

wound healing perspectives®

A CLINICAL PATHWAY TO SUCCESS

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➔ ADVANCED THERAPIES, PART II

A PUBLICATION OF NATIONAL HEALING CORPORATION®

Breakthroughs in medicine

Remarkable medical breakthroughs are made every day around the world, and especially in the United States. Because diabetes is a major factor for so many of our patients, we at National Healing Corporation are particularly excited about a new diabetes treatment that has the medical field buzzing. Pfizer's Exubera®, inhaled insulin, was recently endorsed by an FDA panel of specialists.

We are pleased to bring you this installment of *Wound Healing Perspectives* that focuses on the latest advances in therapies, particularly those related to wound care. Specifically, we'll review Johnson & Johnson's PROMOGRAN™ Matrix, PRISMA™ Matrix, and REGRANEX® Gel; Life Sciences INTEGRA™ Bilayer Matrix Wound Dressing; and HealthPoint's OASIS®.

We hope this edition of *Wound Healing Perspectives* is informative as well as interesting to you. Thank you again for your interest in National Healing Corporation and *Wound Healing Perspectives*.

Sincerely,



Katy Rowland
SVP Clinical Services, National Healing Corporation

New wound healing strategies: Using becaplermin and ORC/collagen

The clinical management of chronic wounds is no longer limited to passive aids that prevent progression – such as dressings, strappings, cleansers, and antibiotics – rather it includes advanced modalities that control the molecular mediators of healing. For example, recombinant growth factors, tissue-engineered products, hyperbaric oxygen, and negative pressure wound therapy are successful modalities that have emerged. Additionally, the angiogenic growth factor, becaplermin (REGRANEX®, Johnson & Johnson Wound Management), is now used for the treatment of non-healing diabetic foot ulcers. A further recent advance is the development of an oxidized regenerated cellulose (ORC/collagen PROMOGRAN™, Johnson & Johnson Wound Management) that protects growth factors and newly formed granulation tissue by inhibiting wound proteases (Li et al 2003).

The following are key observations from an article by Li et al (2003) about optimizing angiogenesis.



NEW WOUND HEALING STRATEGIES INCLUDE ADVANCED MODALITIES THAT CONTROL THE MOLECULAR MEDIATORS OF HEALING.

Wound angiogenesis

Angiogenesis, the growth of new capillary blood vessels in the body, is a naturally occurring process required for wound granulation and tissue repair. In the healthy adult, angiogenesis is regulated by molecules that stimulate or inhibit angiogenesis. Among the most

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First inhaled form of insulin endorsed by FDA panel



According to *The New York Times*, a product that could reduce or eliminate the need for insulin injections by millions of diabetics, moved closer to federal approval this month. Pfizer's Exubera® was recommended 7 to 2 by an advisory panel to the Food and Drug Administration, despite some concerns about the long-term effect that inhaling insulin might have on users' lungs. Many believe the benefits of removing fear of injection from diabetic patients outweigh the possible side-effects. According to Dr. William T. Cefalu of Louisiana State University, two-thirds of diabetics do not control blood glucose as tightly as experts recommend. ■

important stimulators are angiogenic growth factors, specialized proteins that mediate vascular endothelial cell growth and behavior. Under normal circumstances, the effects of these growth factors are counterbalanced by those of naturally present inhibitory molecules that prevent abnormal vascular growth in tissues. Immediately following injury, angiogenic stimulators are released into the wound bed. These include thrombin, growth factors, and other mediators released by platelets, monocytes, and damaged cells. Wound angiogenesis brings oxygen, micronutrients, and survival factors to assist regenerating cells. The influx of inflammatory cells into the wound bed is also facilitated by the microvasculature. Platelets are the first cell type to enter the wound bed. Platelets promote angiogenesis by releasing multiple growth factors, including platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and fibroblast growth factors (FGFs) among others.

Platelet-derived growth factor regulates angiogenesis

PDGF is a multifunctional angiogenic cytokine. Among growth factors, PDGF is unique because of its multiple roles in

stimulating endothelial cells and stabilizing the neovasculature. Diminished PDGF expression occurs in diabetic wounds. Thus, the delivery of recombinant PDGF to diabetic foot ulcers may be viewed as a form of biological "replacement therapy" to restore a growth factor deficiency.

