Journal of Diabetes Science and Technology
Volume 4, Issue 4, July 2010

SYMPOSIUM

The Micrograft Concept for Wound Healing: Strategies and Applications

Atanu Biswas, M.D.,[1] Manish Bharara, Ph.D.,[2] Craig Hurst, M.D., M.S.,[3] David G. Armstrong, D.P.M., M.D., Ph.D.,[2] and Horacio Rilo, M.D.[1,2]

Abstract

The standard of care for wound coverage is to use an autologous skin graft. However, large or chronic wounds become an exceptionally challenging problem especially when donor sites are limited. It is important that the clinician be aware of various treatment modalities for wound care and incorporate those methods appropriately in the proper clinical context. This report reviews an alternative to traditional meshed skin grafting for wound coverage: micrografting. The physiological concept of micrografting, along with historical context, and the evolution of the technique are discussed, as well as studies needed for micrograft characterization and future applications of the technique.

J Diabetes Sci Technol 2010;4(4):808-819

Introduction

The healing of large or chronic wounds is always a challenging problem for the surgeon. The use of skin grafts, whether split thickness or full thickness, has offered the surgeon a reasonable method to address the problem of wound healing. However, limited donor-site skin yields another potential problem for surgeons when encountering complex wounds. Advances such as engineered artificial skin provide a rapid but temporary and costly approach to achieve wound coverage when donor-skin sites are few. Allografts and xenografts also provide immediate although temporary coverage. An ideal graft would be one that is immediately available, non-immunogenic, permanent, and offers low morbidity to the patient. The micrograft concept achieves the aforementioned traits because it is autologous tissue and allows wound coverage by utilizing a minimal amount of donor skin.

Micrograft Concept

In 1869, Jacques-Louis Reverdin[1] described the first method of grafting small, full-thickness pieces of skin for wound healing. Reverdin's method exploited the concept of creating skin islands to promote epithelialization of a wound. Five years later, Karl Thiersch[2] described another method of skin grafting, which is now better known as

Author Affiliations: [1]College of Medicine, Department of Surgery, Center for Cellular Transplantation, University of Arizona, Tucson, Arizona; [2]College of Medicine, Department of Surgery, Southern Arizona Limb Salvage Alliance, University of Arizona, Tucson, Arizona; and [3]College of Medicine, Department of Surgery, Division of Plastic and Reconstructive Surgery, University of Arizona, Tucson, Arizona

Abbreviations: (CEA) cultured epithelial autografts, (EGF) epidermal growth factor, (NPWT) negative pressure wound therapy, (PDGF) platelet-derived growth factor, (TGF-β) transforming growth factor-β

Keywords: diabetic foot ulcers, micrografting, wound healing

Corresponding Author: Horacio Rilo, M.D., Department of Surgery, University of Arizona, Medical Research Building (MRB), Room 126, 1656 E. Mabel St., Tucson, AZ 85724; email address hrilo@surgery.arizona.edu

the "split-thickness graft." In 1914, John Staige Davis[3,4] used a modified version of Reverdin's method of creating skin grafts which became known as the "pinch graft." However, for the next 50 years, the split-thickness graft had largely become the method of choice for coverage of wounds, although several authors proposed alternative micrograft-like methods such as spreading epidermal particles onto the wound bed.[5,6] Von Mangoldt's graft technique became the first known "cultured epidermal autograft," albeit *in vivo*, in modern clinical practice. The technique proposed by Von Mangoldt was largely ignored despite successful results from several authors such as Reschke-Greifswold[7] who injected pulverized epidermis below the surface of granulation tissue and Billingham and Reynolds[8] who described an experimental method of preparing an epidermal cell suspension by controlled tryptic digestion. The poor mainstream approval was primarily due to the assumption that the technique of scraping and pulverizing the cells would cause the cells to lose their regenerative ability of keratinization. As the early to mid 1900s became dominated by war, with the increase in burn wounds being apparent, a new technique to cover wounds needed to be discovered. In 1964, James C. Tanner and colleagues[9] described their method of skin graft expansion in which an ordinary split-thickness graft, when meshed, can cover an area three to six times (3–6:1) as large as the donor area. The healing process is completed by the epithelial migration between the meshed-skin edges. The meshed-skin graft gave surgeons a method to cover wounds when limited donor-skin sites were present, although expected expansion ratios rarely correlated with observed expansion ratios.[10]

The idea that meshed skin can be expanded to cover wounds larger than the donor site gave new light to the concept of micrografting skin. By creating smaller skin islands, the grafted skin has an increased epithelial surface area that is in contact with the wound bed. In this regard, the wound coverage occurs by the epithelial migration between the micrograft skin islands. The predominant factor governing micrograft healing is the distance between the micrograft skin islands, which is directly related to the size of the micrograft skin islands as described by the equation, where L is the distance between the micrograft skin islands, x is the micrograft skin island side length, and Y is the expansion ratio.[11] For example, if the micrograft skin island size is doubled, the distance between the skin islands is doubled as well. Therefore smaller skin island sizes would decrease the distance between the skin islands, which would theoretically reduce the time to heal because of less distance for epithelialization to traverse. Other factors that potentially impact epithelial migration include margin advancement, contact inhibition, and the dressing environment.[11] Because of the smaller graft size, skin micrografting allows expansion of the graft to much larger ratios than meshed skin grafts could provide.

Micrograft Techniques

The following techniques are summarized in **Table 1** for comparison.

Pinch Graft

Reverdin's report to the Société Impériale de Chirurgie on December 8, 1869, regarding the hastening of wound healing by the use of small detached pieces of skin caused universal interest. Reverdin called his technique "epidermic grafting," where he lifted the epidermis with a needle point and cut the lifted epidermis with a scalpel for transplantation to the granulating wound bed.[1] Reverdin's graft method, perhaps the first micrograft, is now widely known as the "pinch graft." Pinch grafting involves harvesting small discs of skin and applying them evenly across an epithelial defect to enable epithelialization from the wound edge and the skin islands. John Staige Davis[3,12,13] expanded on Reverdin's concept by proposing that adding dermis along with the epidermal graft would give a final result that is more like normal skin compared to a thinner graft. Davis's technique, which he called "small deep skin grafts," was essentially the same as Reverdin's technique except that dermis was included with epidermis to create a full-thickness microskin graft. Pinch grafts were widely used for treatment of chronic leg ulcers but soon fell out of favor with modern plastic surgeons who prefer excision of the ulcer bed and placement of split-thickness skin grafts. However, several clinical trials utilizing pinch grafting yielded acceptable as well as mixed results—78.3% healed in a series of 113 patients with 173 leg ulcers;[14] 91.8% healed in a series of 170 patients with chronic venous leg ulcers;[15] 75.7% healed in a series of 33 patients with chronic venous leg ulcers, 100% healed in a series of 14 patient with arteriosclerotic leg ulcers, and 50% healed in a series of 4 patients with arterial leg ulcers;[16] 38% healed in a series of 146 patients with 412 ulcers of various etiologies;[17] 36% healed in a series of 145 ulcers of various etiologies;[18] 47% healed in a series of 45 patients with 55 ulcerated limbs;[19] 40% healed in a series of 20 patients with leg ulcers and rheumatoid arthritis, with 61.1% of these patients reporting a decrease in pain;[20] and 60% healed in a series of 85 patients with 126 leg ulcers.[21] These studies support the use of

pinch grafting as a useful modality for facilitating ulcer healing.

