Review

Current therapies for wound healing: electrical stimulation, biological therapeutics, and the potential for gene therapy

Martin Braddock, BSc, PhD, Callum J. Campbell, BSc, PhD, and Daniel Zuder, MD

From the Wound Healing and Tissue Regeneration Programme, Endothelial Gene Expression Group, Vascular Diseases Unit, Glaxo–Wellcome Medicines Research Centre, Stevenage, Hertfordshire, UK, and Department of Dermatology, University Hospital, Tuebingen, Germany

Correspondence
Martin Braddock, BSc, PhD, Wound Healing and Tissue Regeneration Programme, Glaxo–Wellcome Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, UK

Drug names
Becaplermin, recombinant human PDGF BB: Regranex
autologous platelet releasate: Procuren

Biological processes in normal wound healing

The healing of wounds results from a number of temporally co-ordinated processes that involve several events driven by locally released mediators.1–11 The first event is immediate and consists of the activation of the coagulation cascade and the production of a blood clot. After several minutes, an acute inflammatory response ensues. Subsequently, leukocytes clear the wound of debris and release growth factors to initiate the healing process. Then follows the first stage of collagen repair involving deposition and the formation of granulation tissue which becomes a new and temporary weak tissue. The third and final process is the second phase of collagen repair resulting in extracellular matrix remodeling, angiogenesis, and the reproduction of full strength tissue comparable to the original skin. Much of the normal healing process is driven by growth factors. In addition to their role in blood clot formation, platelets generate a number of growth factors that are found in wound fluid, including transforming growth factor α (TGFα), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), transforming growth factor β (TGFβ), and insulin-like growth factor I (IGF-I).12–15 In the inflammatory response, neutrophil migration is induced by PDGF, interleukin 1α (IL1α), IL8, tumor necrosis factor α (TNFα), granulocyte macrophage colony-stimulating factor (GM-CSF), and granulocyte colony-stimulating factor (G-CSF).16–19 Thus, multiple growth factors and cytokines play a major role in wound healing.

Biological processes in failed wound healing

It has long been known that dermal wounds may show impaired healing in patients with peripheral arterial occlusive disease (PAOD), deep vein thrombosis (DVT), and diabetes. For example, wounds in diabetic patients heal very slowly or not at all when compared with wounds in nondiabetics. Despite intense investigation, the precise molecular mechanisms associated with impaired healing in this patient group are poorly understood. A number of laboratories have shown reductions in the levels of growth factors and their receptors. These include PDGF receptors,20 IGF-I and IGF-II,21 keratinocyte growth factor (KGF),22 TGFβ1,2,3 and receptors.24 Consistent with these findings, several groups have shown that the application of growth factors may induce the acceleration of cutaneous wound healing in murine models of diabetes. These studies are described later.

Healthcare burden for the treatment of chronic wounds

Ulcers associated with pressure and arterial and venous diseases

Dermal ulcers are a common complication and frequent cause of hospital admission for many patients suffering with diabetes. In 1992, in the UK, 2% of the diabetic population were documented as having ulcer history with approximately 0.5% having active ulcers at any one time.25
with increasing age, and the number of patients with active venous ulcers is estimated to be 1,300,000 in the USA. In 1989, in the UK, figures suggested that nursing costs alone accounted for £180 million, consuming over 2% of the overall healthcare resources. It is predicted that there will be an increase in the incidence of venous ulcers of 6% per annum.

In the UK, the risk of diabetics developing an ulcer is 3.1% (compared with 1.6% for having an acute myocardial infarction within the same patient group). Diabetic foot ulceration is frequently the cause of amputation, the rate of which is 15 times higher for those with diabetes than for those without, leading to a total of about 10% of diabetic ulcer patients requiring amputation. Two predisposing features which contribute to the high incidence of amputation are neuropathy and ischemia, both of which can lead to localized tissue trauma and subsequent tissue breakdown with necrosis and infection. In addition to diabetes mellitus, several disease conditions may lead to impaired wound healing. These include venous insufficiency and cerebrovascular incidents. Many of these conditions have a high incidence in elderly patients. In Europe, the overall prevalence of patients with leg and foot ulceration is between 0.15 and 0.3%. In the Netherlands, diabetic foot ulceration caused hospitalization of 3707 patients in 1988 at a cost of Dfl.96 million. The incidence of arterial diabetic ulcers is 2,350,000 in the USA and 170,000 in the UK. The cost of treatment per year is estimated at $16–21 billion in the USA and $3–4 billion in the UK, and the costs of amputation are $1.5 billion in the USA and $30 million in the UK. Again as a consequence of an enlarging elderly population, the market is set to increase at a rate of 14% per annum.

