Innovative Therapies in the Treatment of Keloids and Hypertrophic Scars

MARTHA H. VIERA, MD; SADEGH AMINI, MD; WHITNEY VALINS, BS; BRIAN BERMAN, MD, PhD
University of Miami, Miller School of Medicine, Department of Dermatology and Cutaneous Surgery, Miami, Florida

ABSTRACT

Keloids and hypertrophic scars are benign fibrous overgrowths of scar tissue, which results from an abnormal response to trauma. Several therapeutic modalities have been described for the treatment and prevention of these conditions, but the optimal management approach has not yet been defined. This article reviews the most recent, innovative, therapeutic strategies for the management of hypertrophic scars and keloids, including mitomycin-C, tamoxifen citrate, methotrexate, imidazolaquinolines, retinoids, calcineurin inhibitors, phenylakylamine calcium channel blockers, botulinum toxin, vascular endothelial growth factor inhibitors, hepatocyte growth factor, basic fibroblast growth factor, interleukin-10, manosa-6-phosphate, transforming growth factor beta, antihistamines, and prostaglandin E2. No consensus in treatment regimens has been reached due to the limited evidence-based information found in the literature. Most therapeutic options have potential effectiveness as both monotherapy and as combination therapy. However, recent reports offer novel modalities that may approach scarring from different angles.
(*J Clin Aesthetic Dermatol.* 2010;3(5):20–26.)

Wound healing, as a normal biological process in the human body, is accomplished through different phases: hemostasis, inflammation, proliferation, and remodeling. For a wound to heal effectively, all four phases must occur in the right sequence. Different factors may interfere with one or more phases of this process. Scars are areas of fibrous tissue that replace normal skin (or other tissue) after injury. A scar results from the biological process of wound repair in the skin and other tissues of the body and constitutes a natural part of the healing process. Scarring is considered abnormal when the amount of fibrosis is excessive or suboptimal, as in hypertrophic, atrophic, or keloidal scars; when it affects normal function; and when it is symptomatic. Scars are also considered abnormal when they are disfiguring or aesthetically distressing to the patient. Several therapeutic modalities have been described for the treatment and prevention of scars, but the optimal management approach has not yet been defined. In this article, the most recent innovative therapeutic strategies for the management of hypertrophic scars and keloids are described. Diverse reports of novel treatments for abnormal scarring from the PubMed/ MEDLINE/Clinical trials.gov database were collected. Most therapeutic options have potential effectiveness as both monotherapy and as combination therapy for the management of abnormal scarring.

INNOVATIVE THERAPIES

Mitomycin C. Mitomycin C is an antineoplastic antibiotic with antiproliferative effects on fibroblasts[1] through DNA synthesis inhibition. It leads to cross-linkage of strands of the double helix, inhibiting DNA replication. It can cause fibroblast arrest without sacrificing re-epithelialization.[2] In a study where mitomycin C 1mg/mL was applied on wound beds for three minutes after keloid resection and repeated after three weeks, 4 out of 10 patients were pleased with the treatment outcome, only one was disappointed, and approximately 80 percent were satisfied with the outcome.[3] In another study, mitomycin C 0.4mg/5mL was topically applied to postexcisional wounds for four minutes.[4] Nine out of 10 patients had no keloid recurrence at an average of eight months of follow up (range 6–14 months). In another study where eight patients were treated with keloid excision followed by application with mitomycin C for five minutes, all eight patients were satisfied with the results at up to 14 months

DISCLOSURE: Drs. Viera and Amini and Ms. Valins report no relevant conflicts of interest. Dr. Berman serves on the Advisory Board and Speakers Bureau for Graceway and Sanofi-Aventis; is a shareowner in Renovo; serves as an investigator and on the Advisory Board for Astellas; and is an investigator for Amgen.

ADDRESS CORRESPONDENCE TO: Brian Berman, MD, PhD, University of Miami, Miller School of Medicine, Department of Dermatology and Cutaneous Surgery, 1600 NW 10th Ave, RMSB, Room 2023A (R250), Miami, FL 33136; E-mail: bberman@med.miami.edu

follow up, while two patients experienced complete disappearance of their keloid.[5] On the contrary, in a study using patients as their own controls, Sanders et al[6] reported that topical mitomycin C applied to excised keloids made no difference in keloid recurrence. The mixed results of the mentioned trials may be related to small study sample sizes, short-term follow up, different applied doses of mitomycin C, different application regimens, and a lack of strict randomization. Simman et al[7] studied keloid fibroblasts and found a decrease in fibroblast density and DNA synthesis during the three weeks following mitomycin C exposure. Three weeks later, there was a recovery in DNA synthesis and an increased cell count.[7] No adverse reaction to the mitomycin C has been reported.

Tamoxifen citrate. Tamoxifen citrate is a selective estrogen receptor modulator (SERM) used in the treatment of breast cancer.[8] Evidence suggests that keloid scar formation may be mediated by an unbalance of growth factor activity, including that of transforming growth factor beta 1 (TGF-β1). Tamoxifen may lead to improved wound healing in keloids by decreasing the expression of TGF-β1.[7] It also inhibits the proliferation of keloid fibroblasts and decreases the rate of collagen synthesis through RNA transcription alteration, cell G_1 phase delay or arrest, and insulin growth factor (IGF) suppression.[9–12] Topical tamoxifen citrate chemical treatment has been shown to improve scarring. Prospective studies must be performed to validate the use of tamoxifen for the treatment of hypertrophic scars and keloids.

