PROMOGRAN™
MATRIX FAMILY

PRODUCT
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# PROMOGRAN™ PROTEASE MODULATING MATRIX AND PROMOGRAN PRISMA™ WOUND BALANCING MATRIX

Systagenix™
An Acelity Company

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## PREFACE

The increasing prevalence of wounds that fail to heal with standard therapies has led to development of advanced wound dressings designed to target wound environments that can delay healing. Both PROMOGRAN™ Protease Modulating Matrix and PROMOGRAN PRISMA™ Wound Balancing Matrix help maintain a physiologically moist microenvironment that is conducive to granulation tissue formation, epithelialisation, and rapid wound healing. This document will provide the following:

- Introduction to PROMOGRAN™ Matrix and PROMOGRAN PRISMA™ Matrix
- Clinical literature review of PROMOGRAN™ Matrix and PROMOGRAN PRISMA™ Matrix
- Description of PROMOGRAN™ Matrix and PROMOGRAN PRISMA™ Matrix
- Science supporting PROMOGRAN™ Matrix and PROMOGRAN PRISMA™ Matrix
- Case Studies

## INTRODUCTION

Healthcare systems are being challenged to manage an increasing number of wounds that have failed to complete an orderly process of healing despite treatment with standard therapies. Factors contributing to these non-healing (chronic) wounds include aging populations, increasing prevalence of comorbid conditions (eg, diabetes, obesity) that can impair a patient's healing capability, and imbalances within the wound microenvironment.

Research into the pathophysiology of wound healing has provided insight into the distinctions between healing and non-healing wound environments. In an acute wound that achieves healing, there is an orderly transition from the repair processes that remove damaged process to those that lead to new tissue formation. The microenvironment of a chronic non-healing wound is characterised by a prolonged inflammatory phase, in which proteases (especially human neutrophil-derived elastase [HNE] and matrix metalloproteinases [MMPs]) degrade the growth factors and extracellular matrix required to transition to the proliferative phase of healing.

PROMOGRAN™ Matrix and PROMOGRAN PRISMA™ Matrix are advanced wound dressings composed of collagen and oxidized regenerated cellulose (ORC). PROMOGRAN PRISMA™ Matrix **(Figure 1)** has the added benefit of silver, a well-known antimicrobial agent.

**Figure 1.** PROMOGRAN PRISMA™ Matrix

## CLINICAL EVIDENCE REVIEW

Twelve randomised controlled trials (RCTs) have compared PROMOGRAN™ Matrix and/or PROMOGRAN PRISMA™ Matrix to standard care and reported favourable outcomes with use of the 2 matrix dressings (Table 1). A number of retrospective studies and case series have presented similar results.