Several disadvantages are associated with pinch grafting. For instance, because the donor area is used to harvest full-thickness skin pieces, the donor site is virtually removed from future use for grafts. Also, if the grafts are to be placed close together, a large donor area may be needed.[4] Pinch grafting is less reliable on wounds greater than 4.6 cm^2 in size.[21] Finally, because of the nonuniform distribution of the grafts, the cosmetic result is generally poorer compared to conventional methods.

Pinch grafting does, however, offer a simple and inexpensive alternative for wound healing. Full-thickness skin offers better resistance to pressure and infection. The procedure does not rely on complex machinery, although some technologies have been proposed to provide efficient and more uniform graft islands such as the trigger-fired pinch harvester.[22] For practical purposes, a needle point and a scalpel are the only necessary requirements to perform the procedure.

Patch/Postage Stamp Graft and Scrap Graft

The first report of the patch graft technique was by Gabarro[4] in 1943. Gabarro's main premise for developing such a technique was that no infected area will heal unless there is enough room for discharge to escape. He also wanted to improve on the pinch graft technique by ensuring that the donor site could be used again. The technique involves removing a donor piece of skin that is one-sixth to one-ninth the size of the wound to be covered and placing the skin, dermis side up, on a sheet of sticky paper. The paper with the skin is cut into strips, placed on another piece of paper, and then cut horizontally into small squares. The strips of paper help facilitate placing the skin squares onto the wound bed. This method allowed more uniform skin islands to be

Table 1.
Comparison of Techniques

Micrograft type	Graft size	Expansion ratio	Advantages	Disadvantages
Pinch graft	2–5 mm^2	6–7:1	Easy to cut, resists infection well, resists pressure better than split-skin graft, can be performed as an outpatient procedure, inexpensive	Donor site cannot be used for future grafts, poor cosmetic result, not useful for wounds >4.6 cm^2, tedious procedure for large wounds
Patch/postage stamp graft	1.27 mm^2–various	6–9:1	Easy to cut, resists infection well, can be performed as an outpatient procedure, inexpensive	Poor cosmetic result, tedious procedure, unpredictable expansion ratio
Meek microdermagraft	1.58 mm^2	9:1	Quicker graft preparation	Need custom dermatome
Chinese intermingled technique	0.9–2.5 mm^2	7–10:1	Less contracture formation, use of allograft protective layer	Tedious procedure, possibility of rejection
Microskin graft	<1 mm^2	7–100:1	Easy to prepare, cost efficient, resists infection well, tolerates trauma well	Orientation of grafts may be nonuniform, increased scar contracture formation
Microscopic split-skin ("diced") graft	40–200 μm^2	20–26:1	Easy to prepare, can be prepared as an outpatient procedure, comparative healing rates to meshed skin	Random orientation of grafts
Modified Meek technique	9 mm^2	10:1	Good for poor quality wounds, uniform distribution of skin pieces, orientation is nonrandom, true expansion rate	More demanding technique, higher costs of materials
Modified postage stamp/flypaper graft	25 mm^2	9:1	Less expensive, larger graft size easier to handle and orient, minimal materials needed, true expansion ratios obtained	Tedious procedure
Autologous skin suspension	0.4 mm^2	10:1	Easy to prepare, fast healing rates	Viability of skin particles questionable, poor cosmetic outcome, excessive scar contracture
Microskin spray	0.04–0.25 mm^2	110–150:1	Easy to use, good distribution of grafts, shorter operating time, less donor skin needed	Custom preparation needed

prepared in a quick and efficient manner. Variations of this method have been proposed such as simply cutting irregular pieces of skin for coverage of wounds[23] and placing a split-thickness meshed skin graft on a sheet of micropore surgical tape and remeshing the sheet to produce very small postage stamp grafts also known as "scrap grafts."[24,25] Early studies showed that patch grafts compared to sheet grafts rapidly facilitated complete coverage of burn wounds. In a series of 12 patients, 6 patients treated with patch grafts had complete healing of their wounds at a mean time of 62.1 days compared to a mean time of 136 days in 6 patients treated with large sheet grafts.[23] However, the patch/postage stamp methods became overshadowed with the advent of dermatomes to produce mesh skin grafts.

Meek Microdermagraft

Perhaps the most important figure in modern micrograft technique was C. Parker Meek. Meek's contribution toward micrografting was the development of a dermatome that would produce skin pieces as small as 1.58 mm^2.[26] The main concepts to his creation were (1) split-thickness skin grows from the periphery outward; (2) the smaller the skin piece is, the greater is its surface in relation to its volume; and (3) the ideal for re-epithelializing a denuded area in the quickest manner is to provide the greatest possible growing margin to the area. Since patch grafts require a tedious procedure to cover a large burn wound, Meek developed a dermatome, called the "Meek–Wall Microdermatome," to quickly create skin pieces from a small amount of donor skin. The technique is accomplished by harvesting a thin, conventional split-thickness skin graft and placing the graft, dermal side down, on a cork carrier. The cork carrier with the graft is placed on the cutting block of the microdermatome. After passing the carrier and graft through the dermatome, the carrier is rotated 90° and passed through again to create the microskin grafts. A thin coating of skin glue is brushed onto the micrografts while on the carrier, and then a prefolded bandage is used to adhere to the micrografts for transfer to the wound bed.[27–29] Meek published several case reports utilizing his technique,[26–28] but no further investigations would be reported for almost 25 years.

Chinese Intermingled Technique

A precursor to modern microdermagrafting was experimented with in the 1980s. The technique was different compared to Meek's method, however. Skin autografts combined with an allograft via a procedure known as "intermingled transplantation" was being used in the early 1980s by the Chinese to cover burn wounds when donor sites for autologous skin were limited.[30,31] This technique involved wrapping a sheet of allograft around the wound and punching holes about 1 cm apart within the allograft skin. Autograft skin, taken from the scalp, would be cut into 0.25 cm^2 pieces and then placed into the holes. Yang and associates[30] studied 12 patients who received the procedure and documented the "sandwich phenomenon," which is when the autograft skin migrates in between the allograft's dermis and epidermis. Eventually, the allograft degenerates via host rejection, leaving the autograft intact. The allograft served to protect the autograft during the healing process. The same authors[31] also published a larger series of 100 cases who received the intermingled technique, comparing porcine xenograft to allograft. The authors concluded that there was no statistically significant difference ($p < .05$) between the two groups in terms of overall mortality; however, rejection was more vigorous in the xenograft group, especially in the xenodermal–epidermal junction. Despite a larger rejection reaction toward the xenograft, the xenograft could remain viable for 1–3 weeks, and the intermingled autograft would continue to remain viable and exhibit the sandwich phenomenon with the porcine xenograft. The intermingled technique has also been tried using parental skin for allograft coverage.[32] No evidence of acute rejection was noted in any biopsies taken in a series of 10 patients, although survival of the parental cells was seen on the recipient.