Methotrexate. Methotrexate (MTX) is used for the treatment of cancer, psoriasis, and rheumatoid arthritis, and works by inhibiting dihydrofolate reductase, which prevents the reduction of folate to its active form.[13] In low doses, its anti-inflammatory effect is mediated by adenosine A2 receptors and by an increase in adenosine release at sites of inflammation. When combined with excision, MTX has proven quite successful in leading to complete resolution and preventing keloid recurrences. Oral MTX (15–20mg) was given in a single dose every four days, starting a week prior to excision and continuing post-surgery until keloid resolution for three months and prevented keloid recurrence. In two patients, no recurrences were noticed after four years of follow up.[14]

Imiquimod and resiquimod. Imidazolaquinolines are topical immunomodulators that are toll-like receptors (TLR) 7 and 8 agonists.[15] They induce the production of cytokines including interferon-alpha (IFN-α), a dose-dependent, antifibrotic cytokine.[16] Resiquimod is 10- to 100-fold more potent than imiquimod.[17] Imiquimod use is not advised until 4 to 6 weeks after surgery in patients with incisions that are large, under tension, or closed with flaps or grafts that may splay or dehisce. Berman et al[18] evaluated 11 keloids after application of imiquimod 5% cream for eight weeks following surgical excision. No recurrence was found at 24 weeks. Half of the patients in the study developed pigmentary alteration. Imiquimod 5% cream was applied to eight earlobe keloids after parallel keloid excision in another study. Six out of eight patients did not have recurrence 24 weeks after surgery.[19] Eight large keloids were studied and treated with imiquimod 5% cream daily for six weeks following shave excision. The results showed good cosmesis and no recurrence at 6 and 12 months following treatment.[20] The use of imiquimod 5% cream after surgery for the treatment of keloids appears to be safe and effective in preventing keloid recurrences.[20,21] However, in a recent study, keloid recurrence occurred in 8 out of 10 patients with a keloid on the trunk that was treated with surgical excision, primary closure, and imiquimod 5% cream applied daily for eight weeks. This study suggests that imiquimod 5% cream is not effective in preventing recurrence of trunkal keloids after surgical excision. While this is a small study, the results are in opposition to other studies using imiquimod 5% cream for the prevention of keloid recurrences.[22]

Retinoids. Retinoic acid and other vitamin A derivatives produce a marked reduction in human fibroblast proliferation by interfering with DNA synthesis *in vitro*. Retinoids also exhibit an inhibitory effect on TGF-β1-induced type I collagen gene expression in human fibroblasts.[21–25] The use of isotretinoin and triamcinolone acetonide (TAC) was evaluated on the growth of embryonal human skin fibroblasts *in vitro* and demonstrated that each significantly inhibited the growth of the cells with a greater combined effect than that of either drug used alone.[26] *In-vivo* studies have demonstrated a decrease in scar size after treatment with topical 0.05% tretinoin.[27,28] Other studies demonstrated a marked reduction in scar size and a decrease in pruritus in the majority of cases of intractable scars (28 lesions in total) with daily applications of 0.05% retinoic acid solution.[29] Some authors suggest the use of low-dose isotretinoin for the treatment of acne keloidalis, a condition characterized by pustulopapules that scar, resulting in keloidal plaques. It is likely that retinoids, which are useful in disorders of keratinization, act by downregulating the process of follicular hyperkeratosis and inflammation.[30] Although retinoic acid may significantly reduce the precollagen production of keloid fibroblasts, it may also decrease collagenase production. Although clinical studies have demonstrated that retinoids led to slight reductions in the size and symptoms of keloids, they should not be considered first-line therapy for these conditions.

Calcineurin inhibitors. *Tacrolimus.* Tacrolimus (FK-506) is a potent immunosuppressor that binds to the receptor FKBP12. It inhibits calcineurin and suppresses production of IL-2. In an open-label pilot study,[31] 11 patients were treated with tacrolimus 0.1% ointment twice daily for 12 weeks. A decrease in induration, tenderness, erythema, and pruritus was seen in most patients.[31] An atopic dermatitis patient who was treated with topical tacrolimus coincidentally noted complete resolution of a keloid.[32] Additional clinical trials involving topical tacrolimus are warranted in order to determine its

effectiveness in keloid treatment.

Sirolimus. The mammalian target of rapamycin (mTOR) is a serine/theronine kinase, which plays an important role in the regulation of metabolic processes and translation rates. Reports have shown mTOR to be a regulator of collagen expression and its inhibition induces a decrease in extracellular matrix (ECM) deposition. Sirolimus inhibits mTOR, blocks response to IL-2, and decreases ECM deposition.[32] Increased expression of the gli-1 oncogene is present in kelodis, and sirolimus inhibits gli-1 signal transduction, which may restore the natural apoptosis process with decreased proliferation of the ECM.[33] Studies have demonstrated that there is a higher concentration of vascular endothelial growth factor (VEGF) in the basal layer of the epidermis and higher blood vessel density in keloidal tissue compared to normal skin. Secreted VEGF expression has shown to be down regulated in a dose-dependent manner in the presence of sirolimus in co-cultured keloid keratinocyte and fibroblast. Therefore, sirolimus may inhibit VEGF and may control the expression profile of underlying dermal fibroblasts.[34]

