Carlson, ER., Eichstaedt, RM et al. (1998). Platelet-rich plasma: Growth factor enhancement for bone grafts. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, 85, pp. 638-646, ISSN 1079-2104
- Matsumoto, K. & Nakamura, T. (1996). Emerging multipotent aspects of hepatocyte growth factor. *J Biochem*, 119, pp. 591- 600, ISSN 0021 – 924X
- Matoba, S., Tatsumi, T., Murohara, T et al. (2008) Long-term clinical outcome after intramuscular implantation of bone marrow mononuclear cells (Therapeutic Angiogenesis by Cell Transplantation [TACT] trial) in patients with chronic limb ischemia. *Am. Heart J*, 156(5), pp. 1010-1018, ISSN 0002-8703
- McFarlin, K., Gao, X., Liu, YB et al. (2006). Bone marrowderived mesenchymal stromal cells accelerate wound healing in the rat. *Wound Repair Regen*, 14, pp. 471-478, ISSN 1067-1927
- Menetrey, J., Kasemkijwattana, C., Day, CS et al. (2000). Growth factors improve muscle healing in vivo. *J Bone Joint Surg Br*, 82, pp. 131-137 ISSN 0301-620X
- Metcalf, AD. & Ferguson, MW. (2007). Tissue engineering of replacement skin: the crossroads of biomaterials, wound healing, embryonic development, stem cells and regeneration. *J R Soc Interface*, 4, pp. 413-437, ISSN 1742-5689
- Mehta, S. & Watson, JT. (2008). Platelet rich concentrate: basic science and current clinical applications. *J Orthop Trauma*, 22(6), pp.432-438, ISSN 0890-5339
- Miyamoto, M., Yasutake, M., Takano, H et al. (2004). Therapeutic angiogenesis by autologous bone marrow cell implantation for refractory chronic peripheral arterial disease using assessment of neovascularization by 99mTc-tetrofosmin (TF) perfusion scintigraphy. *Cell Transplant*, 13(4), pp. 429-437, ISSN 0963-6897
- Mizuno, H., Miyamoto, M., Shimamoto, M et al. (2010). Therapeutic angiogenesis by autologous bone marrow cell implantation together with allogeneic cultured dermal substitute for intractable ulcers in critical limb ischaemia. *J Plast Reconstr Aesthet Surg*, 63(11), pp. 1875-1882, ISSN 1748-6815
- Mohle, R., Green, D., Moore, MA et al. (1997). Constitutive production and thrombin-induced release of vascular endothelial growth factor by human megakaryocytes and platelets. *Proc Natl Acad Sci USA*, 94, pp. 663-668, ISSN 0027-8424