Microskin Graft

The interest in microskin grafting revived in the 1980s with more animal and human trials. Zhang and coworkers[33–35] reported a new technique that incorporates ideas of patch grafting and the intermingled technique. A small piece of autograft skin is minced with scissors into pieces smaller than 1 mm^3. The skin pieces are then immersed in normal saline to allow floatation of the skin pieces. The floatation of the skin pieces theoretically allows the grafts to orient themselves with their epidermal sides facing upward. The small skin pieces are dispersed evenly on a silk cloth, and lastly, a sheet of split-thickness allograft is overlaid on top of the silk cloth containing the microskin grafts. Interestingly, the skin pieces are not placed with regard to orientation of their dermal side in contact with the wound bed. The combined autologous minced skin and allograft are allowed to dry for a period of time before transferring the grafts to the wound. The authors' observations, in a series of 12 rabbits, concluded that the minced skin can incorporate into the wound bed regardless of orientation and complete wound coverage, although the preferred

orientation is when the dermis of the microskin graft is in contact with the wound surface.[33] The reason that the orientation of the minced skin did not matter is because the skin pieces embedded in granulation tissue are small enough to have their dermal appendages in contact with the wound. The minced skin grafts that are oriented in a lateral or downward direction would first develop epidermal cysts or columns and then extend upward to cover the wound surface or meet with the epidermal layer from other microskin grafts. As a follow-up to their initial animal study, Zhang and coworkers performed their technique on 8 extensively burned human patients, with 7 patients having good healing within 22 to 45 days,[34] and in 17 burn patients, with 45 treated limbs healing within 35 to 55 days.[35] Other authors using the technique proposed by Zhang and coworkers had similar results, with a wound healing rate ranging from 90% to 95% and an average healing time ranging from 6 to 7 weeks.[36–38] A study comparing microskin grafting and the intermingled technique showed similar healing rates; however, the intermingled technique had a statistically significant ($p < .05$) less contracture formation rate compared to microskin grafting.[39] Another study compared microskin grafting to sheet autografts and also found an increased scar contraction rate in microskin grafts (43% of the original size) compared to sheet autografts (72% of the original size), although the microskin grafts were noted to exhibit mechanical stability and tolerate trauma well.[40] Another study noted a 40-fold increase in wound closure rate by microskin grafting; however, the authors note that the number of skin pieces had no effect on the rate of re-epithelialization.[41] Svensjö and colleagues[42] compared minced skin grafts to split-thickness skin grafts and cultured/noncultured keratinocytes. Their wound model was fluid-treated with saline and antibiotics. The authors noted that re-epithelialization of wounds was completed at a faster rate compared to controls, but no significant difference was noted when compared to cultured/noncultured keratinocytes. Also, no significant difference in wound morphology or differentiation of the epithelium overlying the granulation tissue was noted. Minced skin grafting was found to have a dose-dependent inhibition of contraction which adheres to the principle that the degree of contraction of a full-thickness wound during healing correlates inversely to the thickness of the applied graft's dermis.[43]

Interest in a readily available and economical overlay for the micrograft skin prompted further experiments with xenografts,[44,45] synthetic materials,[46–48] and amniotic membranes.[49] Lin and associates, using the technique proposed by Zhang and coworkers, overlaid the micrografts with a porcine xenograft in studies involving rabbits and humans.[44,45] The authors concluded that xenografts, like allografts, can be used as a successful temporary coverage for the micrografts. The xenografts, although less firm than allografts, do not interfere with the underlying active radial epithelialization of the microskin grafts, primarily because the xenografts were able to provide a protective cover-up to 14 days before ischemic necrosis and eschar formation occurs. Synthetic materials have been an attractive modality for wound coverage largely due to their relative lack of immunogenicity, commercial availability, relative inexpensiveness, easy storage, and ability to be sterilized. Although many synthetic materials exist, the only studies involving microskin grafts utilized Biobrane. Biobrane is a bilaminate material with a bottom woven nonbiodegradable nylon mesh layer and an outer Silastic coating that acts as a mechanical barrier to vapor loss and bacterial ingress.[50] Lin and associates investigated Biobrane as an overlay for microskin grafts.[46–48] The interface between the nylon mesh of Biobrane and the neo-epithelium was a cellular mass, which did not interfere with the growth of the micrografts; however, the longer Biobrane stayed on the wound, the more likely necrosis of entrapped tissue would occur. Although Biobrane can be used as a suitable protective overlay for the micrografts, allograft skin is still considered the most effective temporary biologic dressing due to its ability to undergo vascularization from the recipient within 48 to 72 h of application. Human amniotic membrane has been used to facilitate chronic leg ulcer and burn wound healing by promoting angiogenesis and stimulating granulation tissue formation. Amniotic membrane used for micrograft coverage was shown to be effective in 16 out of 22 patients receiving the technique with epithelialization completing by 10 days.[49] The angiogenic and growth-promoting factors were hypothesized as the contributing variables for the rapid healing.

Patients with extensive wounds that require debridement to fascia are faced with a challenging problem. Without an adequate dermis to graft to, skin grafting on top of fascia yields a poor functional and aesthetic outcome as well as chronic ulcer or hypertrophic scar development. Acellular dermal matrices have often been used to facilitate coverage of large wounds or fascial defects. Chen and associates[51] employed microskin grafts over an acellular dermal matrix to cover a burn wound on the knee in a six-year-old boy. The author observed a thicker, more elastic skin result with less contracture compared to microskin grafts alone.

Preparing the micrografts by manually cutting the skin was thought to be cumbersome. Also, the resulting skin particles were not uniform in shape and not placed into the wound bed with regard to orientation. Adequate healing has been observed, but good cosmetic appearance was still left to be desired. New techniques started to evolve to reduce the time for micrograft preparation and to prepare microskin pieces with more uniform shape. Lin and Horng[52,53] utilized a common dermatome found in many hospitals and clinics called the Zimmer Meshgraft II Manual Dermatome. The skin is placed on the dermacarrier and is run through the dermatome once. The dermacarrier is then rotated 90° and then passed through the dermatome once more. The resulting skin patches are uniform square pieces measuring approximately 1.2 × 1.2 mm^2. Even smaller pieces (<1 mm^2) with expansion ratios up to 100:1 were made by performing the same technique, except the skin was passed through the mesher four times in different orientations.[54,55]

Microscopic Spit-Skin ("Diced") Graft

The attractiveness of skin expansion for wound coverage led Blair and coworkers[56] to develop a technique that allows for expansion ratios up to 26:1. The technique involves using a histological tissue slicer to prepare diced grafts that are 200 μm^2 in area. The diced grafts are spread into the wound bed with a knife and then covered with an adherent hydrocolloid dressing. The authors reported no significant difference in healing rates or time to complete healing between diced and meshed split-thickness grafts in a series of seven patients with venous ulcers.[56,57] However, diced skin grafts were noted to be simple to prepare and could be performed in an outpatient setting with only local anesthesia.