Phenylalkylamine calcium channel blockers. Calcium antagonists appear to work by reducing collagen production and may be a reasonable and safe alternative to corticosteroid injection for the treatment of keloids.[35] Intralesional verapamil decreases ECM collagen production and induces collagenase synthesis.[36] A 54-percent cure rate was reported after the use of intralesional verapamil as an adjuvant therapy with surgical excision and topical silicone versus an 18-percent cure rate in the control group without verapamil.[37] Skara[38] reported the administration of intralesional verapamil at doses of 2.5 mg/mL administrated for 15 days and reapplied after one month of the surgical removal. Study results showed that at one year of follow up, 4 out of 6 keloids and 1 out of 2 hypertrophic scars had complete resolution. Monthly applications can be continued until complete resolution. To avoid recurrence, a combination of verapamil and triamcinolone can be applied. Other studies[39] reported a 55-percent cure rate in 16 patients with earlobe keloids at up to 28-month follow up after surgical excision, intralesional verapamil, and pressure earring therapy.

Botulinum toxin A. Botulinum toxin A (BTA) immobilizes the local muscles, reduces skin tension caused by muscle pull, and, therefore, decreases microtrauma and subsequent inflammation. Reduction of the tensile force during the course of cicatrisation and effective regulation of the balance between fibroblast proliferation and cellular apoptosis may represent a novel therapeutic target for treating keloids. *In-vitro* studies have suggested that cultured fibroblasts have a distinctive behavior in their differential cell-cycle distribution, which partly explains why cell cycles in the presence of BTA can improve the eventual appearance of hypertrophic scar and inhibit the growth of hypertrophic scars.[40] Zhibo et al[41] conducted a prospective, uncontrolled study to evaluate the effects of BTA in the treatment of keloids. Intralesional BTA was injected into 12 keloids at a concentration of 35 units/mL, with the total dose varying from 70 to 140 units per session. The treatment was given at three-month intervals for a maximum of nine months. At one-year follow up, the therapeutic outcome was excellent in three patients, good in five patients, and fair in four patients. None of the patients showed failure of therapy or signs of recurrence.[41] Xiao et al[42] studied 19 patients with hypertrophic scars who received intralesional injections of BTA (2.5 units/cm^3 of lesion at 1-month intervals) for three months. At six-months follow up, all of the patients showed acceptable improvement of the scars and the therapeutic satisfaction was very high. The erythema, pruritus, and pliability score after the BTA injections were significantly lower than before the injections.[42] Some reports suggest that using intramuscular BTA in conjunction with scar revision on the face helps to reduce the development of a widened scar.[43] Larger, randomized, controlled studies need to be conducted to test the effect of chemoimmobilization in scarring.

Vascular endothelial growth factor. VEGF is important in the promotion of neovascularization and cell growth in both normal and pathological wound healing. It serves as an endothelial cell mitogen, increases vascular hyperpermeability, and promotes deposition of an extravascular fibrin matrix.[44] Multiple studies have indicated that VEGF is expressed at higher levels in the underlying dermis, in epidermal keratinocytes, and in capillary lining cells and fibroblasts of keloids in comparison with normal skin.[45–49] The use of short interfering ribonucleic acid (siRNA) sequences for the inhibition of the VEGF gene represents a potential therapeutic strategy for keloids.[49]

Basic fibroblast growth factor. Basic fibroblast growth factor (bFGF) promotes the growth and differentiation of many cell types. It has both angiogenic and mitotic properties, influencing tissue remodeling, wound healing, neovascularization, and promoting tumor growth.[50] bFGF has been found to significantly inhibit the differentiation of mesodermal progenitor cells into myofibroblasts, which are the key mediators of tissue fibrosis and the primary producer of collagen.[50] It also accelerates wound healing and improves scar quality by regulating the extracellular matrix production and degradation, as seen in studies involving rabbit ear models.[51] In a study by Ono et al,[52] bFGF was administered locally into 230 sutured wounds immediately following surgery. Subjects received either low-dose dermal injections (0.1μg/m per wound), high-dose injections (1μg/m per wound), or a rinse with high-dose bFGF (1μg/m wound). At 6 to 12 months postoperation, the degree of scar formation was assessed. The amount of scarring in all three treated groups was significantly lower than in the control group (p<0.001 in all groups). No adverse events were observed.[52] bFGF represents an important tool for the future treatment of keloids and scarring.

Hepatocyte growth factor. Hepatocyte growth factor (HGF) is a cytokine that has regenerative, angiogenic, antiapoptotic, and antifibrotic properties. It has been found to alter the levels of cytokines, such as VEGF and TGF-β1,

and, therefore, may play a role in the prevention of scar formation.[53] Ono et al[54] administered the HGF gene intradermally to incisional wounds made on the backs of rats and found that it suppressed apoptosis and the proliferation of fibroblasts and led to enhancement of the healing process with less noticeable scarring.[54] Further clinical trials examining the therapeutic uses of this cytokine are warranted.