Control of protease activity supports angiogenesis

Proteases are a family of enzymes associated with the early inflammatory stage of wound healing. During angiogenesis, proteases are expressed transiently at the growing tip of blood vessels to facilitate vascular invasion. Proteases also digest the extracellular matrix, as well as assist in tissue remodeling and removal of necrotic tissue in normally healing wounds. Chronic wounds exhibit excessive protease activity. Abnormally elevated protease levels are of clinical concern in wound care because their uncontrolled activity may destroy growth factors, inhibit angiogenesis, and break down granulation tissue. Control of protease activity is thus a critical goal in modern wound management.

Conclusion

Growth factor therapy promotes the formation of granulation tissue that

is vital to healing. While modalities such as bioengineered tissue equivalents, negative pressure wound therapy, and hyperbaric oxygen all promote local growth factor production within the wound bed, becaplermin is presently the only FDA-approved pure growth factor that can be delivered exogenously to stimulate angiogenesis. Every wound requires granulation to heal, so becaplermin has broad potential in the management of a wide range of complex wounds. Becaplermin can be applied either alone or in combination with other modalities, such as bioengineered tissue equivalents (Apligraf®, Dermagraft™) and negative pressure wound therapy (V.A.C.®).

The ability to control proteases in wound exudate is a recent major advance in promoting angiogenesis. ORC/collagen, a biologically-active dressing, inhibits protease activity and may be rationally applied with becaplermin to enhance applied growth factor effects. Both becaplermin and ORC/collagen are readily available to wound specialists, and they are now being used to promote therapeutic angiogenesis in the chronic wound. ■

REGRANEX® Gel (becaplermin)

Product description

REGRANEX® Gel actively stimulates angiogenesis and granulation tissue formation.

- Demonstrates biological activity similar to that of endogenous PDGF
- Promotes recruitment and proliferation of chemotactic cells, including monocytes and fibroblasts, necessary for stimulation of a variety of wound healing processes and aiding in the creation of granulation tissue
- Clinically proven to actively stimulate granulation tissue formation and enhance natural wound healing

Indications

REGRANEX Gel is indicated for the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond

Contraindications

REGRANEX Gel is contraindicated in patients with known neoplasms at the site of application or with known hypersensitivity to any component of this product (e.g., parabens). Erythematous rashes occurred in 2% of patients treated with REGRANEX Gel or placebo gel. REGRANEX Gel should not be used in wounds that close by primary intention.

Clinical trials

In 4 clinical trials, REGRANEX Gel was compared to placebo and to standardized good wound care to assess the incidence of wound closure and time required to complete healing. Of 922 patients studied, 478 received REGRANEX Gel or becaplermin 0.01%.

All patients had deep diabetic neuropathic ulcers that extended into the subcutaneous tissue or

ranged from 1.4 cm² to 1.5 cm².

In general, where REGRANEX Gel was associated with higher incidences of complete ulcer closure, differences in the incidence first became apparent after approximately 10 weeks and increased with continued treatment. In a 3-month follow-up period, in which no standardized regimen of preventive care was utilized, the incidence of ulcer recurrence was approximately 30% in all treatment groups, demonstrating that the durability of ulcer closure was comparable in all treatment groups (study 2). ■

REGRANEX GEL HAS BEEN CLINICALLY PROVEN TO ACTIVELY STIMULATE GRANULATION TISSUE FORMATION AND ENHANCE NATURAL WOUND HEALING

and have an adequate blood supply. When used as an adjunct to, and not a substitute for, good ulcer care practices including initial sharp debridement, pressure relief, and infection control, REGRANEX Gel increases the incidence of complete healing of diabetic ulcers.

beyond. All wounds had an adequate blood supply. Ninety-three percent of patients had foot ulcers, and 7% had ankle or leg ulcers. All ulcers were of at least 8 weeks' duration (median duration: 32 weeks). Ninety-five percent of ulcers were less than or equal to 10 cm² and median ulcer size