Scalp Microdermis Graft

A problem with microskin grafting is applying the skin pieces with the dermal side facing the wound surface. Previous attempts of resolving this issue consisted of suspending the skin pieces in saline and allowing the skin pieces to "float" to the surface. The skin pieces theoretically should float to the top with their epidermal side facing upward; however, some skin pieces were facing their dermal side upward. Another issue with the floatation process is that some skin pieces are lost due to adherence to the bottom or walls of the container. To reduce the influence of these issues, Lin[53] proposed using minced scalp dermis for microskin grafts. Scalp dermis, composed mainly of hair follicle cells, was used because it has no orientation requirements. The scalp dermis was minced into 1.2 × 1.2 mm^2 square pieces by using the Zimmer Meshgraft II Manual Dermatome as previously described.[52] Lin performed these grafts on burn wounds and noted successful healing when the grafts were placed on granulation tissue or after fascial excision but not when placed on fat.[53]

Modified Meek Technique

Kreis and colleagues[58,59] published a modified version of Meek's original technique. The procedure follows Meek's version, however, prefolded synthetic gauze is placed over the micrograft pieces and is then removed after five days and replaced with meshed allograft. Other modifications include a dermatome that runs on compressed air, cork cutting squares, and carrier enlargement to allow larger pieces of autograft to be expanded. The authors performed the modified Meek technique on nine patients and reported a 92% take rate and a 90% epithelialization rate within five weeks with no clinical graft failures.[59] The modified technique allowed proper orientation of the skin pieces upon transplantation as well as increased efficiency in performance of the procedure. Another advantage of the modified technique was that the procedure was well suited for granulating wounds of poor quality.[60] A larger clinical trial consisting of 103 grafting procedures reported a mean take rate of 91% with epithelialization completing after 3–5 weeks.[61] The authors noted several advantages of the modified Meek technique compared to traditional mesh grafting: (1) a true expansion ratio is achieved, (2) small graft remnants can be used, (3) grafting of 70% to 75% total burn surface area can be accomplished with one harvest of the donor site, (4) the reliability of the graft is equal or better than standard mesh grafting, and (5) the skin pieces combined with cultured epithelial autografts (CEA) provides a timely and durable wound closure and avoids the problems associated with grafting CEA on fascia. The disadvantages of the modified Meek technique, however, include costly materials and more personnel required to perform the procedure in a timely manner. Several authors found similar results, with 93% take rate and epithelialization completing by three weeks[62] and 90% take rate and epithelialization completing by 4–5 weeks,[63] depending on the expansion ratio used. However, the authors noted subjectively better aesthetic results when micrografts were used for wound coverage. The functional results of the micrografts were noted to be comparable to, or better than, traditional mesh grafts. The incidence of infection was not significantly greater between micrografts and mesh grafts, but the authors observed that the micrografts seemed to be less compromised in the event of infection. Hsieh and

colleagues treated 37 burn victims with 68 grafting procedures over a term of five years and noted a 90% to 95% take rate with complete epithelialization occurring within 1–4 weeks, depending on the expansion ratio.[64] No overlay to protect the micrografts was used. Satisfactory aesthetic and functional outcomes were noted, although a small number of cases were noted to have scar contracture and hypertrophic scar formation. Another study investigated the modified Meek technique on six burn wounds, which resulted in a >85% take rate after 10 days with complete epithelialization within 3–5 weeks, depending on the expansion ratio used.[65] The authors noted that the patients who received modified Meek micrografts had a higher Baux score (age + total burn surface area),[66] but the procedure had no effect on length of stay or number of operations needed. Also, the authors in this study did not use any temporary coverage for the micrografts and note that there is no indication to do so.

A variation of the modified Meek technique involved using Integra to form a neodermis and then using micrografts to cover the neodermis.[67] Integra is a biodegradable bilayer membrane with an outer silicone layer and an inner porous layer made of bovine collagen and glycosaminoglycans from shark cartilage. The Integra allows a softer scar to form compared to standard split-thickness skin grafts; however, a second-stage operation is needed to cover the neodermis. Integra is also on-demand, which is of use when facilities do not have skin banking capabilities. Although micrografts have been extensively used in burn wounds, Kopp and associates[68] applied the Integra with modified Meek graft on a patient with a giant congenital melanocytic nevus. The skin of the entire back was removed and then covered with Integra. The top silicone layer of Integra was removed after 20 days, and micrograft was placed on top of the remaining Integra. The authors noted subjectively acceptable cosmetic outcome and excellent biomechanical integrity of the healed outcome.

Modified Postage Stamp Graft (Flypaper Technique)

The postage stamp grafts were revisited with clinical trial data in the early 1990s. Chang and Yang[69] reported a nearly 100% success rate using the traditional technique described by Gabarro, with a slight modification via a nitrofurazone gauze to orient the skin pieces. The use of scissors to cut the donor skin into square pieces was a tedious process. Also, the original postage stamp method had an unpredictable expansion ratio because of the irregularly distributed skin. To address the shortcomings of the original postage stamp method, Lee and coworkers[70] proposed a modified version of the postage stamp technique that also was less expensive than the modified Meek technique and did not require the need for extra materials such as prefolded gauze or cork squares. The modified technique involved placing the donor skin on manufactured "quick cutting plates". A cutting wheel is used to slice the skin into squares measuring 0.5 × 0.5 cm. Next, the squares are placed onto a chessboard-like diagram to achieve a desired expansion ratio. Petroleum gauze is then placed over the skin squares for transfer to the wound bed. The authors coined the term "flypaper" to describe the adherence of the skin squares to the petroleum gauze, thus calling their technique the "flypaper technique."[71] Using the flypaper technique, Lee and asociates[72] reported a healing time of 27.2 days for 6:1 expansion ratios and 34 days for 9:1 expansion ratios. A further modification of the flypaper technique is known as the "shift to right flypaper technique," which positions the skin squares so that the largest distances between the skin squares are shortened. Using this modification, the authors reported a take rate of approximately 90% and a mean healing time of 26 days in five burn patients.

Fine-Particle Graft (Autologous Skin Suspension)

A controversial technique of historical interest is the autologous skin suspension. Just as micrografts were conceived to achieve wide expansion ratios, autologous skin suspensions were created to achieve theoretically very large expansion ratios. The technique was originally described by Najarian and McCorkle,[73,74] where a sheet of split-thickness skin was made into small skin pieces using a conventional kitchen blender. The skin suspension was applied to 40 rabbits, with 92.5% of rabbits showing complete epithelialization by three weeks. The rate of epithelialization was the same regardless if the suspension was placed on granulation tissue, fascia, or denuded skin; however, marked contraction and a hyperplastic, hyperkeratotic epidermis was noted. Similar observations were noted by Cox and Nichol,[75] especially with regard to scar contracture formation—up to 10% of the original scar size by four weeks. Poor functional and cosmetic results left the method abandoned, although Rissin and colleagues[76] used a modified version of the skin suspension technique by pulse blending sheets of split-thickness skin and then spreading the particles over a synthetic fenestrated sheet (Telfa). The modified suspension technique failed to reveal a statistically significant ($p > .05$) healing rate compared to controls. The resulting skin had a thin epithelial layer and was without papillae; however, the dermis was markedly thicker and less organized.