Mannose 6 phosphate. Mannose-6-phosphate (M6P) surface receptors are involved in the proteolytic activation of TGF-β. When injected into wounds, M6P competes with latent M6P for the M6P receptors, inhibiting TGF-β1 and β2 activation, which can lead to reduced fibrosis.[55] A phase I dose-escalation trial found M6P to be safe and well tolerated and found that it accelerated epithelialization significantly. Current trials are further exploring the role of M6P in the acceleration of wound healing and testing two dose levels and two routes of administration (intradermally and topically).[56]

Interleukin-10. IL-10 is a major suppressor of the inflammatory response. It downregulates levels of IL-6 and IL-8, which are promoters of fibrosis. Overexpression of it may lead to wound healing with scarring.[57] In animal models, wound sites were injected with IL-10 48 hours before wounding. Three days post wounding, the release of inflammatory mediators was decreased and there was no collagen deposition and restoration of the normal dermal architecture when compared to wound sites injected with placebo.[58] Currently, Phase 2 trials are underway to establish which of eight intraepidermal doses are most effective and safe in scar reduction.[59]

Transforming growth factor beta. TGF-β is cytokine produced and released by platelets, fibroblasts, and endothelial, epithelial, and inflammatory cells, such as macrophages and lymphocytes, after a wound occurs. TGF-β participates in the regulatory process of cell proliferation with an important role in tissue repair.[60–63] Evidence indicates that TGF-β isoforms 1 and 2 are particularly involved in collagen synthesis promotion and scarring, while isoform 3 is involved in scar prevention.[64] Avotermin, human recombinant TGF-β3, has been studied in several Phase 2, double-blind, placebo-controlled, randomized, controlled trials (RCTs) showing that the intradermal injection given at or immediately after surgery was safe and produced a statistically significant improvement in scar appearance.[65] Currently, a Phase 3 efficacy trial in scar revision is being conducted and is expected to report results by 2011.[66] TGF-β1 and 2 inhibition have also been studied *in vitro* and in animal studies.[61,67,68] Postsurgical injections of antisense TGF-β1 oligonucleotides, which are associated with a reduction in the expression of the TGF-β1 gene, have demonstrated to be effective and have obtained long-lasting inhibition of TGF-β-mediated scarring.[67,68] Neutralizing antibodies against TGF-β1 and 2 injected in the margins of healing dermal wounds in adult rats applied at time of wounding or post-wounding have obtained good results in the prevention of scars.[69,70] Two proteoglycans ubiquitously found in the extracellular matrix, decorin (chondroitin/dermatan sulfate) and biglycan can bind TGF-β forming complexes inhibiting TGF-β-mediated biological effects and signaling, disrupting glucose- and TGF-β/Smad-dependent transcriptional events in human mesangial cells.[71–75] Several molecules that are capable of modulating TGF-β signaling with a potential therapeutic effect in fibrotic diseases have recently been identified, including 1) a peptide targeting the transcriptionally active Smad complexes to provide selective inhibition of Smad-dependent TGF-β responses, displaying the Smad-binding domain from the protein "Smad anchor for receptor activation" (SARA)[76,77] and 2) PCTA [PML (promyelocytic leukemia protein) competitor for TGIF (TG-interacting factor) association], involved in presenting Smad2 and Smad3 to the TGF-β receptor for phosphorylation.[78,79] Further studies are needed to elucidate their role in treatment of keloids.

Antihistamines. Histamine H_1 blockers are anti-inflammatory and antiproliferative agents that have been shown to inhibit the deposition of collagen[80,81] and the synthesis of collagen in keloidal fibroblasts through suppression of the release of TGF-β1 from fibroblasts.[82] In an *in-vitro* study,[83] 60 percent of cultured fibroblasts from normal human and keloidal skin showed elevated growth rates when exposed to histamine in a dose-dependent fashion, stimulation that was reverted in the presence of diphenhydramine hydrochloride in histamine-sensitive keloidal strains. A reduction in the proliferation rate (63%), in DNA synthesis (63%), and in the collagen synthesis rate (73%) was obtained after fibroblasts cultured from abnormal scars were exposed to pheniramine maleate.[84] Relief of burning sensation, pain, and pruritus associated with keloids has also been reported.[85,86]

Prostaglandin E2. Prostaglandins are major eicosanoid products of fibroblasts, synthesized from arachidonic acid by constitutive cyclooxygenase (COX)-1 and inducible COX-2 enzyme isoforms. Prostaglandin E2 (PGE2) has shown to be a potent inhibitor of fibroblast migration, proliferation, and collagen synthesis,[87–94] and a promoter of collagen degradation.[95,96] Furthermore, keloid-derived fibroblasts have diminished capacity to produce PGE2 and express less of the PGE2-specific receptor, E prostanoid receptor 2 (EP2).[97,98] This suggests that PGE2 may have a dual pro- and anti-fibrotic action, and that it is its deregulation that leads to abnormal scar formation.

CONCLUSION

Prevention and treatment of abnormal scarring represents a challenge in the medical field. Management of hypertrophic scars and keloids has transitioned from invasive methods, including gross excision and radiation, to intralesional and topical therapies that act at a cellular level. No consensus in treatment regimens has been elucidated and there is limited evidence-based literature to guide the correct management. However, recent reports offer novel modalities that may approach scarring from novel angles. Continued investigation of original therapies will provide further insight into the mechanism of action of

scarring and will offer more opportunities to effectively prevent and treat this difficult-to-manage condition.