- Morishita, R., Nakamura, S.; Hayashi, S et al. (1999). Therapeutic angiogenesis induced by human recombinant hepatocyte growth factor in rabbit hind limb ischemia model as cytokine supplement therapy. *Hypertension*, 33, pp. 1379–1384, ISSN 0194-099X
- Morishita, R., Sakaki, M., Yamamoto, K et al. (2002). Impairment of collateral formation in Lp(a) transgenic mice: therapeutic angiogenesis induced by human hepatocyte growth factor gene. *Circulation*, 105, pp. 1491–1496, ISSN 0009-7322
- Morishita, R., Aoki, M., Hashiya, N., (2004). Therapeutic angiogenesis using hepatocyte growth factor (HGF). *Curr Gene Ther.* 4, pp. 199–206, ISSN 1566-5232
- Morishita, R., Aoki, M., Hashiya, N., (2004). Safety evaluation of clinical gene therapy using hepatocyte growth factor to treat peripheral arterial disease. *Hypertension*, 44, pp. 203–209, ISSN 0194-911X
- Nakamura, Y., Morishita, R., Higaki, J et al. (1996). Hepatocyte growth factor is a novel member of the endothelium- specific growth factors: additive stimulatory effect of hepatocyte growth factor with basic fibroblast growth factor but not with vascular endothelial growth factor. *J Hypertens*, 14, pp. 1067–1072, ISSN 0263-6352
- Nikol, S., Baumgartner, I., Van Belle E et al. (2008). Therapeutic angiogenesis with intramuscular NV1FGF improves amputation-free survival in patients with critical limb ischemia. *Mol Ther*, 16, pp. 972–978, ISSN 1525-0016
- O'Connell, SM., Impeduglia, T., Hessler, K et al. (2008). Autologous platelet-rich fibrin matrix as cell therapy in the healing of chronic lower-extremity ulcers. *Wound Repair Regen*, 16(6), pp. 749-56, ISSN 1067-1927
- Powell, RJ., Simons, M., Mendelsohn, FO et al. (2008). Results of a double-blind, placebo-controlled study to assess the safety of intramuscular injection of hepatocyte growth factor plasmid to improve limb perfusion in patients with critical limb ischemia. *Circulation*, 118, pp. 58–65, ISSN 0009-7322
- Ramsey, SD., Newton, K., Blough, D et al. (1999). Incidence, outcomes, and cost of foot ulcers in patients with diabetes. *Diabetes Care*, 22, pp. 382–387, ISSN 0149-5992
- Rajagopalan, S., Olin, J., Deitcher, S et al. (2007). Use of a constitutively active hypoxia-inducible factor-1alpha transgene as a therapeutic strategy in no-option critical limb ischemia patients: phase I doseescalation experience. *Circulation*, 115, pp. 1234–1243, ISSN 0009-7322
- Roberts, AB. & Sporn, MB. (1993). Physiological actions and clinical applications of transforming growth factor-beta (TGFbeta). *Growth Factors*, 8, pp. 1-9, ISSN 0897-7194
- Rogers, LC., Bevilacqua, NJ. & Armstrong, DG. (2008). The use of marrow-derived stem cells to accelerate healing in chronic wounds. *Int Wound J*, 5(1), pp.20-5, ISSN 1742-4801
- Rosengart, TK., Lee, LY., Patel, SR et al. (1999). Six-month assessment of a phase I trial of angiogenic gene therapy for the treatment of coronary artery disease using direct intramyocardial administration of an adenovirus vector expressing the VEGF121 cDNA. *Ann Surg*, 230, pp. 466–470, ISSN 0003-4932.
- Rosengart, TK., Lee, LY., Patel, SR et al. (1999). Angiogenesis gene therapy: phase I assessment of direct intramyocardial administration of an adenovirus vector expressing VEGF121 cDNA to individuals with clinically significant severe coronary artery disease. *Circulation*, 100, pp. 468–474, ISSN 0009-7322
- Sanchez-Guijo, FM., Oterino, E., Barbado, MV et al. (2010). Both CD133(+) cells and monocytes provide significant improvement for hindlimb ischemia, although they do not transdifferentiate into endothelial cells. *Cell Transplant*, 19(1), pp. 103-112, ISSN 0963-6897