**Table 1:** Key Clinical Evidence Supporting Use of PROMOGRAN™ Matrix/PROMOGRAN PRISMA™ Matrix

| Author | Study Type and Patients | Results/Conclusions |
|---|---|---|
| Veves A et al[1] (2002) | • A 12-week multicentre RCT involving DFU patients<br>• PROMOGRAN™ Matrix (n=138) vs saline-moistened gauze (n=138) | • More wounds achieved complete healing with PROMOGRAN™ Matrix, especially in wounds <6 months duration (45% vs 33%, $p$=0.056). |
| Vin F et al[2] (2002) | • A 12-week multicentre RCT involving VLU patients<br>• PROMOGRAN™ Matrix Wound Dressing + compression (n=37) vs Control (non-adherent dressing + compression; n=36) | • 47.6% more wounds (62% vs 42%, p=0.0797) were characterised as healing or improved (≥ 50% wound area reduction at week 12) in the PROMOGRAN™ Matrix + compression group than in the Control group.<br>• A significant reduction in wound areas was achieved in the PROMOGRAN™ Matrix + compression group compared to Control (54.4% vs 36.5%, $p$<0.0001). |
| Nisi G et al[3] (2005) | • A 6-week RCT involving pressure injury patients<br>• PROMOGRAN™ Matrix (n=40) vs Control (moist wound healing – vaseline gauze and hydropolymer patch; n=40) | • More patients with pressure injuries completely healed compared in the PROMOGRAN™ Matrix group compared to the Control group (90% vs 70%, respectively).<br>• The time to complete healing was shorter and more cost effective in the PROMOGRAN™ Matrix group (360 days overall hospitalisation vs 1164 days in the Control group). |
| Wollina U et al[4] (2005) | • A 2-week RCT involving chronic VLU patients<br>• PROMOGRAN™ Matrix + good ulcer care (n=30) vs Control (good ulcer care only; n=10) | • A significantly greater mean wound area reduction was achieved in the PROMOGRAN™ Matrix group compared to Control ($p$<0.05).<br>• Wounds allocated to the PROMOGRAN™ Matrix group reported a significant reduction in pain scores at week 2 (baseline mean pain score was 8.72 compared to 3.84 at week 2, $p$<0.05). |
| Lobmann et al[5] (2002) | • A single-blinded RCT measuring wound size reduction and biochemistry in DFU patients over an 8-day period<br>• PROMOGRAN™ Matrix (n=18) vs Control (good standard of wound care; n=15) | • Clinical data showed 16% vs 1.65% reduction in wound size in 8 days with PROMOGRAN™ Matrix vs Control.<br>• Wound fluid biochemistry data also indicated a more favorable environments in wounds to which PROMOGRAN™ Matrix was allocated. |

## CLINICAL EVIDENCE REVIEW (CONT.)

| Author | Study Type and Patients | Results/Conclusions |
|---|---|---|
| Kakagia DD et al[6] (2007) | • An 8-week RCT involving DFU patients<br>• PROMOGRAN™ Matrix (n=17) vs autologous growth factors (n=17) vs combination (PROMOGRAN™ Matrix + autologous growth factors) (n=17) | • PROMOGRAN™ Matrix was more effective at reducing ulcer size than autologous growth factors; however, the combination was significantly better than the other groups ($p$<0.001). |
| Lazaro-Martinez JL et al[7] (2007) | • A 6-week single centre RCT<br>• PROMOGRAN™ Matrix (n=20) vs Control (moist wound healing – standard wound care protocol; n=20) | • Significantly more wounds achieved complete healing with PROMOGRAN™ Matrix versus Control (63% vs 15%; $p$<0.03).<br>• Mean time to achieve healing was 23.3 days in the PROMOGRAN™ Matrix group compared with 40 days in the Control group ($p$<0.01). |
| Smeets R et al[8] (2008) | • A 12-week RCT involving VLU patients<br>• PROMOGRAN™ Matrix (n=17) vs Control (Hydrocolloid dressing; n=10) | • Wound fluid biochemistry data indicated a more favourable environment in wounds to which PROMOGRAN™ Matrix was allocated. |
| Ulrich D[9] (2011) | • An RCT measuring wound area reduction and biochemistry in DFU patients (Wagner Status 2-4) over a 12-week period<br>• PROMOGRAN™ Matrix (n=22) vs Control (Hydrocolloid dressing) | • There were significant differences ($p$<0.05) in wound area reduction on days 14 and 28 in the PROMOGRAN™ Matrix group vs Control.<br>• Wound fluid biochemistry data also indicated a more favorable environment in wounds to which PROMOGRAN™ Matrix was allocated. |
| Gottrup F et al[10] (2013) | • A 14-week multicentre RCT<br>• PROMOGRAN PRISMA™ Matrix (n=24) vs Control (best standard of care; n=15) | • Significantly more responders (≥50% reduction in wound area measured by the Margolis index) in the PROMOGRAN PRISMA™ Matrix group compared with the Control group (79% vs. 43%, respectively; $p$=0.035) at week 4.<br>• There were significantly fewer withdrawals due to infection in the PROMOGRAN PRISMA™ Matrix group compared with the Control group (0% vs. 31%, respectively; $p$=0.012).<br>• At week 14, the number of wounds completely healed was 52% vs 31%, respectively. |
| Kloeters et al[11] (2015) | • A 12-week RCT involving pressure injury patients<br>• PROMOGRAN™ Matrix (n=23) vs Control (TIELLE™ Dressing; n=10) | • Compared to the Control group, the PROMOGRAN™ Matrix matrix-treated pressure injury patients showed a significantly ($p$<0.05) faster healing rate. |
| Motzkau et al[12] (2011) | • An RCT involving chronic diabetic foot lesion patients<br>• PROMOGRAN™ Matrix (n=18) vs Control (standard good wound care; n=15) | • No differences in the mRNA levels of MMPs, IL-1β and TNF-α were observed between both groups. |