Micrograft Spray

An innovative method involving spraying the micrografts onto the wound bed has been investigated in a published report.[77] In this method, the donor skin is cut into pieces measuring 0.2 to 0.5 mm in size. The resulting expansion ratios ranged from 110–150:1. The authors reported a statistically significant ($p < .05$) decrease in average wound healing time (29.7 days) compared to conventional microskin grafting (37.3 days) in their study. Other advantages noted include well-distributed grafts, simpler use, less donor skin needed, and shorter operating time.

Discussion: Future of Micrografting

Micrografting offers an alternative method to traditional split-thickness skin grafting for coverage of wounds. Currently, the most accepted indication for its use is for large burn wounds when donor sites are limited. The overwhelming majority of published reports have studied micrograft application to burn wounds, but few other types of wounds have been examined using micrograft techniques. With the exception of several early reports of pinch grafting for chronic ulcer healing, no studies utilizing micrograft techniques on diabetic ulcers or pressure ulcers have been published. Moreover, only a few randomized trials that investigate micrografting versus traditional mesh grafting and/or tissue-engineered skin exist in the literature. It would seem appropriate to perform a large, prospective, multicenter trial to fully investigate if micrografting has a role in the wound healing armamentarium.

The lack of popularity with micrografting is partly due to increased scar contracture formation. Quantification of wound healing mediators and proteins at different stages of the healing process when using micrografts has not been investigated. Previous studies have demonstrated that cytokines and growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), basic fibroblast growth factor, and epidermal growth factor (EGF) promote fibroblast chemotactic migration *in vitro*.[78–80] It would be interesting to see if there is an upregulation or downregulation of these cytokines and growth factors at different phases of wound healing to better understand the healing process of micrografts compared to standard mesh grafts, if any. Protein (collagen I and III, fibronectin, procollagens) and enzyme expression (matrix metalloproteinases and tissue inhibitors of metalloproteinases) involved with extracellular matrix changes at different stages of wound healing would also need to be investigated as to why excessive contracture formation occurs.

Genetic engineering strategies to enhance *in vivo* cutaneous regeneration and wound healing have been investigated.[81–88] Using deoxyribonucleic acid delivery techniques to modify gene expression such as EGF,[84,85] PDGF,[89] TGF-β,[90] and keratinocyte growth factor[91] could be applied to micrografts to further clarify the molecular mechanisms involved with micrograft healing. These molecular details of micrograft wound healing could potentially yield new ideas and technologies designed to decrease scar contracture formation.

A wide range of adjunctive clinical possibilities to enhance micrograft efficiency needs to be investigated. For example, mechanical pressure therapy has been demonstrated to be effective in causing regression of hypertrophic scarring in 60–85% of patients.[92] Mechanical pressure itself rather than simple scar occlusion by the pressure dressing has been shown to be necessary for scar reduction in a comparison of low versus normal pressure therapy.[93] In fact, several studies have reported that pressures >25 mm Hg decreases scar edema, vascularity, mucopolysaccharide production, mast cell degranulation, oxygen saturation, myofibroblast proliferation, and increases collagen bundle rearrangement.[92,94,95] During micrograft healing, pressure therapy could potentially help reduce scar formation, especially during the early phases of wound healing, as it is widely recognized that pressure therapy is most effective at the early stages of graft and scar contracture formation.[96,97]

Negative pressure wound therapy (NPWT) using vacuum-assisted devices have been used extensively with skin grafts, and NPWT's role in the healing of complex wounds has been documented with increased graft take due to total immobilization of the graft, thereby limiting shear forces, elimination of fluid collections, bridging of the graft, and decreasing bacterial contamination.[98–102] Enhanced quality of wound appearance has been noted using NPWT with skin grafts.[103] However, NPWT has not been evaluated with micrografts. Characterization of micrograft adherence and mechanical stability with NPWT would need to be studied.

Combination therapy with micrografting and CEA has been investigated by several groups.[61,104] The use of CEA holds promise in creating less scar within the wound, because a greater wound area has to be re-epithelialized.[42] The healing rate may be enhanced with CEA, because cells with high proliferative capacity can be selected during culture. Also, the culture conditions can be manipulated and controlled to enhance viability and proliferative potential.

An avenue of potential interest is the use of biodegradable scaffolds combined with a micrograft overlay. The use of Integra as a dermal regeneration template prior to micrograft application has been previously described.[67,68] Many biologic, bioartificial, and synthetic scaffolds are used in wound healing for their extracellular matrix-mimicking properties.[105,106] Cadaveric acellular dermis has been used extensively for facilitating wound and soft-tissue defect coverage, with one report used with micrografting.[51] Hydrogel therapy is another extracellular matrix-like modality that offers several advantages because it is easy to use, nonadherent, and virtually painless on application.[107–109] Hydrogels have an added advantage in that they can be injected or preprepared with medications and antibiotics. Also, hydrogels provide graft immunologic protection in the host that could be of interest in micrografting of allogenic skin. Micrograft immersion in a hydrogel with proper permeability that allows diffusion and transport of oxygen, essential nutrients, metabolic waste, and secretory products could provide an easily applicable protective scaffold for the micrografts to communicate in.

Finally, efficient harvesting, preparation, and delivery techniques need to be developed for mainstream micrograft use. Specialized dermatomes and cutting surfaces are being used for the creation of micrografts, but the procedures require more personnel and operating time compared to standard mesh-graft techniques. Delivery methods such as a spray have been introduced; however, other methods such as gel immersion or macroencapsulation are being investigated in our lab.

Micrografting is a conceptually appealing strategy for wound coverage; however, appropriate studies to identify its true potentials and pitfalls are severely lacking. Complex wounds such as diabetic ulcers may benefit from micrografting techniques because of smaller donor sites needed to cover a larger wound area; however, the various micrograft techniques may need to be compared for a wide range of wounds to discern which technique is clinically beneficial for the particular type of wound. Experimental studies are also needed to characterize the micrografts' physiological and biomechanical behavior compared to standard mesh grafting both *in vitro* and *in vivo*. For now, however, the simplicity of the approach, true expansion ratio, and applicability when donor sites are limited make micrografting a useful tool for surgeons to use on large or complex wounds.