Pressure sores are described as localized areas of tissue damage resulting from direct pressure on the skin (causing ischemia), or from shearing forces and friction (causing mechanical stresses to the skin). The prevalence amongst hospital patients in the UK and USA is 7–8% and, as with venous stasis leg ulcers, the prevalence increases with age. The incidence in the USA is 2,900,000. The estimated costs of care for pressure sores are £150 million per annum in the UK and $3 billion in the USA and the market is set to grow at 5% per annum.

Burns
In Northern America, approximately 1% of the population (2.5 million people) are seen by a physician each year for a burn-related injury. In 1964, the mortality associated with a 50% body burn was in excess of 50% of people, whereas in 1984 this figure was reduced to less than 10%. This accomplishment is due to the establishment of specialist burn centres. Good burn care includes rapid and sustained cooling of the affected area with water, cleansing, and debridement. Prevention of sepsis is encouraged by application of silver sulfadiazine. This treatment is usually sufficient for first and second degree burns to heal. Third and fourth degree burns may need the attention of a plastic surgeon who may employ skin grafting as required. As all burns should be monitored for at least 6 weeks for hypertrophic scarring, it is inevitable that a proportion of burns would benefit from therapies that may reduce the incidence of red, thick, raised, and oftenitchy or painful hypertrophic scars. An ideal therapy would not only promote the rapid healing process, but would act as an antiscarring therapy. In terms of healthcare burden, the cost is estimated to be in excess of $0.7 billion per annum in the USA.

UK and European treatment regimes
In the UK and in Europe, the vast majority of patients with pressure sores or venous or arterial ulcers receive a treatment regime from their physician which comprises eschar debridement, antibiotic treatment where appropriate, and regular dressing. In the UK, there is little prospect for further treatment other than referral for skin grafting, which is only applicable when the wound bed is well vascularized. For both venous and arterial ulcers, extensive tissue debridement, provision of a nonweight-bearing regime, administration of antibiotics if infection is present, and regular changes of moist saline dressings constitute good ulcer care. Other dressings, such as hydrogels, hydrocolloids, or alginates, may also be used. Venous ulceration is treated by compression therapy (utilizing bandages which provide a graded compression from heel to knee), whereas arterial or diabetic ulcers require regular changes of disinfected dressings. Pressure sores, once disinfected if necessary, are encouraged to heal by the relief of pressure at the injury site. This is achieved, for example, by the construction of padded surgical boots for pressure relief on the affected foot.

US treatment regimes
In addition to the standard healthcare provided in the UK and the rest of Europe, patients in the USA may demand additional or alternative treatments. Some alternative treatments comprise administration of growth factors to the wounded area, or physical warming of the wound by “warm up” therapy. Various devices exist for warming a wounded area. The concept is that a wound does not have the ability to maintain a temperature of 37 °C as a result of tissue loss. The wound warming device restores the wound to 37 °C to provide the opportunity for healing by, in part, increasing localized blood flow.

Growth factor treatment includes the use of Regranex (recombinant human PDGF B; reviewed later) and a cocktail of growth factors produced from a platelet releasate.
Although not as yet prescribed by the majority of centers in Europe, the use of growth factors may become more widespread if the current cost and hence burden to healthcare services can be reduced.

**Current therapies to promote healing**

**Tissue engineered skin**

Tissue engineering offers the possibility of creating physiologically compatible human skin. With reference to wound care, the trend is to test artificial skin substitutes on burn wounds first and then progress to chronic wounds. The principal goal behind the use of a skin substitute is to prevent bacterial infection and allow the wound the chance to heal by normal reparative processes. For all applications of tissue engineered skin, it is paramount that any pre-existing infection has been cleared by the use of antibiotics such as Penbritin or Floxapen. Some skin substitutes, e.g. Dermagraft (Advanced Tissue Sciences/Smith & Nephew), are designed to replace the dermis and to provide essential stimulatory growth factors. In addition to Dermagraft being approved for full thickness diabetic foot ulcers under a Food and Drug Administration (FDA) investigational device exemption, Dermagraft TC is indicated for the treatment of burns. Apligraf (Organogenesis/Novartis), indicated for venous stasis ulcers, gained FDA approval in May 1998 and comprises both a dermal and epidermal layer. Further clinical trials for burn treatment are underway.