# PROMOGRAN™ MATRIX AND PROMOGRAN PRISMA™ MATRIX

## Product Descriptions

PROMOGRAN™ Matrix is an absorbent, open-pored, sterile, freeze-dried, hexagonal matrix composed of 45% ORC and 55% collagen.

PROMOGRAN PRISMA™ Matrix is a sterile, freeze-dried composite that consists of 44% ORC, 55% bovine collagen, and 1% silver/ORC of which 1/4 of the total weight of the silver-ORC is silver **(Figure 2)**. Thus, PROMOGRAN PRISMA™ Matrix contains 0.25% total silver.

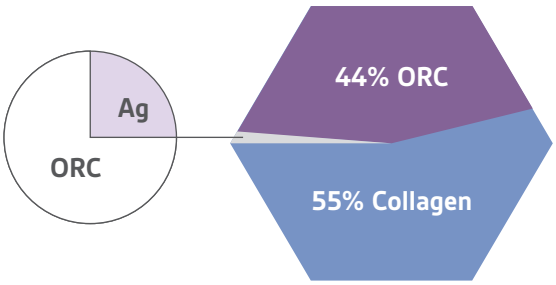


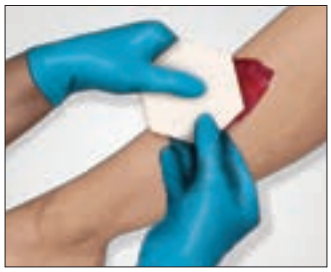

**Figure 2.** PROMOGRAN PRISMA™ Matrix

The PROMOGRAN PRISMA™ Matrix also has an increased density (approximately twice as much collagen and ORC) of collagen and ORC, compared to the PROMOGRAN™ Matrix. Depending on wound exudate levels, the collagen and ORC in the PROMOGRAN PRISMA™ Matrix may take a longer time to biodegrade in the wound.

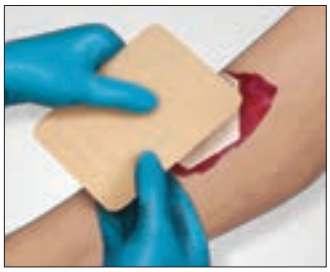
There are many similarities between the two matrix dressings. In the presence of fluid/exudate in the wound, both dressings transform into a soft, conformable, biodegradable gel that allows contact with all areas of the wound. In a wound with low or no exudate, the matrix dressing should be hydrated with saline solution to initiate the transformation of the dressing into a gel matrix. Both matrix dressings must be covered with a semi-occlusive or non-occlusive moist wound healing secondary dressing and, if needed, fixed to the skin with non-irritating tape **(Figure 3)**.

**Figure 3.** Dressing application: Matrix Dressing

**A.** Removal from package



**B.** Placement over wound



**C.** Application of secondary dressing

With the supervision of a healthcare professional, both may be used under compression bandages. Also, both can be cut with clean scissors to fit the wound shape or pre-moistened to form a gel that can be molded to fit the wound. Residual matrix from both dressings does not need to be removed during dressing changes.