References:

1. Reverdin JL. Graffe epidermique. Experience faite dans le service de M. le docteur Guyon, a l'hopital Necker. Bull Imp Soc Chir Paris. 1869;10:511–5.
2. Thiersch C. Ueber die feineren anatomischen Veränderungen bei Aufheilung von Haut auf Granulationen. Verhandlungen der deutschen Gesellschaft für Chirurgie. 1874;3:69–75.
3. Davis JS. Address of the president: the story of plastic surgery. Ann Surg. 1941;113(5):641–56.
4. Gabarro P. A new method of grafting. Br Med J. 1943;1:723–4.
5. Von Mangoldt F. Die Ueberhäutung von Wundflächen und Wundhöhlen durch Epithelaussaat, eine neue Methode der Transplantation. Dtsch Med Wchnschr. 1895;21(48):798–9.
6. Noesske K. Klinische und histologische Studien über Hautverpflanzung, besonders über Epithelaussaat. Dtsch Z Chir. 1906;83(3-4):213–53.
7. Reschke-Greifswold H. Epithelisierungsversuche. Arch F Klin Chir. 1922;121:233.
8. Billingham RE, Reynolds J. Transplantation studies on sheets of pure epidermal epithelium and on epidermal cell suspensions. Br J Plast Surg. 1952;5(1):25–36.
9. Tanner JC Jr, Vandeput J, Olley JF. The mesh skin graft. Plast Reconstr Surg. 1964;34:287–92.
10. Peeters R, Hubens A. The mesh skin graft--true expansion rate. Burns Incl Therm Inj. 1988;14(3):239–40.
11. Lin TW. The algebraic view-point in microskin grafting in burned patients. Burns. 1994;20(4):347–50.
12. Davis JS. The use of small deep skin grafts. JAMA. 1914;63:985–9.
13. Davis JS. The small deep graft: relationship to the true reverdin graft. Ann Surg. 1929;89(6):902–16.
14. Pontěn B. Plastic surgery treatment of chronic venous ulcers of the leg. Scand J Plast Reconstr Surg. 1972;6(1):74–82.
15. Ho LC, Bailey BN, Bajaj PB. Pinch grafts in treatment of chronic venous leg ulcers. Chirurgia Plastica. 1976;3(3):193–200.
16. Millard LG, Roberts MM, Gatecliffe M. Chronic leg ulcers treated by the pinch graft method. Br J Dermatol. 1977;97(3):289–95.
17. Christiansen J, Ek L, Tegner E. Pinch grafting of leg ulcers. A retrospective study of 412 treated ulcers in 146 patients. Acta Derm Venereol. 1997;77(6):471–3.
18. Ahnlide I, Bjellerup M. Efficacy of pinch grafting in leg ulcers of different aetiologies. Acta Derm Venereol. 1997;77(2):144–5.
19. Oien RF, Hansen BU, Håkansson A. Pinch grafting of leg ulcers in primary care. Acta Derm Venereol. 1998;78(6):438–9.
20. Oien RF, Håkansson A, Hansen BU. Leg ulcers in patients with rheumatoid arthritis–a prospective study of aetiology, wound healing and pain reduction after pinch grafting. Rheumatology (Oxford). 2001;40(7):816–20.
21. Oien RF, Håkansson A, Hansen BU, Bjellerup M. Pinch grafting of chronic leg ulcers in primary care: fourteen years' experience. Acta Derm Venereol. 2002;82(4):275–8.
22. Greenwood JE, Parry AD, Williams RM, McCollum CN. Trigger-fired pinch-graft harvester for use in chronic venous ulcers. Br J Surg. 1997;84(3):397–8.
23. Lewis GK. The use of the patch graft in extensive skin loss. Plast Reconstr Surg (1946). 1953;12(2):116–22.
24. Vandeput J, Tanner JC Jr, Carlisle JD. The ultra postage stamp skin graft. Plast Reconstr Surg. 1966;38(3):252–4.
25. Tanner JC Jr, Vandeput J, Lewis JR Jr. The scrap technique of skin grafting. Plast Reconstr Surg. 1968;41(2):182–3.