REFERENCES

1. Lee DA. Antifibrosis agents and glaucoma surgery. *Invest Ophthalmol Vis Sci*. 1994;35:3789–3791.
2. Stewart CE IV, Kim JY. Application of mitomycin-C for head and neck keloids. *Otolaryngol Head Neck Surg*. 2006;135:946–950.
3. Bailey JN, Waite AE, Clayton WJ, et al. Application of topical mitomycin C to the base of shave-removed keloid scars to prevent their recurrence. *Br J Dermatol*. 2007;156:682– 686.
4. Stewart CE IV, Kim JY. Application of mitomycin-C for head and neck keloids. *Otolaryngol Head Neck Surg*. 2006;135:946 –950.
5. Talmi YP, Orenstein A, Wolf M, Kronenberg J. Use of mitomycin C for treatment of keloid: A preliminary report. *Otolaryngol Head Neck Surg*. 2005;132:598–601.
6. Sanders KW, Gage-White L, Stucker FJ. Topical mitomycin C in the prevention of keloid scar recurrence. *Arch Facial Plast Surg*. 2005;7:172–175.
7. Simman R, Alani H, Williams F. Effect of mitomycin C on keloid fibroblasts: an *in vitro* study. *Ann Plast Surg*. 2003;50:71–76.
8. Gragnani A, Warde M, Furtado F, Ferreira LM. Topical tamoxifen therapy in hypertrophic scars or keloids in burns. *Arch Dermatol Res*. 2010;302(1):1–4. Epub 2009 Jul 28.
9. Mancoll JS, Zhao J, McCauley RL, Phillips LG. The inhibitory effect of tamoxifen on keloid fibroblasts. *Surg Forum*. 1996;47:718–720.
10. Hu D, Hughes MA, Cherry GW. Topical tamoxifen—a potential therapeutic regime in treating excessive dermal scarring? *Br J Plast Surg*. 1998;51(6):462–469.
11. Mikulec AA, Hanasono MM, Lum J, et al. Effect of tamoxifen on transforming growth factor beta1 production by keloid and fetal fibroblasts. *Arch Facial Plast Surg*. 2001;3(2):111–114.
12. Chau D, Mancoll JS, Lee S, et al. Tamoxifen downregulates TGF-beta production in keloid fibroblasts. *Ann Plast Surg*. 1998;40(5):490–493.
13. Wallace CA. The use of methotrexate in childhood rheumatic diseases. *Arthritis Rheum*. 1998;41:381–391.
14. Onwukwe MF. Treating keloids by surgery and methotrexate. *Arch Dermatol*. 1980;116:158.
15. Sauder DN, Smith MH, Senta-McMillian T, Soria I, Meng TC. Randomized, single-blind, placebo-controlled study of topical application of the immune response modulator resiquimod in healthy adults. *Antimicrob Agents Chemother*. 2003;47:3846–3852.
16. Jimenez SA, Freundlich B, Rosenbloom J. Selective inhibition of human diploid fibroblast collagen synthesis by interferons. *J Clin Invest*. 1984;74:1112–1116.
17. Tomai MA, Gibson SJ, Imbertson LM, et al. Immunomodulating and antiviral activities of the imidazoquinoline S-28463. *Antiviral Res*. 1995;28:253–264.
18. Berman B, Kaufman J. Pilot study of the effect of postoperative imiquimod 5% cream on the recurrence rate of excised keloids. *J Am Acad Dermatol*. 2002;47:S209–S211.
19. Martin-Garcia RF, Busquets AC. Postsurgical use of imiquimod 5% cream in the prevention of earlobe keloid recurrences: results of an open-label, pilot study. *Dermatol Surg*. 2005;31:1394–1398.
20. Stashower ME. Successful treatment of earlobe keloids with imiquimod after tangential shave excision. *Dermatol Surg*. 2006;32:380–386.
21. Jacob SE, Berman B, Nassiri M, Vincek V. Topical application of imiquimod 5% cream to keloids alters expression genes associated with apoptosis. *Br J Dermatol*. 2003;149 Suppl 66:62–65.
22. Cação FM, Tanaka V, Messina MC. Failure of imiquimod 5% cream to prevent recurrence of surgically excised trunk keloids. *Dermatol Surg*. 2009;35(4):629–633.
23. Daly TJ, Weston WL. Retinoid effects on fibroblast proliferation and collagen synthesis *in vitro* and on fibrotic disease *in vivo*. *J Am Acad Dermatol*. 1986;15:900–902.
24. Abergel RP, Meeker CA, Oikarinen H, Oikarinen AI, Uitto J. Retinoid modulation of connective tissue metabolism in keloid fibroblast cultures. *Arch Dermatol*. 1985;121:632–635.
25. Oikarinen H, Oikarinen AI, Tan EM, et al. Modulation of procollagen gene expression by retinoids. Inhibition of collagen production by retinoic acid accompanied by reduced type I procollagen messenger ribonucleic acid levels in human skin fibroblast cultures. *J Clin Invest*. 1985;75:1545–1553.
26. Cruz NI, Korchin L. Inhibition of human keloid fibroblast growth by isotretinoin and triamcinolone acetonide *in vitro*. *Ann Plast Surg*. 1994;33(4):401–405.
27. Panabiere-Castaings MH. Retinoic acid in the treatment of keloids. *J Dermatol Surg Oncol*. 1988;14:1275–1276.
28. Hansen DA. Treatment of hypertrophic scars with retinoic acid. *S Afr Med J*. 1979;56:1114.
29. Janssen de Limpens AM. The local treatment of hypertrophic scars and keloids with topical retinoic acid. *Br J Dermatol*. 1980;103:319–323.
30. Goh MS, Magee J, Chong AH. Keratosis follicularis spinulosa decalvans and acne keloidalis nuchae. *Australas J Dermatol*. 2005;46(4):257–260.
31. Berman B, Amini S, Viera M. Keloid and hypertrophic scar. WebMD Health Professional Network. www.emedicine.com. Accessed February 18, 2010.
32. Ong CT, Khoo YT, Mukhopadhyay A, et al. mTOR as a potential therapeutic target for treatment of keloids and excessive scars. *Exp Dermatol*. 2007;16:394–404.
33. Kim A, DiCarlo J, Cohen C, et al. Are keloids really "gli-loids"? High-level expression of gli-1 oncogene in keloids. *J Am Acad Dermatol*. 2001;45:707–711.
34. Ong CT, Khoo YT, Tan EK, et al. Epithelial-mesenchymal interactions in keloid pathogenesis modulate vascular endothelial growth factor expression and secretion. *J Pathol*. 2007;211:95–108.
35. Juckett G, Hartman-Adams H. Management of keloids and hypertrophic scars. *Am Fam Physician*. 2009;80(3):253–360.
36. Berman B, Villa A, Ramirez C. Novel opportunities in the treatment and prevention of scarring. *J Cutan Med Surg*.