Other dermal skin substitutes, which include BioBran (Dow B Hickman) and Integra (Integra), have been tested in burns victims, and Alloderm (LifeCell) has recently been launched in the USA for patients with third degree burns and limited donor site tissue. Of the epidermal replacement products currently available, the most advanced comprises cultured autologous epithelial cells grown to confluence in vitro. Epicel (Genzyme) is indicated for the treatment of burns. Acticel, which is a nonautologous variation of Epicel, is in clinical trial as an active wound dressing for patients with burns or ulcers.

It should be borne in mind that, unlike in burns patients, the condition in patients with chronic ulcers results from underlying diseases, which if effectively treated would reduce the use of skin replacement. Consequently, treatment of the underlying disease in addition to stimulation of the wound healing process, either by physical stimuli or by the application of exogenous growth factors, may achieve a greater incidence of healing.

**Physical devices**

Numerous physical devices have been employed in an attempt to promote the healing of wounds. These range from compression bandages as the standard treatment for venous ulcers to laser treatment, hyperbaric oxygen and electrical stimulation for the treatment of arterial ulcers. One particular regime of electrical stimulation that has achieved some success is the use of Dermapulse, which we will review at length.

For about 60 years it has been presumed that the application of low-dose direct current could have a positive effect on wound healing. This was demonstrated in numerous animal studies and in tissue culture. In 1991, application of pulsed direct current achieved a reduction in the wound area to under 45% of the original area for patients with skin ulcers of different etiologies after 4 weeks of treatment. In the control group, 67% of the wound area remained. Since then different groups of investigators have documented the specific treatment of burns, pressure necrosis, diabetic foot syndrome, keloids, and skin infections with direct current.

In 1983, it was postulated that tissue layers deeper than the skin have a negative potential as compared to the skin. This allows the skin wound to become charged by a positive potential. The negative battery potential arises through the sodium ion pump. Throughout the wound the distribution of charge in the skin is disturbed. During wound healing, the flow of current is measurable, but ceases during the end of the wound healing process or during the nonphysiologic conditions in a dry ulcer. This offers, in part, an explanation for the fact that wounds in a moist environment heal better. Tissue cells, such as macrophages, mast cells, or granulocytes, migrate along the path of a voltage gradient. Direct current attracts granulocytes towards the cathode and establishes them in relatively higher numbers in human wound exudate. In a variety of investigations, in animal models as well as in humans, the improvement in the blood flow in the vicinity of the cathode can be demonstrated.

The Dermapulse instrument is a battery-powered medical device that delivers pulsed electrical stimulation. The instrument is powered by a 6-V lantern battery of the spring terminal type, which has a capacity of 20 A-h. The specifications of the instrument are described in Table 1. The device does not need calibration. There are external controls for the intensity, polarity, and frequency of the current signals. The intensity and the remaining treatment time may be read from digital displays. The instrument may be simultaneously connected to as many as four treatment electrodes and two dispersion electrodes. The sterile treatment electrode is designed for single use and consists of a 10.7 × 10.7 cm carbon-filled silicone rubber sheet which has a high conductivity. The nonwoven fabric covering and the polyester, saline-filled gauze pad have antiadhesive characteristics. The dispersion electrode has a surface area of 1.3 × 17.8 cm and is made from silver ink applied to carbon-filled vinyl. A hydrogel adhesive serves
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43.5% ($P < 0.039$). The oxygen level in the skin at the ulcer margin improved by 80%. The inflammatory erythema in the ulcer, as registered by the laser Doppler flux, decreased negligibly.

In this study, it has been demonstrated that therapy resistant venous leg ulcers can be reduced in size or healed in a short period of time. The positive experiences of the electrostimulation of venous ulcers reported here will now stand the test of a prospective placebo-controlled study. The potential role of Dermapulse in the modulation of growth factor and receptor expression is currently under investigation.