26. Meek CP. Successful microdermagrafting using the Meek-Wall microdermatome. Am J Surg. 1958;96(4):557–8.
27. Meek CP. Medical debridement and microdermagrafting of burns. South Med J. 1963;56:1074–6.
28. Meek CP. Extensive severe burn treated with enzymatic debridement and microdermagrafting: case report. Am Surg. 1963;29:61–4.
29. Meek CP. Microdermagrafting: the Meek technic. Hosp Top. 1965;43:114–6.
30. Yang CC, Shih TS, Chu TA, Hsu WS, Kuo SY, Chao YF. The intermingled transplantation of auto- and homografts in severe burns. Burns. 1980;6(3):141–5.
31. Yang CC, Shih TS, Xu WS. A Chinese concept of treatment of extensive third-degree burns. Plast Reconstr Surg. 1982;70(2):238–54.
32. Phipps AR, Clarke JA. The use of intermingled autograft and parental allograft skin in the treatment of major burns in children. Br J Plast Surg. 1991;44(8):608–11.
33. Zhang ML, Chang ZD, Han X, Zhu M. Microskin grafting. I. Animal experiments. Burns Incl Therm Inj. 1986;12(8):540–3.
34. Zhang ML, Wang CY, Chang ZD, Cao DX, Han X. Microskin grafting. II. Clinical report. Burns Incl Therm Inj. 1986;12(8):544–8.
35. Zhang ML, Chang ZD, Wang CY, Fang CH. Microskin grafting in the treatment of extensive burns: a preliminary report. J Trauma. 1988;28(6):804–7.
36. Fang CH, Yu GS, Fan YF, Wang K, Alexander JW. A preliminary report on transplantation of microskin autografts overlaid with sheet allograft in the treatment of large burns. J Burn Care Rehabil. 1988;9(6):629–33.
37. Fang CH, Yu GS, Zhang ML, Alexander JW. Burn treatment. Covering burn wounds with autologous microskin grafts. AORN J. 1989;49(2):526, 528, 530–4.
38. Sun Y, Pan Y, Chen S, Zhao Y, Wang Y, Zheng X. Clinical application of microskin grafting to repair granulation or decrustation wounds. J Burn Care Res. 2006;27(4):515–9.
39. Yeh FL, Yu GS, Fang CH, Carey M, Alexander JW, Robb EC. Comparison of scar contracture with the use of microskin and Chinese-type intermingled skin grafts on rats. J Burn Care Rehabil. 1990;11(3):221–3.
40. Fang CH, Alexander JW. Wound contraction following transplantation of microskin autografts with overlaid skin allograft in experimental animals. Burns. 1990;16(3):190–2.
41. Shvets VN, Malakhov SF, Egorov BB, Bautin EA, Vnukova ZE. Ability of microautotransplants to re-epithelialize deep and extensive skin injuries. Burns. 1991;17(3):243–9.
42. Svensjö T, Pomahac B, Yao F, Slama J, Wasif N, Eriksson E. Autologous skin transplantation: comparison of minced skin to other techniques. J Surg Res. 2002;103(1):19–29.
43. Livesey SA, Herndon DN, Hollyoak MA, Atkinson YH, Nag A. Transplanted acellular allograft dermal matrix. Potential as a template for the reconstruction of viable dermis. Transplantation. 1995;60(1):1–9.
44. Lin SD, Chou CK, Lai CS, Yang CC. Microskin grafting of rabbits with pigskin xenograft overlay. Burns. 1991;17(6):473–7.
45. Lin SD, Lai CS, Chou CK, Tsai CW, Wu KF, Chang CW. Microskin autograft with pigskin xenograft overlay: a preliminary report of studies on patients. Burns. 1992;18(4):321–5.
46. Lin SD, Lai CS, Chou CK, Tsai CW. Microskin grafting of rabbit skin wounds with Biobrane overlay. Burns. 1992;18(5):390–4.
47. Lin SD, Chai CY, Lai CS, Chou CK. Allogeneic microskin grafting of rabbits' skin wounds. Burns. 1993;19(3):208–14.
48. Lin SD, Chai CY, Lai CS, Chou CK. A mixture of allogeneic and autologous microskin grafting of rabbit skin wounds with Biobrane overlay. Burns. 1994;20(1):30–5.
49. Subrahmanyam M. Amniotic membrane as a cover for microskin grafts. Br J Plast Surg. 1995;48(7):477–8.
50. Greenwood JE, Clausen J, Kavanagh S. Experience with biobrane: uses and caveats for success. Eplasty. 2009;9:e25.
51. Chen XL, Xia ZF, Fang LS, Wang YJ, Wang CH. Co-graft of acellular dermal matrix and autogenous microskin in a child with extensive burns. Ann Burns Fire Disasters. 2008;21(2).
52. Lin TW, Horng SY. A new method of microskin mincing. Burns. 1994;20(6):526–8.
53. Lin TW. An alternative method of skin grafting: the scalp microdermis graft. Burns. 1995;21(5):374–8.
54. Mardovin W, Miller SF, Eppinger M, Finley RK. Micrografts: the "super" expansion graft. J Burn Care Rehabil. 1992;13(5):556–9.
55. Nelson CV, Miller SF, Eppinger M, Finley RK. Micrografts. II: Evaluation of 25:1, 50:1, and 100:1 expansion skin grafts in the porcine model. J Burn Care Rehabil. 1995;16(1):31–5.
56. Blair SD, Nanchahal J, Backhouse CM, Harper R, McCollum CN. Microscopic split-skin grafts: a new technique for 30-fold expansion. Lancet. 1987;2(8557):483–4.
57. Nanchahal J. Stretching skin to the limit: a novel technique for split skin graft expansion. Br J Plast Surg. 1989;42(1):88–91.
58. Kreis RW, Vloemans AF, Hoekstra MJ, Mackie DP, Hermans RP. The use of non-viable glycerol-preserved cadaver skin combined with widely expanded autografts in the treatment of extensive third-degree burns. J Trauma. 1989;29(1):51–4.
59. Kreis RW, Mackie DP, Vloemans AW, Hermans RP, Hoekstra MJ. Widely expanded postage stamp skin grafts using a modified Meek technique in combination with an allograft overlay. Burns. 1993;19(2):142–5.
60. Kreis RW, Mackie DP, Hermans RR, Vloemans AR. Expansion techniques for skin grafts: comparison between mesh and Meek island (sandwich-) grafts. Burns. 1994;20 Suppl 1:S39–42.
61. Raff T, Hartmann B, Wagner H, Germann G. Experience with the modified Meek technique. Acta Chir Plast. 1996;38(4):142–6.
62. Zermani RG, Zarabini A, Trivisonno A. Micrografting in the treatment of severely burned patients. Burns. 1997;23(7-8):604–7.
63. Lari AR, Gang RK. Expansion technique for skin grafts (Meek technique) in the treatment of severely burned patients. Burns. 2001;27(1):61–6.
64. Hsieh CS, Schuong JY, Huang WS, Huang TT. Five years' experience of the modified Meek technique in the management of extensive burns. Burns. 2008;34(3):350–4.
65. Lumenta DB, Kamolz LP, Frey M. Adult burn patients with more than 60% TBSA involved-Meek and other techniques to overcome restricted skin harvest availability--the Viennese Concept. J Burn Care Res. 2009;30(2):231–42.
66. Baux S, Mimoun M, Saade H, Lioret N, Esteve M, Nolland XB, Bertiere MN. Burns in the elderly. Burns. 1989;15(4):239–40.
67. Papp A, Härmä M. A collagen based dermal substitute and the modified Meek technique in extensive burns. Report of three cases. Burns. 2003;29(2):167–71.
68. Kopp J, Magnus Noah E, Rübben A, Merk HF, Pallua N. Radical resection of giant congenital melanocytic nevus and reconstruction with meek-graft covered integra dermal template. Dermatol Surg. 2003;29(6):653–7.

69. Chang LY, Yang JY. Clinical experience of postage stamp autograft with porcine skin onlay dressing in extensive burns. Burns. 1998;24(3):264–9.

70. Lee SS, Tsai CC, Lai CS, Lin SD. An easy method for preparation of postage stamp autografts. Burns. 2000;26(8):741–9.

71. Lee SS, Lin TM, Chen YH, Lin SD, Lai CS. "Flypaper technique" a modified expansion method for preparation of postage stamp autografts. Burns. 2005;31(6):753–7.

72. Lee SS, Chen YH, Sun IF, Chen MC, Lin SD, Lai CS. "Shift to right flypaper technique" a refined method for postage stamp autografting preparation. Burns. 2007;33(6):764–9.

73. Najarian JS, McCorkle HJ. Experimental grafting of a suspension of skin particles. Surg Forum. 1957;7:125–9.

74. Najarian JS, Crane JT, McCorkle HJ. An experimental study of the grafting of a suspension of skin particles. Surgery. 1957;42(1):218–27.

75. Cox WA, Nichol WW. Evaluation of the fine-particle skin autograft technique. AMA Arch Surg. 1958;77(6):870–4.

76. Rissin Y, Fodor L, Talmon G, Fishelson O, Ullmann Y. Investigating human microskin grafting technique in a new experimental model. Burns. 2009;35(5):681–6.

77. Xie W, Wang L, Tan H, Wang D, Liu J, Hu B, Huang W, Ren S, Sun K. [Microskin grafting by spraying in burn management]. Zhonghua Shao Shang Za Zhi. 2002;18(1):26–8.

78. Petri JB, König S, Haupt B, Haustein UF, Herrmann K. Molecular analysis of different phases in human wound healing. Exp Dermatol. 1997;6(3):133–9.

79. Hayashi N, Takehara K, Soma Y. Differential chemotactic responses mediated by platelet-derived growth factor alpha- and beta-receptors. Arch Biochem Biophys. 1995;322(2):423–8.

80. Ashcroft GS, Horan MA, Ferguson MW. The effects of ageing on cutaneous wound healing in mammals. J Anat. 1995;187(Pt 1):1–26.

81. Hengge UR, Chan EF, Foster RA, Walker PS, Vogel JC. Cytokine gene expression in epidermis with biological effects following injection of naked DNA. Nat Genet. 1995;10(2):161–6.