2005;8(3):32–36.
37. D'Andrea F, Brongo S, Ferraro G, Baroni A. Prevention and treatment of keloids with intralesional verapamil. *Dermatology*. 2002;204(1):60–62.
38. Skaria AM. Prevention and treatment of keloids with intralesional verapamil. *Dermatology.* 2004;209(1):71.
39. Lawrence WT. Treatment of earlobe keloids with surgery plus adjuvant intralesional verapamil and pressure earrings. *Ann Plast Surg*. 1996;37(2):167–169.
40. Zhibo X, Miaobo Z. Botulinum toxin type A affects cell cycle distribution of fibroblasts derived from hypertrophic scar. *J Plast Reconstr Aesthet Surg*. 2008;61(9):1128–1129. Epub 2008 Jun 13.
41. Zhibo X, Miaobo Z. Intralesional botulinum toxin type A injection as a new treatment measure for keloids. *Plast Reconstr Surg*. 2009;124(5):275e–277e.
42. Xiao Z, Zhang F, Cui Z. Treatment of hypertrophic scars with intralesional botulinum toxin type A injections: a preliminary report. *Aesthetic Plast Surg*. 2009;33(3):409–412. Epub 2009 Apr 9.
43. Venus MR. Use of botulinum toxin type A to prevent widening of facial scars. *Plast Reconstr Surg*. 2007;119(1):423–424; author reply 424.
44. Salem A, Assaf M, Helmy A, et al. Role of vascular endothelial growth factor in keloids: a clinicopathologic study. *Int J Dermatol*. 2009;48(10):1071–1077.
45. Tiscornia G, Singer O, Ikawa M, et al. A general method for gene knockdown in mice by using lentiviral vectors expressing small interfering RNA. *Proc Natl Acad Sci U S A*. 2003;100(4):1844–1848.
46. Gira AK, Brown LF, Washington CV, et al. Keloids demonstrate high-level epidermal expression of vascular endothelial growth factor. *J Am Acad Dermatol*. 2004; 50(6):850–853.
47. Steinbrech DS, Mehrara BJ, Chau D, et al. Hypoxia upregulates VEGF production in keloid fibroblasts. *Ann Plast Surg*. 1999;42(5):514–519; discussion 519–520.
48. Le AD, Zhang Q, Wu Y, et al. Elevated vascular endothelial growth factor in keloids: relevance to tissue fibrosis. *Cells Tissues Organs*. 2004;176(1-3):87–94.
49. Zhang GY, Yi CG, Li X, et al. Inhibition of vascular endothelial growth factor expression in keloid fibroblasts by vector-mediated vascular endothelial growth factor shRNA: a therapeutic potential strategy for keloid. *Arch Dermatol Res*. 2008;300(4):177–184.
50. Tiede S, Ernst N, Bayat A, et al. Basic fibroblast growth factor: a potential new therapeutic tool for the treatment of hypertrophic and keloid scars. *Ann Anat*. 2009;191(1):33–44.
51. Xie JL, Bian HN, Qi SH, et al. Basic fibroblast growth factor (bFGF) alleviates the scar of the rabbit ear model in wound healing. *Wound Repair Regen*. 2008;16(4):576–581.
52. Ono I, Akasaka Y, Kikuchi R, et al. Basic fibroblast growth factor reduces scar formation in acute incisional wounds. *Wound Repair Regen*. 2007;15(5):617–623.
53. Naim R, Naumann A, Barnes J, et al. Transforming growth factor-beta1-antisense modulates the expression of hepatocyte growth factor/scatter factor in keloid fibroblast cell culture. *Aesthetic Plast Surg*. 2008;32(2):346–352.
54. Ono I, Yamashita T, Hida T, et al. Local administration of hepatocyte growth factor gene enhances the regeneration of dermis in acute incisional wounds. *J Surg Res*. 2004;120(1):47–55.
55. Viera MH, Amini S, Konda S, Berman B. Do postsurgical interventions optimize ultimate scar cosmesis. *G Ital Dermatol Venereol*. 2009;144(3):243–257.
56. A double blind, placebo controlled trial to investigate the efficacy and safety of two concentrations of juvidex (Mannose-6-Phosphate) in accelerating the healing of split thickness skin graft donor sites using different dosing regimes. ClinicalTrials.gov Identifier: NCT00664352. http://clinicaltrials.gov/ NCT00664352. Accessed February 18, 2010.
57. Liechty KW, Kim HB, Adzick NS, et al. Fetal wound repair results in scar formation in interleukin-10-defcient mice in a syngeneic murine model of scarless fetal wound repair. *J Pediatr Surg*. 2000;35:866–872;discussion 872–863.
58. Peranteau WH, Zhang L, Muvarak N, et al. IL-10 overexpression decreases inflammatory mediators and promotes regenerative healing in an adult model of scar formation. *J Invest Dermatol*. 2008;128(7):1852–1860.
59. A single-centre, placebo- and standard-care-controlled, double-blind, randomised trial to investigate the efficacy of eight doses of RN1003 in the reduction of scarring from the approximated wound margins of incisional wounds. ClinicalTrials.gov Identifier: NCT00984646. http://clinical trials.gov/NCT00664352. Accessed February 18, 2010.
60. Liu W, Wang DR, Cao YL. TGF-beta: a fibrotic factor in wound scarring and a potential target for anti-scarring gene therapy. *Curr Gene Ther*. 2004;4(1):123–136.
61. Gao Z, Wang Z, Shi Y, et al. Modulation of collagen synthesis in keloid fibroblasts by silencing Smad2 with siRNA. *Plast Reconstr Surg*. 2006;118(6):1328–1337.
62. Massague J. How cells read TGF-beta signals. *Nat Rev Mol Cell Biol*. 2000;1(3):169–178.
63. Wrana JL, Attisano L, Wieser R, Ventura F, Massague J. Mechanism of activation of the TGF-beta receptor. *Nature*. 1994;370(6488):341–347.
64. Meier K, Nanney LB. Emerging new drugs for scar reduction. *Expert Opin Emerg Drugs*. 2006;11(1):39–47.
65. Ferguson MW, Duncan J, Bond J, et al. Prophylactic administration of avotermin for improvement of skin scarring: three double-blind, placebo-controlled, phase I/II studies. *Lancet*. 2009;373(9671):1264–1274.
66. A double blind, within patient, placebo controlled trial to assess the efficacy of Juvista (avotermin) in conjunction with scar revision surgery for the improvement of disfiguring scars. ClinicalTrials.gov Identifier: NCT00742443. http://www.clinicaltrials.gov/ct2/show/ NCT00742443. Accessed February 16, 2010.
67. Cordeiro MF, Mead A, Ali RR, et al. Novel antisense oligonucleotides targeting TGF-beta inhibit in vivo scarring and improve surgical outcome. *Gene Ther*. 2003;10(1):59–71.
68. Choi BM, Kwak HJ, Jun CD, et al. Control of scarring in adult wounds using antisense transforming growth factor-beta 1 oligodeoxynucleotides. *Immunol Cell Biol*.