REGRANEX Gel and sharp debridement



According to DL Steed et al's 1996 study, sharp debridement alone can improve the incidence of complete wound closure in a clinical trial studying diabetic neuropathic ulcers. Importantly, the addition of sharp debridement to REGRANEX Gel therapy nearly tripled the incidence of completely healed wounds (>80%) when compared with debridement alone (25%). ■

SOURCE: REGRANEX (BECAPLERMIN) GEL 0.01%, PRODUCT INSERT: ORTHO-MCNEIL PHARMACEUTICAL, RARITAN, N.J., MARCH 1999.

PROMOGRAN™ Matrix

Product description

PROMOGRAN™ is a unique advanced wound care device comprised of a sterile, freeze-dried, bioresorbable, open-

absorbed by the body. Collagen is a natural structural protein found in all three phases of wound healing. In the presence of exudate, the PROMOGRAN Matrix transforms

and inactivating proteases in the wound environment, and it also directly binds growth factors and then sustain releases them back into the wound bed. By binding to matrix

ONE CAN THINK OF ORC/COLLAGEN AS A "SPONGE" THAT SOAKS UP AND INACTIVATES WOUND PROTEASES, THEREBY PROTECTING GROWTH FACTORS THAT THESE PROTEASES WOULD NORMALLY DEGRADE - CULLEN (2002).

pored matrix composed of 45% ORC and 55% collagen. Oxidized regenerated cellulose (ORC) is a plant material that has been chemically altered to be

into a soft, conformable, biodegradable gel, thus allowing contact with all areas of the wound. It binds to and protects growth factors by binding

metallo-proteases (MMPs), and growth factors, PROMOGRAN Matrix maintains a physiologically moist

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PROMOGRAN Matrix



Indications

PROMOGRAN Matrix is indicated for the treatment of exuding wounds including, but not limited to, diabetic, venous, and pressure ulcers.

Contraindications

PROMOGRAN Matrix is not indicated for wounds with active vasculitis, third-degree burns, or patients with known sensitivity to ORC or collagen. ■

SOURCE: PROMOGRAN WEB SITE

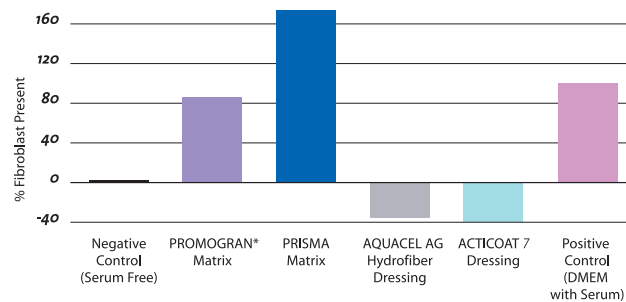
PRISMA™ Matrix uses low-dose silver to protect fibroblasts

Clinicians have known about the bactericidal properties of silver for many years. However, until 2005, only high-dose silver products such as Aquacel® AG and Acticoat™ 7 have been available. PRISMA™ Matrix fills the gap between these high-dose products that impair

fibroblasts in healing wounds while keeping bacteria away and products with no silver protection at all.

The graph shows the results of fibroblast growth in cell culture media which have been exposed to one dressing without silver and three different

dressings with silver. The first bar in the graph is the negative control – cell culture media without a nutritional source – shows a lack of cell growth. The rest of the samples in the study included a nutritional source, so any lack of growth in them is due to an alternate cause. The amount of cell growth (or lack thereof) may be attributed to the amounts of silver released into the media. The high-dose products show a significant reduction in the number of fibroblasts present. ■



SOURCE: ETHICON, INC

PRISMA™ Matrix

PRISMA™ Matrix, launched by Johnson & Johnson at the 2005 Symposium on Advanced Wound Care (SAWC), is similar to the flagship PROMOGRAN Matrix, with the added benefit of silver. Silver is a com-

mon and effective antimicrobial agent known to have bactericidal activity against more than 150 strains of clinically relevant bacteria. However, its action on cells is not specific, e.g., it is capable of damaging

host cells like fibroblasts, as well as bacterial cells. A unique feature of PRISMA Matrix is that it releases sufficient silver without causing damage to the host cells in vitro. ■

PRISMA MATRIX DELIVERS LOW LEVELS OF SILVER TO CONTROL BACTERIA WITHOUT DAMAGING HOST CELLS

PROMOGRAN™ Matrix *(continued from page 4)*

microenvironment at the wound surface, which is conducive to new tissue granulation, epithelialization, and rapid wound healing.