Growth factors

There have been many excellent reviews published on growth factors as applied to the healing of wounds, and it is not our intention simply to add to the collection with another general review. Neither is it possible in this review to describe the vast amount of literature that supports the role of growth factors in re-epithelialization, angiogenesis, and matrix remodeling. We will provide a sampling of publications which demonstrate a role for growth factors in healing. Over the last 5 years, numerous growth factors have been shown to accelerate cell proliferation in vitro and to promote wound healing in animal models. TGFβ has received considerable attention in the context of wound repair as it promotes cell proliferation, differentiation, and matrix production. TGFβ, administered either topically or systemically, accelerated the rate of cutaneous wound repair in animal models. A further study showed that the enhancement of wound healing by TGFβ was dependent upon the formulation of the topical delivery system. Likewise PDGF B has been reported to promote re-epithelialization and revascularization in ischemic tissue and diabetic animals. The effect of PDGF is to significantly induce the ingrowth of repair tissue in wounds by upregulating granulation tissue formation and collagen gene expression. In addition to a role for the promotion of healing within wounds, PDGF B has recently been demonstrated to be effective for healing of the patellar ligament in a rat model of ligament injury, and PDGF and nerve growth factor (NGF) have been shown to be effective for repair of nerve damage in a rat model of spinal cord injury. These observations suggest that growth factors may have a general role for the improvement of soft tissue repair.

Heparin binding epidermal growth factor-like growth factor (HB-EGF) has been shown to accelerate healing of partial thickness burn wounds in murine models of burn injury when topically supplied via slow release cholesterol-lecithin pellets. In this study, the application of HB-EGF was associated with an increase in keratinocyte proliferation and production of endogenous TGFα.

Table 1 Specifications for the Dermapulse stimulator

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Pulse rate</td>
<td>64 Hz, 128 Hz</td>
</tr>
<tr>
<td>Pulse width</td>
<td>140 µs</td>
</tr>
<tr>
<td>Polarity</td>
<td>Positive, negative</td>
</tr>
<tr>
<td>Intensity</td>
<td>0–42 mA, peak value of 500 Ω load</td>
</tr>
<tr>
<td>Charge per pulse</td>
<td>5.9 µC maximum</td>
</tr>
<tr>
<td>Average direct current</td>
<td>0–630 µA at 128 Hz, 0–315 µA at 64 Hz</td>
</tr>
</tbody>
</table>

*True root mean square (RMS), $0\sim 5.6$ mA at $500$ Ω load. (Constant current is regulated from $0$ to $1660$ Ω.)

as the skin contact medium. This electrode is usable for at least a week by a single patient.

In one study, patients with chronic venous insufficiency, who had suffered for years with therapy resistant ulcers, were treated with low-frequency pulsed current. The patients generally found the treatment to be pleasant. For the majority of the treated patients, there was a reduction in wound pain during the first few days, which substantially increased the acceptance of the electrostimulation therapy. During therapy, the cutaneous microcirculation and the ulcer size were closely investigated. As shown in Fig. 1, some patients reached a reduction to 36.4% ($P < 0.01$) of the original ulcer area during an average treatment period of 38 days. The nutritive cutaneous perfusion was improved in all of the ulcers. The immediate vicinity of the wound and the ulcer itself were investigated with the capillary microscope in order to document the morphologic characteristics and the increase in capillary density. In the study, the capillary density in the ulcer significantly improved by Figure 1 Patients presenting with therapy resistant ulcers associated with chronic venous insufficiency were treated with Dermapulse. The duration of the disease and the changes in ulcer size were monitored throughout the treatment period.