## Indications for Use

The PROMOGRAN™ Matrix and PROMOGRAN PRISMA™ Matrix are intended for the management of exudating wounds including diabetic ulcers, venous ulcers, pressure injuries, ulcers caused by mixed vascular etiologies, full-thickness and partial-thickness wounds, donor sites and other bleeding surface wounds, abrasions, traumatic wounds healing by secondary intention, and dehisced surgical wounds.

### Contraindications

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

### Precautions

PROMOGRAN PRISMA™ Matrix may be used when visible signs of infection are present in the wound area only when proper medical treatment addresses the underlying cause. PROMOGRAN PRISMA™ Matrix is not intended to be a substitute for appropriate treatment of infection. Clinicians and healthcare professionals should be aware that there are very limited data on prolonged and repeated use of silver containing dressings, particularly in children and neonates.

## SCIENCE SUPPORTING PROMOGRAN™ MATRIX AND PROMOGRAN PRISMA™ MATRIX

**The following are summaries of *in vitro*, *in vivo*, and *ex vivo* studies supporting the use of ORC/collagen dressings.**

An *in vitro* study evaluated the effect of an ORC/collagen dressing on wound fluid taken from patients with diabetic foot ulcers (DFUs) with surface area >1cm² and duration >30 days.[13] Compared to control samples (wound fluid only), samples exposed to ORC/collagen showed a marked decrease in collagenase-like activity during the first hour of testing, an effect that was maintained for the rest of the 28 hour test. MMP-2 and MMP-9 levels were also significantly reduced in wound fluid incubated with ORC/collagen. Other tests demonstrated that ORC/collagen was more effective at scavenging oxygen free radicals than collagen/alginate or carboxymethyl-cellulose and that ORC was able to bind iron and zinc ions. Compared to ORC and collagen tested separately, the combination of ORC/collagen was able to bind and protect a significantly greater amount of growth factors in wound fluid. This study demonstrated that ORC/collagen was able to bind and inactivate proteases while also having no detrimental effect on growth factors in chronic wound fluid.[13]

Another preclinical study also showed that ORC/collagen has a positive role in promoting cell proliferation.[14] This study investigated the effects of ORC/collagen on fibroblast migration and proliferation *in vitro* and its effects on accelerated wound repair in a diabetic mouse model. *In vitro* results showed that ORC/collagen was found to promote fibroblast proliferation and cell migration. *In vivo* studies demonstrated that ORC/collagen significantly ($p<0.01$) accelerated diabetic (mouse) wound closure and resulted in a measurable improvement in the histological appearance of wound tissues.[14]

An *in vivo* rat model was used to investigate the effects of ORC/collagen on dermal and epidermal healing and growth factor concentration in acute wounds.[15] Full-thickness excision wounds were created, and each wound received either an ORC/collagen plus a hydrocolloid dressing or a hydrocolloid dressing alone. Results showed that rat wounds treated with ORC/collagen displayed a significantly ($p>0.05$) greater area of reepithelialization than wounds treated with hydrocolloid alone (Control). Furthermore, ORC/collagen treated wounds showed significantly higher levels of platelet-derived growth factor and increased dermal and epidermal insulin-like growth factor-I protein concentration compared to Control wounds. No significant differences were found in collagen morphology or deposition, neo-angiogenesis, or vascular endothelial growth factor concentration between both groups. The authors concluded that in this model ORC/collagen enhanced epidermal regeneration and increased specific growth factor concentrations, which had beneficial effects on acute wounds.[15]

### Case Studies

As with any case study, the results and outcomes should not be interpreted as a guarantee or warranty of similar results. Individual results may vary, depending on patient circumstances and conditions.