1996;74(2):144–150.
69. Shah M, Foreman DM, Ferguson MW. Control of scarring in adult wounds by neutralising antibody to transforming growth factor beta. *Lancet*. 1992;339(8787):213–214.
70. Shah M, Foreman DM, Ferguson MW. Neutralising antibody to TGF-beta 1,2 reduces cutaneous scarring in adult rodents. *J Cell Sci*. 1994;107 (Pt 5):1137–1157.
71. Robson MC. Proliferative scarring. *Surg Clin North Am*. 2003;83(3):557–569.
72. Schonherr E, Broszat M, Brandan E, et al. Decorin core protein fragment Leu155-Val260 interacts with TGF-beta but does not compete for decorin binding to type I collagen. *Arch Biochem Biophys*. 1998;355(2):241–248.
73. Zhao J, Sime PJ, Bringas P Jr, et al. Adenovirus-mediated decorin gene transfer prevents TGF-beta-induced inhibition of lung morphogenesis. *Am J Physiol*. 1999;277(2 Pt 1):L412–L422.
74. Abdel-Wahab N, Wicks SJ, Mason RM, Chantry A. Decorin suppresses transforming growth factor-beta-induced expression of plasminogen activator inhibitor-1 in human mesangial cells through a mechanism that involves Ca2+-dependent phosphorylation of Smad2 at serine-240. *Biochem J*. 2002;362(Pt 3):643–649. Erratum in: *Biochem J*. 2002;366(Pt 3):999.
75. Kolb M, Margetts PJ, Sime PJ, Gauldie J. Proteoglycans decorin and biglycan differentially modulate TGF-beta-mediated fibrotic responses in the lung. *Am J Physiol Lung Cell Mol Physiol*. 2001;280(6):L1327–L1334.
76. Runyan CE, Schnaper HW, Poncelet AC. The role of internalization in transforming growth factor beta1-induced Smad2 association with Smad anchor for receptor activation (SARA) and Smad2-dependent signaling in human mesangial cells. *J Biol Chem*. 2005;280(9):8300–8308.
77. Zhao BM, Hoffmann FM. Inhibition of transforming growth factor-beta1-induced signaling and epithelial-to-mesenchymal transition by the Smad-binding peptide aptamer Trx-SARA. *Mol Biol Cell*. 2006;17(9):3819–3831.
78. Faresse N, Colland F, Ferrand N, et al. Identification of PCTA, a TGIF antagonist that promotes PML function in TGF-beta signalling. *EMBO J*. 2008;27(13):1804–1815.
79. Liu F. PCTA: a new player in TGF-beta signaling. *Sci Signal*. 2008;1(46):pe49.
80. Tanaka K, Honda M, Kuramochi T, Morioka S. Prominent inhibitory effects of tranilast on migration and proliferation of and collagen synthesis by vascular smooth muscle cells. *Atherosclerosis*. 1994;107(2):179–185.
81. Miyazawa K, Hamano S, Ujiie A. Antiproliferative and c-myc mRNA suppressive effect of tranilast on newborn human vascular smooth muscle cells in culture. *Br J Pharmacol*. 1996;118(4):915–922.
82. Suzawa H, Kikuchi S, Arai N, Koda A. The mechanism involved in the inhibitory action of tranilast on collagen biosynthesis of keloid fibroblasts. *Jpn J Pharmacol*. 1992:60(2):91–96.
83. Topol BM, Lewis VL Jr, Benveniste K. The use of antihistamine to retard the growth of fibroblasts derived from human skin, scar, and keloid. *Plast Reconstr Surg*. 1981;68(2):227–232.