Clinical trials

Cullen et al (2002) conducted a study in which they looked at overall pro-

nal within 30 minutes. This data indicates that PROMOGRAN is able to protect PDGF in a degradative environment.

- Additional in vitro studies by Cullen et al of ORC/collagen's ability to protect other growth

bind to and sustain release PDGF over time.

- Approximately 81% of the bound PDGF is released from the PROMOGRAN Matrix (ORC/collagen) within three days under physiological conditions. This indicates that

20% OF ALL INFECTED WOUNDS EXHIBIT NO CLINICAL SIGNS OF INFECTION

teolytic activity in pooled human wound fluid obtained from a group of diabetic patients treated with either PROMOGRAN Matrix (ORC/collagen), plain gauze, or no dressing. Following are highlights of the findings:

- There was a significant reduction in MMP activity when the wound fluid was incubated with PROMOGRAN Matrix (ORC/collagen), decreasing to 6% of origi-

factors in the presence of different enzymes and combinations of enzymes have demonstrated that it can not only protect PDGF in the presence of plasmin and elastase, but also fibroblast growth factor (FGF), epidermal growth factor (EGF), and transforming growth factor beta (TGF-β).

- PROMOGRAN Matrix (ORC/collagen) can also

PROMOGRAN not only inactivates proteases and protects growth factors, but also binds and slowly releases active growth factors over a period of days.

- Therefore, PROMOGRAN Matrix may be useful in treating chronic wounds for protecting the activity of growth factors. ■

PRISMA Matrix



Clinical trials

PRISMA Matrix has been shown to provide significant reductions in bacterial counts in a standard in vitro assay of antimicrobial activity. The assay is the Log 10 reduction test. In this test, a solution containing a known amount of a particular strain of bacteria is placed into a test tube and a sample of the antimicrobial agent is added, in this case, a sample of PRISMA Matrix; the solution is stirred continuously and small aliquots are removed at specific time points after adding the product. Bacterial counts of the aliquots are measured and compared to the original counts to determine log reductions.

In this assay, PRISMA Matrix released sufficient amounts of silver ions to achieve 4-5 log reductions of common wound pathogens and antibiotic resistant bacteria within 1-2 hours. ■

SOURCE: ETHICON, INC

INTEGRA Bilayer Matrix Wound Dressing



INTEGRA Clinical Trial Highlights

■ According to a study conducted by Stern et al (1990), INTEGRA Dermal Regeneration Template achieves an intact dermis with no scar formation.

Following are highlights from a 2004 study conducted by Gottlieb et al:

- INTEGRA provides excellent coverage over exposed bone, tendon, cartilage, and joints. Of 166 instances of exposed internal structures that are ordinarily closed with flaps, INTEGRA closed 90% of them.
- In a study of 107 patients having 158 documented individual ulcers, 92% of patients healed completely by INTEGRA alone or with small subsidiary flaps (excluding poorly selected patients). ■

SOURCE: INTEGRA LIFE SCIENCES WEB SITE

MARC GOTTLIEB, MD, FACS, IS THE MEDICAL DIRECTOR OF NATIONAL HEALING'S WOUND HEALING CENTER AT ARIZONA HEART HOSPITAL. GOTTLIEB HAS BEEN WITH NATIONAL HEALING SINCE THE OPENING OF THE CENTER IN 1999. IN ADDITION TO HIS RESPONSIBILITIES AS MEDICAL DIRECTOR FOR NHC, GOTTLIEB IS ENGAGED IN A PRIVATE PRACTICE OF RECONSTRUCTIVE SURGERY AND HAND SURGERY.