- Schumacher, B., Pecher, P., von Specht, BU et al. (1998). Induction of neoangiogenesis in ischemic myocardium by human growth factors: first clinical results of a new treatment of coronary heart disease. *Circulation*, 97, pp. 645– 650. ISSN 0009-7322
- Shashikiran, ND., Reddy, VV., Yavagal, CM et al. (2006). Applications of platelet-rich plasma (PRP) in contemporary pediatric dentistry. *J Clin Pediatr Dent*, 30(4), pp. 283-286, ISSN 1053-4628
- Sivan-Loukianova, E., Awad, O., Stepanovic, V et al. (2003). CD34\_ blood cells accelerate vascularization and healing of diabetic mouse skin wounds. *J Vasc Res*, 40, pp. 368–377, ISSN 1018-1172
- Stadelmann, WK., Digenis, AG. & Tobin GR. (1998). Physiology and healing dynamics of chronic cutaneous wounds. *Am J Surg*, 176, pp. 26S–38S, ISSN 0002-9610
- Starkey, R., Cohen, S. & Orth D. (1975). Epidermal growth factor: identification of a new hormone in human urine. *Science*, 189, pp. 800-802, ISSN 0036-8075
- Tanaka, R., Ichioka, S., Sekiya, N et al. (2007). Elastic plasma protein film blended with platelet releasate accelerates healing of diabetic mouse skin wounds. *Vox Sang*, 93(1), pp. 49-56, ISSN 0042-9007
- Taniyama, Y., Morishita, R., Aoki, M et al. (2001). Therapeutic angiogenesis induced by human hepatocyte growth factor gene in rat and rabbit hind limb ischemia models: preclinical study for treatment of peripheral arterial disease. *Gene Ther*, 8, pp. 181–189, ISSN 0969-7128
- Taniyama, Y., Morishita, R., Hiraoka, K et al. (2001). Therapeutic angiogenesis induced by human hepatocyte growth factor gene in rat diabetic hind limb ischemia model: molecular mechanisms of delayed angiogenesis in diabetes. *Circulation*, 104, pp. 2344–2350, ISSN 0009-7322
- Tateishi-Yuyama, E., Matsubara, H., Murohara, T et al. (2002). Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: a pilot study and a randomised controlled trial. *Lancet*, 360, pp. 427–435, ISSN 0140-6736
- Tateno, K., Minamino, T., Toko, H et al. (2006). Critical roles of muscle-secreted angiogenic factors in therapeutic neovascularization. *Circ Res*, 98(9), pp. 1194-1202, ISSN 0009-7330
- Vale, PR., Losordo, DW., Milliken, CE et al. (1999). Images in cardiovascular medicine: Percutaneous myocardial gene transfer of phVEGF-2. *Circulation*, 100, pp. 2462–2463, ISSN 0009-7322
- Vale, PR., Losordo, DW., Milliken, CE et al. (2000). Left ventricular electromechanical mapping to assess efficacy of phVEGF165 gene transfer for therapeutic angiogenesis in chronic myocardial ischemia. *Circulation*, 102, pp. 965–974, ISSN 0009-7322
- Wu, Y., Zhao RC. & Tredget, EE. (2010). Concise review: bone marrow-derived stem/progenitor cells in cutaneous repair and regeneration. *Stem cells*, 28(5), pp. 905-915, ISSN 1066-5099
- Yamaguchi, Y., Kubo, T., Murakami, T et al. (2005). Bone marrow cells differentiate into wound myofibroblasts and accelerate the healing of wounds with exposed bones when combined with an occlusive dressing. *Br J dermatol*, 152, pp. 616-622, ISSN 0007-0963
- Yannas, IV. & Burke, JF. (1980). Design of an artificial skin I . Basic design principles. *J Biomed Mater Res*, 14, pp. 65-81, ISSN 1552-4973
- Yazawa, M., Ogata, H., Nakajima, T et al. (2003). Basic studies on the clinical applications of platelet-rich plasma. *Cell Transplant*, 12, pp. 509-518, ISSN 0963-6897



## **Skin Grafts - Indications, Applications and Current Research**

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The procedure of skin grafting has been performed since 3000BC and with the aid of modern technology has evolved through the years. While the development of new techniques and devices has significantly improved the functional as well as the aesthetic results from skin grafting, the fundamentals of skin grafting have remained the same, a healthy vascular granulating wound bed free of infection. Adherence to the recipient bed is the most important factor in skin graft survival and research continues introducing new techniques that promote this process. Biological and synthetic skin substitutes have also provided better treatment options as well as HLA tissue typing and the use of growth factors. Even today, skin grafts remain the most common and least invasive procedure for the closure of soft tissue defects but the quest for perfection continues.

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