## CASE STUDY 1

Patient was a 70-year-old white male with a history of long standing diabetes mellitus and diabetic peripheral neuropathy who presented with a chronic, non-healing DFU on the right foot **(Figure 4A)**. Multiple treatments, debridements and antibiotic topical therapy were provided by other physicians but with no success. The DFU remained a non-infected full-thickness wound with hypergranulation on the first submetatarsal head with minimal exudate drainage. There was no gross deformity or bony involvement. A gastrocnemius equinus contracture was noted on patient's right lower extremity that increased the forefoot pressures. Upon vascular examination, patient had intact pedal pulses with adequate ankle brachial index and digital pressures, but there was loss of protective sensation. Management consisted of a full-thickness, sharp excisional debridement into and through the subcutaneous tissue, which removed any fibrotic tissue. Wound was debrided down to a healthy pink granular base, followed by application of PROMOGRAN PRISMA™ Matrix. An offloading boot was also provided to reduce the forefoot pressures. At 3 and 7 weeks post initiation of PROMOGRAN PRISMA™ Matrix **(Figures 4B and 4C)**, the DFU continued to heal. At 3 months, the DFU was fully closed **(Figure 4D)**.

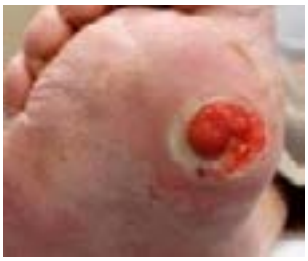


**Figure 4A.** DFU at presentation

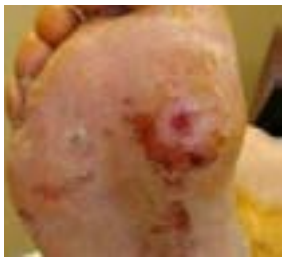


**Figure 4B.** 3 weeks post sharp excisional debridement and initiation of PROMOGRAN PRISMA™ Matrix, wound size was notably decreased

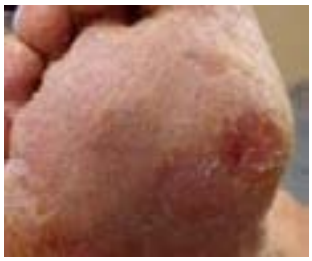


**Figure 4C.** At 7 weeks, DFU was nearly re-epithelialized

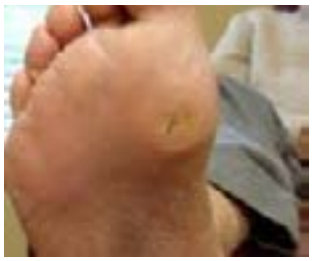


**Figure 4D.** After 3 months of PROMOGRAN PRISMA™ Matrix and offloading, DFU was closed

Patient data and photos courtesy of Dr. Lawrence A. DiDomenico

## CASE STUDY 2

Patient was an 81-year-old male with Type 2 diabetes and a recurrent venous leg ulcer of 11 months duration with failure to progress for approximately 6 months. This patient did have a remote history of a previous ulcer, which was able to achieve complete healing.

The patient presented with an inactive ulcer to his right lateral malleolus **(Figure 5A)**. The ulcer measured 3.5cm$^2$ with an approximate depth of 0.3cm and no apparent undermining. The surrounding skin was macerated, erythematous and excoriated with eczema and atrophe blanche. Exudate levels were moderate, and there was a slight odour present. He had previously been treated with a sodium carboxymethylcellulose primary wound dressing (Aquacel® EXTRA™, ConvaTec, Greensboro, NC) and had also treated the wound himself with Manuka honey. He was complaining of mild, intermittent pain.

The wound was dressed with a PROMOGRAN PRISMA™ Matrix. As a result of presenting symptoms, it was felt the use of silver in the dressing may prevent the development of any local infection. The dressing was prescribed for use twice weekly, in conjunction with modified compression therapy. The patient had been unable to tolerate high compression bandaging in the past. A thin knitted viscose secondary dressing (N-A™ Ultra Silicone Coated Knitted Viscose Dressing, Systagenix, an ACELITY Company, Gargrave, UK) was used with gauze padding. A steroid cream (Eumovate) and white soft paraffin were applied to protect the surrounding skin. Tracings and photographs were taken every 1-2 weeks.