INTEGRA™ Bilayer Matrix Wound Dressing

INTEGRA™ Bilayer Matrix Wound Dressing is an advanced wound care device comprised of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan and a semi-permeable polysiloxane (silicone) layer. The semi-permeable silicone membrane controls water vapor loss, provides a flexible adherent covering for the wound surface, and adds increased tear strength to the device. The collagen-glycosaminoglycan biodegradable matrix provides a scaffold for cellular invasion and capillary growth.

Once implanted, the dermal cells begin migrating into the matrix and establish a new vascular network. As healing progresses, the collagen (protein) in the INTEGRA

template is replaced by collagen organically produced by new dermal skin cells. Once the new dermal layer is formed, the INTEGRA silicone layer is removed. The INTEGRA collagen template biodegrades and is absorbed into the body, leaving new dermal skin. The healing process is completed by applying a thin epidermal autograft over the new dermal skin. Training through INTEGRA's official program is required prior to using INTEGRA Bilayer Matrix Wound Dressing.

Indications

- INTEGRA Bilayer Matrix Wound Dressing is indicated for the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers,

surgical wounds (donor sites/grafts, post-Mohs' surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), and draining wounds. The device is intended for one-time use.

- It is ideal for partial and full-thickness soft tissue trauma and chronic wounds
- It also offers excellent performance in deep donor sites.

Contraindications

- 3rd degree burns
- This device should not be used in patients with known sensitivity to bovine collagen or chondroitin materials. ■

SOURCE: INTEGRA LIFE SCIENCES WEB SITE

ACCORDING TO A STUDY CONDUCTED BY STERN ET AL (1990), INTEGRA DERMAL REGENERATION TEMPLATE ACHIEVES AN INTACT DERMIS WITH NO SCAR FORMATION.



OASIS®

Product description

The OASIS® Wound Matrix is a biologically derived extracellular matrix-based wound product that is compatible with human tissue. Unlike other collagen-based wound care materials, OASIS is unique because it is a complex scaffold that provides an optimal environment for a favorable host tissue response, a response characterized by restoration of tissue structure and function. OASIS is comprised of porcine-derived acellular small intestine submucosa (SIS). The OASIS Wound Matrix is indicated for use in all partial and full thickness wounds and skin loss injuries, as well as superficial and second-degree burns.

Clinical trials

Demling, Niezgodna et al (2004) conducted an interim analysis of a prospective, randomized, controlled, clinical trial being conducted to exam-

ine the effectiveness of SIS wound matrix in treating full-thickness venous leg ulcers. Neizgodna found that 71 percent of venous ulcers were healing at 12 weeks with SIS, compared to 46 percent with standard care, a significant group difference. The authors concluded that, in the subset of patients being analyzed, the SIS wound matrix showed a higher incidence of wound closure as compared to standard of care treatment.

Pre-clinical studies with SIS biomaterial repeatedly demonstrated the ability of SIS biomaterial to regenerate as host tissue, induce rapid capillary in-growth, be resistant to infection, and induce little or no immunologic

reaction. The mechanisms behind these physiological phenomena are beginning to be understood as inherent properties of the architecture and composition of the SIS biomaterial. (Etris et al, 2002) ■



OASIS

Indications

OASIS is used for the management of partial and full-thickness skin loss injuries including:

- Surgical wounds (donor sites/grfts, post-Mohs' surgery, post-laser surgery, podiatric wounds, wound dehiscence)
- Trauma wounds (abrasions, lacerations, second-degree burns, skin tears)
- Partial and full-thickness wounds
- Venous ulcers
- Diabetic ulcers
- Drainage wounds
- Pressure ulcers
- Chronic vascular ulcers

Contraindications

- OASIS is derived from a porcine source and should not be used in patients with known sensitivity to porcine material.
- OASIS is not indicated for use in third-degree burns. ■