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Measurement of growth factors in rodent models of streptozotocin-induced diabetes or genetically diabetic rodents has shown a reduction or a delay in expression of a number of growth factors, in particular acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF), TGFβ-like growth factors, PDGF B, and IGF-I.22,23,61–64 This had led to the use of platelet releasates which contain a cocktail of growth factors that have been shown to increase skin healing in animal models62 and, more importantly, in humans. As provided by Curative Technologies Inc., Procuren, an autologous platelet releasate, contains at least five growth factors that aid in the formation of granulation tissue and re-epithelialization.5 The growth factors, which are PDGF, platelet-derived activating factor (PDAF), platelet-derived epithelial growth factor (PDEGF), TGFβ, and platelet factor 4 (PF-4), have all been shown to aid wound repair. This autologous growth factor mix, while not requiring FDA approval, has achieved some success in human subjects with ulcerated limbs.65–67 These results in humans are supported by earlier studies in animal models whereby growth factor combinations were shown to synergistically activate healing in partial thickness porcine wounds68,69 and in a genetically diabetic mouse.70 Nevertheless, this increased rate of healing obtained both in animal models and humans with multiple growth factors is indicative of the requirement of not a single growth factor but a complex mix of cell proliferative agents. Other growth factors that may accelerate wound healing are EGF and bFGF. In a guinea pig skin excision model, both EGF and bFGF increased the thickness of the neodermis,49 and PDGF,71 bFGF,72 NGF,73 and aFGF74 were able to reverse the healing impairment in protein-malnourished diabetic mice. Similarly, IGF-I was shown to accelerate healing in severely wounded senescent mice.75 KGFs may also play a role in tissue repair. KGF (FGF-7) is a potent mitogen for keratinocytes, and application of exogenous KGF caused a significant stimulation of the repair process, whereby re-epithelialization was partially improved.76–78 In addition, a polypeptide of less than 3 kDa from keratinocyte-conditioned medium79 has been shown to stimulate cell proliferation. Finally, endothelial cell growth factor (ECGF), when delivered in a controlled release formulation, has been shown to stimulate angiogenesis in rats,80 and this may have important implications for wound healing.

Biologicals in the clinic

As of 1st January 1999, there are currently two biological therapeutics in the clinic. Procuren, as described previously, is an autologous mixture of naturally occurring growth factors obtained from the alpha granules of the patient’s own platelets. Procuren is indicated for the treatment of chronic nonhealing ulcers, including diabetic, venous stasis, and pressure ulcers. Of the 29,683 patients treated with topically applied growth factors between 1988 and 1995, 78% of patients who presented with dermal ulcers and who completed the program were healed.5,10

Regranex (Johnson & Johnson) is indicated for the treatment of diabetic neuropathic ulcers. It is supplied as a gel formulation for topical administration and PDGF B is its active biological. Supplied at either 0.003% or 0.01% doses. Patients were randomized to receive either good ulcer care alone or Regranex. In studies 1 and 2, the incidence of complete ulcer healing was significantly greater in patients receiving Regranex compared with a placebo gel. In study 3, Regranex promoted approximately a two-fold increase in the number of ulcers healed over a 20-week trial period. The fourth study, a multicenter, evaluator blind study, showed no significant difference. Although these trial results show some promise, there is clear room for improvement, and it is tempting to speculate that the administration of two or more growth factors may further increase the number and rate of ulcers healed.

Clinical trials

Despite the vast interest in growth factor and cytokine biology and their potential for wound healing, clinical trials have in most cases been disappointing. Topically applied bFGF has shown some efficacy in the treatment of chronic pressure sores,82 and TGFβ for the treatment of venous stasis ulcers.83 Some attempts at treatment have, however, proved to be ineffective. In one study, EGF failed to heal venous stasis ulcers,84 and in another IL-1 failed to treat pressure sores effectively.5,10 Equivocal results were reported with bFGF.86 TGFβ1 has been shown to accelerate healing without affecting the amount of scar formation.87 More recently, despite encouraging results in animal models and entry into human clinical trials by Novartis, TGFβ3 was withdrawn from phase III trials in 1998 due to a lack of sufficient efficacy data. This highlights a dilemma that plagues both academic researchers and their potential corporate sponsors alike: the relevance of animal models for wound studies. There is no chronic animal model of ulceration and models of streptozotocin-induced diabetes do not develop ulcers. Given these shortcomings, it is in everybody’s interest to temper results obtained with growth factors and cytokines in acute models of wound with optimism and caution. A contributory factor to the discrepancies attained in efficacy between animal models and humans may be ascribed to the levels of endogenous growth factors and cytokines. The levels of PDGF, bFGF, EGF,
The skin is an accessible barrier that represents a prime site for gene delivery. Such therapies may be directed against cutaneous conditions, e.g., psoriasis and dermal wounds. As described above, DNA-coated particle bombardment by gene gun is one route into the skin. Other direct physical “injection” techniques include the use of microinjection, microfabricated needles, and puncture-mediated DNA transfer. In addition, delivery of DNA complexed with lipids or liposomes has been demonstrated. Transport of macromolecules, as yet untested with DNA, has been achieved using depth-targeted pulsed electric fields and ultrasound. The development of gene-activated matrices (biodegradable polymers incorporating a therapeutic gene) takes the possibilities for wound treatment beyond gene therapy and into the realms of tissue engineering.