## CASE STUDY 2 (CONT.)

Two weeks after commencing treatment, the wound bed appeared healthier, with granulation tissue visible at the base. The wound measured 2.5cm$^2$ in area, and depth had decreased to 0.2cm. Two weeks later, the wound appeared to be 100% granulating with no depth and an area of 1cm$^2$.

On the last recorded assessment, the wound was unchanged in area but had a slight depth again of 0.2cm **(Figure 5B)**. The wound remained healthy in appearance. He had also reduced the amount of compression during this time, which may have affected gauze padding. A steroid cream (Eumovate) and white soft paraffin were applied to protect the surrounding skin healing. Over the course of 6 weeks, the patient has made good progress towards healing with the use of a PROMOGRAN PRISMA™ Matrix in conjunction with compression therapy plus gauze padding, a steroid cream (Eumovate), and white soft paraffin applied to protect the surrounding skin.

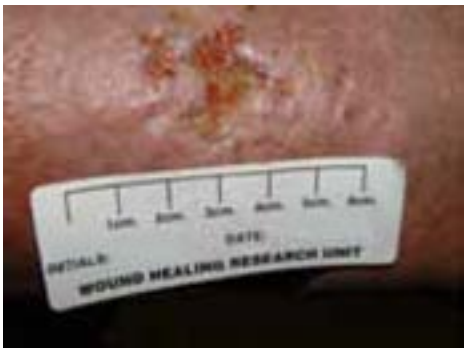



**Figure 5A.** Non-healing ulcer on right malleolus prior to treatment with the PROMOGRAN PRISMA™ Matrix

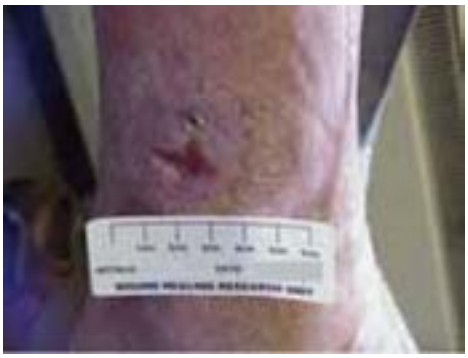


**Figure 5B.** Appearance after 3 weeks of treatment with the PROMOGRAN PRISMA™ Matrix

## CASE STUDY 3

The patient was a 59-year-old female hospitalised on January 23, 2010, with the diagnosis of non-healing left transmetatarsal amputation site. Past medical history was significant for chronic obstructive pulmonary disease, hypertenstion, hypothyroidism, renal failure requiring hemodialysis 3 times per week, and peripheral vascular disease. Past surgical history was significant for: right below the knee amputation, left femoral-popliteal bypass in December 2009 and a left transmetatarsal amputation in December 2009, due to non-healing toe wounds.

Upon admission, the left transmetatarsal amputation was debrided via pulse lavage and negative pressure wound therapy (NPWT, V.A.C.® Therapy, KCI, an ACELITY Company, San Antonio, TX) was initiated to prepare the wound for a split-thickness skin graft (STSG). On February 1, 2010, the patient underwent surgical debridement of the left transmetatarsal amputation and fourth metatarsal resection with placement of a STSG over the defect **(Figure 6A)**.

The donor site on the left lateral thigh measured 10cm x 7cm and was covered initially with a thin film dressing, which was left in place until post-operative day 5 and was changed and ordered to be changed weekly. On post-operative day 11, the donor site had become more exudative, requiring an increased frequency of dressing changes by the staff daily. The donor site was re-evaluated and found to have a gelatinous slough covering the base. The measurements remained the same from the initial harvest. The skin surrounding the donor site developed dermatitis **(Figure 6B)**.

The donor site was cleansed with antibacterial soap and normal saline, rinsed, and then patted dry with the application of skin prep to protect the surrounding skin. A PROMOGRAN PRISMA™ Matrix was applied over the donor site and covered with an adhesive hydropolymer foam dressing (TIELLE™ Hydropolymer Adhesive Dressing with LIQUALOCK™ Technology, Systagenix, an ACELITY Company, Gargrave, UK) **(Figure 6C)**. On postoperative day 14, the dressing was changed. There was an increase

in healthy granulation tissue, and new areas of re-epithelialization were noted. The surrounding dermatitis had also improved (Figure 6D).