82. Meuli M, Liu Y, Liggitt D, Kashani-Sabet M, Knauer S, Meuli-Simmen C, Harrison MR, Adzick NS, Heath TD, Debs RJ. Efficient gene expression in skin wound sites following local plasmid injection. J Invest Dermatol. 2001;116(1):131–5.

83. Sun L, Xu L, Chang H, Henry FA, Miller RM, Harmon JM, Nielsen TB. Transfection with aFGF cDNA improves wound healing. J Invest Dermatol. 1997;108(3):313–8.

84. Ciernik IF, Krayenbühl BH, Carbone DP. Puncture-mediated gene transfer to the skin. Hum Gene Ther. 1996;7(8):893–9.

85. Eriksson E, Yao F, Svensjö T, Winkler T, Slama J, Macklin MD, Andree C, McGregor M, Hinshaw V, Swain WF. *In vivo* gene transfer to skin and wound by microseeding. J Surg Res. 1998;78(2):85–91.

86. Andree C, Swain WF, Page CP, Macklin MD, Slama J, Hatzis D, Eriksson E. *In vivo* transfer and expression of a human epidermal growth factor gene accelerates wound repair. Proc Natl Acad Sci U S A. 1994;91(25):12188–92.

87. Ghazizadeh S, Harrington R, Taichman L. *In vivo* transduction of mouse epidermis with recombinant retroviral vectors: implications for cutaneous gene therapy. Gene Ther. 1999;6(7):1267–75.

88. Gruss CJ, Satyamoorthy K, Berking C, Lininger J, Nesbit M, Schaider H, Liu ZJ, Oka M, Hsu MY, Shirakawa T, Li G, Bogenrieder T, Carmeliet P, El-Deiry WS, Eck SL, Rao JS, Baker AH, Bennet JT, Crombleholme TM, Velazquez O, Karmacharya J, Margolis DJ, Wilson JM, Detmar M, Skobe M, Robbins PD, Buck C, Herlyn M. Stroma formation and angiogenesis by overexpression of growth factors, cytokines, and proteolytic enzymes in human skin grafted to SCID mice. J Invest Dermatol. 2003;120(4):683–92.

89. Eming SA, Whitsitt JS, He L, Krieg T, Morgan JR, Davidson JM. Particle-mediated gene transfer of PDGF isoforms promotes wound repair. J Invest Dermatol. 1999;112(3):297–302.

90. Benn SI, Whitsitt JS, Broadley KN, Nanney LB, Perkins D, He L, Patel M, Morgan JR, Swain WF, Davidson JM. Particle-mediated gene transfer with transforming growth factor-beta1 cDNAs enhances wound repair in rat skin. J Clin Invest. 1996;98(12):2894–902.

91. Jeschke MG, Richter G, Herndon DN, Geissler EK, Hartl M, Hofstätter F, Jauch KW, Perez-Polo JR. Therapeutic success and efficacy of nonviral liposomal cDNA gene transfer to the skin *in vivo* is dose dependent. Gene Ther. 2001;8(23):1777–84.

92. Renò F, Sabbatini M, Lombardi F, Stella M, Pezzuto C, Magliacani G, Cannas M. *In vitro* mechanical compression induces apoptosis and regulates cytokines release in hypertrophic scars. Wound Repair Regen. 2003;11(5):331–6.

93. Van den Kerckhove E, Stappaerts K, Fieuws S, Laperre J, Massage P, Flour M, Boeckx W. The assessment of erythema and thickness on burn related scars during pressure garment therapy as a preventive measure for hypertrophic scarring. Burns. 2005;31(6):696–702.

94. Parks DH, Evans EB, Larson DL. Prevention and correction of deformity after severe burns. Surg Clin North Am. 1978;58(6):1279–89.

95. Costa AM, Peyrol S, Pôrto LC, Comparin JP, Foyatier JL, Desmoulière A. Mechanical forces induce scar remodeling. Study in non-pressure-treated versus pressure-treated hypertrophic scars. Am J Pathol. 1999;155(5):1671–9.

96. Williams F, Knapp D, Wallen M. Comparison of the characteristics and features of pressure garments used in the management of burn scars. Burns. 1998;24(4):329–35.

97. Horswell BB. Scar modification. Techniques for revision and camouflage. Atlas Oral Maxillofac Surg Clin North Am. 1998;6(2):55–72.

98. Giovinco NA, Bui TD, Fisher T, Mills JL, Armstrong DG. Wound chemotherapy by the use of negative pressure wound therapy and infusion. Eplasty. 2010;10:e9.

99. Körber A, Franckson T, Grabbe S, Dissemond J. Vacuum assisted closure device improves the take of mesh grafts in chronic leg ulcer patients. Dermatology. 2008;216(3):250–6.

100. Hinchliffe RJ, Valk GD, Apelqvist J, Armstrong DG, Bakker K, Game FL, Hartemann-Heurtier A, Löndahl M, Price PE, van Houtum WH, Jeffcoate WJ. A systematic review of the effectiveness of interventions to enhance the healing of chronic ulcers of the foot in diabetes. Diabetes Metab Res Rev. 2008;24 Suppl 1:S119–44.

101. Armstrong DG, Lavery LA, Diabetic Foot Study Consortium. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. Lancet. 2005;366(9498):1704–10.

102. Blackburn JH II, Boemi L, Hall WW, Jeffords K, Hauck RM, Banducci DR, Graham WP IV. Negative-pressure dressings as a bolster for skin grafts. Ann Plast Surg. 1998;40(5):453–7.

103. Moisidis E, Heath T, Boorer C, Ho K, Deva AK. A prospective, blinded, randomized, controlled clinical trial of topical negative pressure use in skin grafting. Plast Reconstr Surg. 2004;114(4):917–22.

104. Dorai AA, Lim CK, Fareha AC, Halim AS. Cultured epidermal autografts in combination with MEEK Micrografting technique in the treatment of major burn injuries. Med J Malaysia. 2008;63 Suppl A:44.

105. Nair LS, Laurencin CT. Polymers as biomaterials for tissue engineering and controlled drug delivery. Adv Biochem Eng Biotechnol. 2006;102:47–90.

106. Barnes CP, Sell SA, Boland ED, Simpson DG, Bowlin GL. Nanofiber technology: designing the next generation of tissue engineering scaffolds. Adv Drug Deliv Rev. 2007;59(14):1413–33.

107. Burd A. Evaluating the use of hydrogel sheet dressings in comprehensive burn wound care. Ostomy Wound Manage. 2007;53(3):52–62.

108. Akita S, Akino K, Imaizumi T, Tanaka K, Anraku K, Yano H, Hirano A. A polyurethane dressing is beneficial for split-thickness skin-graft donor wound healing. Burns. 2006;32(4):447–51.

109. Kiyozumi T, Kanatani Y, Ishihara M, Saitoh D, Shimizu J, Yura H, Suzuki S, Okada Y, Kikuchi M. Medium (DMEM/F12)-containing chitosan hydrogel as adhesive and dressing in autologous skin grafts and accelerator in the healing process. J Biomed Mater Res B Appl Biomater. 2006;79(1):129–36.