Transcription factors (TFs) as therapeutic genes
TFs may have gene therapy applications for wound healing. Hypoxia inducible factor-1 (HIF-1) is a basic helix-loop-helix protein that activates the transcription of hypoxia-inducible genes by binding to a hypoxic response element (HRE) in the gene promoter. Genes that are regulated by HIF-1 include VEGF, erythropoietin, heme oxygenase-1, inducible nitric oxide synthase, and the glycolytic enzymes aldolase A, enolase I, lactate dehydrogenase A, phosphofructokinase I, and phosphoglycerate kinase I. HIF-1 exists in an active form as a heterodimer of HIF-1α and HIF-1β subunits. VEGF exists in a number of isoforms, and is hypoxia inducible. Both VEGF-121 and VEGF-165 isoforms, produced as splice variants of VEGF A, have been used in gene therapy, and VEGF B also has a role in therapeutic angiogenesis. HIF-1 will activate the expression of all the VEGFs and, in theory, should elevate endogenous VEGFs to a higher constitutive level than achieved under hypoxia, given that HIF-1 has been shown to superactivate an HRE-containing promoter under hypoxic conditions. The relative lack of promoter specificity may be an advantage as activation of other known HRE-dependent genes may not be deleterious. To date, studies have been confined to in vitro cell-based assays, where transient transfection of HIF-1α may activate expression of HRE-dependent genes. The potential for HIF-1α to stimulate angiogenesis is being evaluated in animal models of hypoxia (Genzyme), however, and a further application may include the treatment of ischemic ulcers. Provision of a TF gene payload by topical delivery that will activate multiple members of
the VEGF family of growth factors may induce revascularization of the wounded area.

Emerging therapeutic targets: a route to small molecule treatment?

There are currently very few effective small molecule treatments available for the promotion of dermal healing. The healing effects of antibiotic treatments are to resolve infection of the wounded area and cannot strictly be classed as substances to promote accelerated healing.

 Provision of continuous lactate infusion as poly lactate spheres has shown some positive effect in animal models (EMBRO Corporation). Rhamnolipids, agents which inhibit fibroblast and keratinocyte cell proliferation, have been shown in vivo to reduce wound contraction and to limit scarring (Tajco Inc.) Recently, the sphingolipid metabolite, sphingosylphosphorylcholine, was shown to accelerate dermal healing in a murine diabetic (db/db) model. Sphingosine-1-phosphate is a high-affinity ligand for the G-protein-coupled receptor Edg-1, which has been implicated as a second messenger in cell proliferation and survival. The discovery of small molecule agonists for this receptor may prove effective in stimulating granulation and keratinocyte proliferation.

Conclusions

The healing of skin involves a wide range of cellular, molecular, physiologic, and biochemical events. These processes may be defective in diseases such as PAOD, DVT, and diabetes, or overstimulated in the scarring process that results from acute traumatic injury. The understanding of the biological and pathologic events in wound healing has led to three areas of treatment that are currently available in the clinic: (i) growth factors: Regranex is indicated for diabetic neuropathic ulcers; Procu ren is indicated for the treatment of diabetic, venous stasis, and pressure ulcers; (ii) tissue engineered skin: Dermagraft is indicated for the treatment of diabetic neuropathic ulcers; Dermagraft TC, Biobrane, Integra, Alloderm, and Epidel are all indicated for burns; and (iii) physical devices: laser treatment, hyperbaric oxygen, and electrical stimulation (Dermapulse) are indicated for the treatment of chronic ulcers.

We believe as we enter the next millennium that gene therapy will play a major role in the treatment of diseases and their sequelae, such as chronic wounds, where topical delivery of DNA is feasible and development of therapeutic gene cassettes and delivery vehicles is economically viable.

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