## CASE STUDY 3 (CONT.)

On post-operative day 15, the surgeon evaluated the donor site, so the dressing was changed. The wound continued to improve with more epithelial islets noted **(Figure 6E)**. The PROMOGRAN PRISMA™ Matrix and the hydropolymer foam dressings were left in place and changed on postoperative day 17, prior to the patient's discharge to an extended care facility (Figure 6F).

The patient's donor site re-epithelialized completely by the next dressing change on postoperative day 20. The dressing maintained a moist wound environment without maceration of the peri-donor skin, and the improved exudate management with the combination of the PROMOGRAN PRISMA™ Matrix and the hydropolymer foam dressings helped the dermatitis resolve.

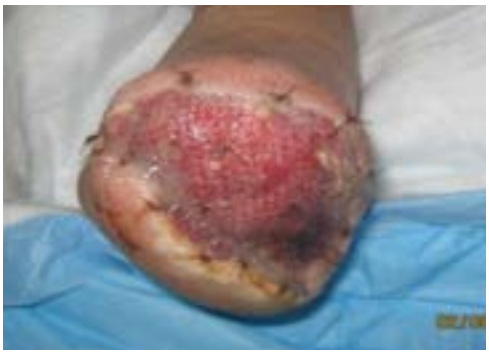


**Figure 6A.** STSG over wound

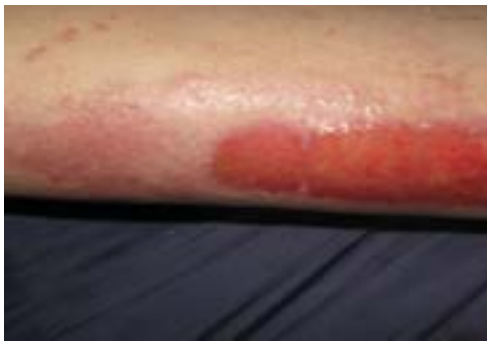


**Figure 6B.** Left lateral thigh donor site with dermatitis

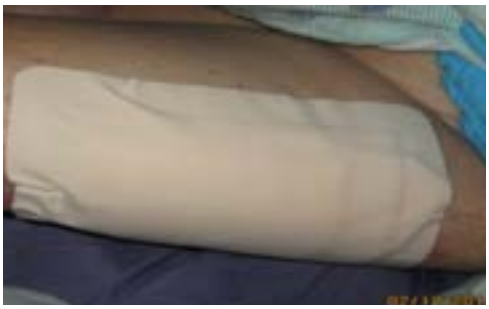


**Figure 6C.** Hydropolymer foam dressing applied over PROMOGRAN PRISMA™ Matrix, which covered the donor site

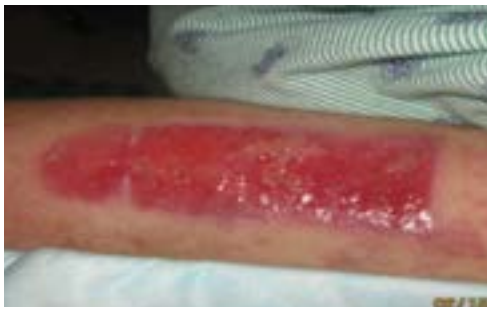


**Figure 6D.** Donor site post-operative day 14 after removing the PROMOGRAN PRISMA™ Matrix and hydropolymer foam dressings