84. Venugopal J, Ramakrishnan M, Habibullah CM, Babu M. The effect of the anti-allergic agent avil on abnormal scar fibroblasts. *Burns*. 1999;25(3):223–228.
85. Shigeki S, Murakami T, Yata N, Ikuta Y. Treatment of keloid and hypertrophic scars by iontophoretic transdermal delivery of tranilast. *Scand J Plast Reconstr Surg Hand Surg*. 1997:31(2):151–158.
86. Yamada H, Tajima S, Nishikawa T, et al. Tranilast, a selective inhibitor of collagen synthesis in human skin fibroblasts. *J Biochem (Tokyo)*. 1994;116(4):892–897.
87. Kampfer H, Brautigam L, Geisslinger G, et al. Cyclooxygenase-1-coupled prostaglandin biosynthesis constitutes an essential prerequisite for skin repair. *J Invest Dermatol*. 2003;120(5):880–890.
88. Muller-Decker K, Hirschner W, Marks F, Furstenberger G. The effects of cyclooxygenase isozyme inhibition on incisional wound healing in mouse skin. *J Invest Dermatol*. 2002;119(5):1189–1195.
89. Talwar M, Moyana TN, Bharadwaj B, Tan LK. The effect of a synthetic analogue of prostaglandin E2 on wound healing in rats. *Ann Clin Lab Sci*. 1996;26(5):451–457.
90. Lundberg C, Gerdin B. The inflammatory reaction in an experimental model of open wounds in the rat. The effect of arachidonic acid metabolites. *Eur J Pharmacol*. 1984;97(3-4):229–238.
91. Wilgus TA, Bergdall VK, Tober et al. The impact of cyclooxygenase-2 mediated inflammation on scarless fetal wound healing. *Am J Pathol*. 2004;165(3):753–761.
92. Bitterman PB, Wewers MD, Rennard SI, Adelberg S, Crystal RG. Modulation of alveolar macrophage-driven fibroblast proliferation by alternative macrophage mediators. *J Clin Invest*. 1986;77(3):700–708.
93. Lama V, Moore BB, Christensen P, et al. Prostaglandin E2 synthesis and suppression of fibroblast proliferation by alveolar epithelial cells is cyclooxygenase-2-dependent. *Am J Respir Cell Mol Biol*. 2002;27(6):752–758.
94. Sandulache VC, Parekh A, Li-Korotky H, et al. Prostaglandin E2 inhibition of keloid fibroblast migration, contraction, and transforming growth factor (TGF)-beta1-induced collagen synthesis. *Wound Repair Regen*. 2007;15(1):122–133.
95. Varga J, Diaz-Perez A, Rosenbloom J, Jimenez SA. PGE2 causes a coordinate decrease in the steady state levels of fibronectin and types I and III procollagen mRNAs in normal human dermal fibroblasts. *Biochem Biophys Res Commun*. 1987;147(3):1282–1288.
96. Riquet FB, Lai WF, Birkhead JR, et al. Suppression of type I collagen gene expression by prostaglandins in fibroblasts is mediated at the transcriptional level. *Mol Med*. 2000;6(8):705–719.
97. Yeh FL, Shen HD, Lin MW, et al. Keloid-derived fibroblasts have a diminished capacity to produce prostaglandin E2. *Burns*. 2006;32(3):299–304
98. Hayashi T, Nishihira J, Koyama Y, et al. Decreased prostaglandin E2 production by inflammatory cytokine and lower expression of EP2 receptor result in increased collagen synthesis in keloid fibroblasts. *J Invest Dermatol*. 2006;126(5):990–997.