SOURCE: HEALTHPOINT WEB SITE

Selected bibliography

Cullen B, Smith R, McCulloch E, Silcock D, Morrison L. (2002). Mechanism of action of PROMOGRAN, a protease modulating matrix, for the treatment of diabetic foot ulcers. *Wound Rep Reg.* 10:16-25. • Demling R, Niezgodna J, Haraway D, Mostow EN. (2004). Small intestinal submucosa wound matrix and full-thickness venous ulcers: preliminary results. *Wounds: a compendium of clinical research and practice.* 16(1): 18-22. • Gottlieb M, Furman J. (2004). Successful management and surgical closure of chronic and pathological wounds using Integra. *Journal of Burns & Surgical Wound Care,* (3)4. • Etris M, Cutshall WD, Hiles MC. (2002). A new biomaterial derived from small intestine submucosa and developed into a wound matrix device. *Wounds: a compendium of clinical research and practice.* 14(4):150-166. • Lee AR, Moon HK. (2003). Effect of topically applied silver sulfadiazine on fibroblast cell proliferation and biomechanical properties of the wound. *Archives of Pharmacol Research.* (26)10, 855-860 • Li WW, Li VW. (2003) Therapeutic angiogenesis for wound healing: new strategies using becaplermin and ORC/collagen. *Sixteenth Annual SAWC.* (15)9. Supplement 3S. • Ovington L, Cullen B. (2002). Matrix metalloprotease modulation and growth factor protection in wound healing. *Podiatry Today* Oct(Suppl): 2-13. • Steed DL, Donohoe D, Webster MW, Lindsley L. (1996). Effect of extensive debridement and treatment on the healing of diabetic foot ulcers. Diabetic Ulcer Study Group. *J Am Coll Surg.* 183:61-64. • Stern R, McPherson M, Longaker MT. (1990). Histologic study of artificial skin used in the treatment of full thickness thermal injury. *J Burn Rehabil.* 11:7-13.

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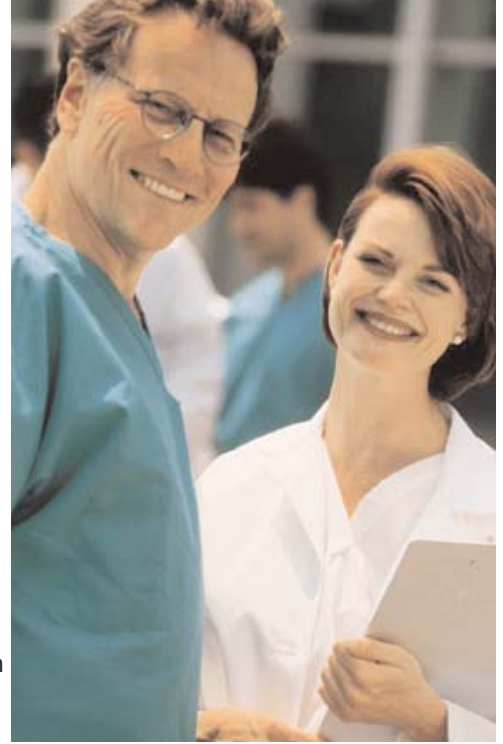
Working with a Wound Healing Center specializing in advanced therapies

Wound Healing Centers have dedicated, skilled physicians trained specifically in the use of advanced wound technologies. Not only are the Centers uniquely equipped to administer these therapies, they are also designed to help primary care physicians avoid upfront costs and the time-consuming training generally associated with advanced wound care. For example, by partnering with a Wound Healing Center in offering advanced wound

therapies, your practice will:

- Avoid upfront costs
- Avoid storage problems
- Provide access to clinicians with experience dealing with extensive wound population
- Ensure follow-up patient education
- Stay informed about

healing progress with regular reports from our Outcomes Disease Management System ■



CONSIDER REFERRING YOUR PATIENTS TO A WOUND HEALING CENTER FOR ADVANCED WOUND CARE IF:

- A wound persists for more than 30 days with conservative treatment
- Your patient has a wound and also has circulatory problems, diabetes, or is obese
- Your patient has a wound or suffers from chronic pain and has had radiation therapy in the past
- Your patient has had a recent revascularization procedure or has a questionable vascular supply
- You are considering surgical procedures



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