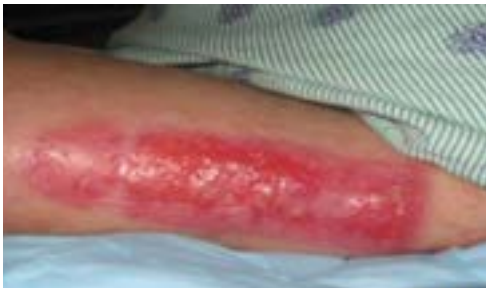


**Figure 6E.** Donor site postoperative day 15 after removal of PROMOGRAN PRISMA™ Matrix and hydropolymer foam dressings

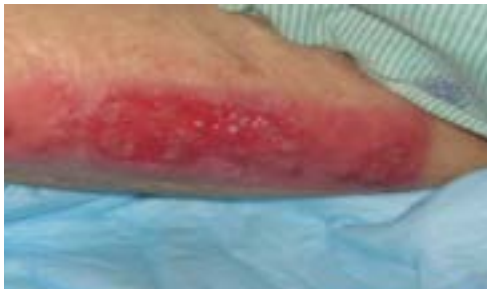


**Figure 6F.** Donor site postoperative day 17 at time of hospital discharge

## CASE STUDY 4

A 74-year-old male presented with a 2.5cm 27-month-old diabetic foot ulcer (DFU) on the bottom of the right foot **(Figure 7A)**. The patient had a history of diabetes mellitus and had previously undergone a transmetatarsal amputation.

Wound fluid and measurements were taken at wound presentation and every 2 weeks up to 14 weeks. A PROMOGRAN PRISMA™ Matrix was applied over the wound. Wound fluid was tested for elastase and matrix metalloprotease-9 (MMP-9) activity using either a fluorogenic substrate or immunocapture activity assay.

At presentation, MMP-9 activity was measured at 227.2 relative fluorescence units (RFU)/minute/ml and elastase measured at 568.6 RFU/minute/ml. At week 4, the wound showed a healthy pink granulation bed and slight enlargement of the wound **(Figure 7B)**. At week 12, MMP-9 and elastase activity measured 5.4 RFU/minute/ml and 277.1 RFU/minute/ml, respectively. This decrease in activity was calculated to a 97.6% reduction of MMP-9 activity and 51.3% reduction in elastase activity. By week 14, the wound was fully re-epithelialized **(Figure 7C)**.

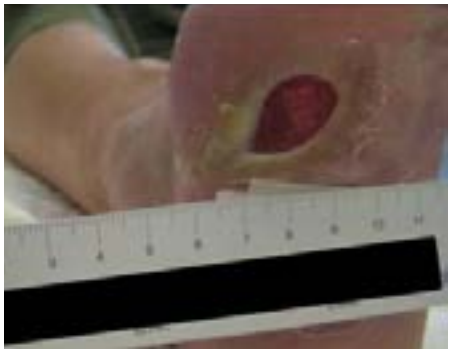


**Figure 7A.** Diabetic foot ulcer on bottom of right foot at presentation

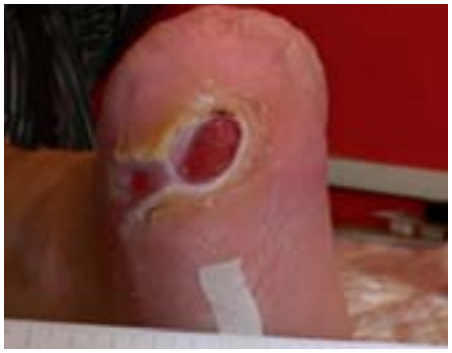


**Figure 7B.** Wound at week 4

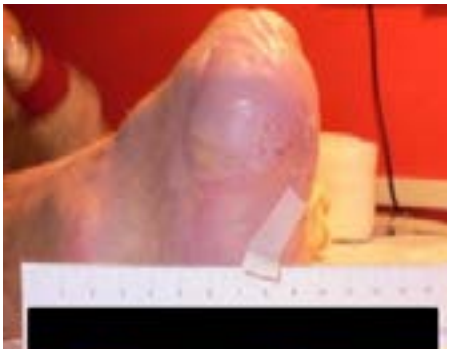


**Figure 7C.** Wound fully re-epithelialized at week 14

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