

# GRAFTJACKET®

regenerative tissue matrix (RTM)

# GRAFTJACKET® Xpress

flowable soft tissue scaffold (FSTS)

## Product Monograph

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## Preface

This monograph provides an overview of GRAFTJACKET® regenerative tissue matrix (RTM) and GRAFTJACKET® Xpress flowable soft tissue scaffold (FSTS) for wound healing.

Topics include:

- Introduction
- Detailed product descriptions
- Proprietary technology
- Medical evidence reporting results using GRAFTJACKET® RTM and GRAFTJACKET® Xpress FSTS to treat wounds
- Clinical case study
- US Regulatory indications, contraindications, safety testing, and classification (Appendix 1)

## Introduction

The body normally uses scar formation to close wounds. The result of the first phase of healing (hemostasis) is the development of a provisional fibrin scaffold or extracellular matrix (ECM) that supports and organizes initiation of the healing cascade. Because scar tissue developed by fibrosis does not have the same structure, function, or physiology as the original tissue,<sup>1</sup> a wound healed with excessive scar tissue does not have the same strength and flexibility as the original tissue. Madden and colleagues reported that, in their rat study, scar strength ranged between 70-80% of the strength of original tissue. In fact, clinically scar tissue is considered "a pathological state exhibiting suboptimal functional, biomechanical, and physiological characteristics compared to native connective tissue."<sup>1</sup>

A wide variety of engineered tissue products have been developed and used successfully in reconstructive surgery and for treatment of burns and complex wounds.<sup>2</sup> These bioengineered tissues both provide coverage and interact with the wound environment to stimulate the healing process.<sup>3</sup> Generally, these skin substitutes are classified by whether they contain living cells (cellular) or not (acellular) and further by their source material (biological tissue [human or animal], synthetic materials, or a composite of both).<sup>2</sup>

Composition and processing methodology determine the mechanisms of action of the various types of bioengineered tissues and the body's responses to the implants. A temporary resorbable, synthetic matrix or poorly processed ECM can trigger an inflammatory response that results in resorption of the components and scar formation. A cross-linked ECM can trigger a foreign body response resulting in encapsulation with potential for extrusion of the implant and an increased risk of infection.<sup>1</sup> Thus, while various bioengineered tissues stimulate the wound healing process through different mechanisms of action, their effectiveness is decreased by side effects related to their different processing technologies. An ideal solution would be a matrix that stimulates the body's healing processes with minimal inflammatory response and results in a better quality of tissue than that provided by scar formation.

The goal of regenerative healing is to provide a scaffold that functions as an ECM, which the body populates with its own cells and ultimately transforms into tissue that closely resembles what was lost.<sup>1</sup> Because human and animal cells trigger the body's specific immune response, an acellular matrix is preferable. However, an acellular matrix that is damaged or denatured during processing will trigger a non-specific immune response.

GRAFTJACKET® regenerative tissue matrix (RTM) and GRAFTJACKET® Xpress flowable soft tissue scaffold (FSTS) are examples of human acellular dermal matrices that – as a result of a proprietary production process – maintain the essential native structure of dermis.<sup>1</sup> Because GRAFTJACKET® RTM and GRAFTJACKET® Xpress FSTS are not cross-linked and do not contain cellular components, they are much less likely to trigger specific or non-specific immune response that results in either resorption coupled with scar formation or encapsulation with potential extrusion of the implant.<sup>1</sup> This was demonstrated in a preclinical primate study.<sup>4</sup> Correlation of these results to results in humans has not been demonstrated.

## GRAFTJACKET® RTM

GRAFTJACKET® RTM is an intact acellular human dermal matrix that has been processed using a patented method designed to minimize damage to the scaffold and, thereby, reduce potential inflammatory response by the patient.

## Proprietary Processing Technology

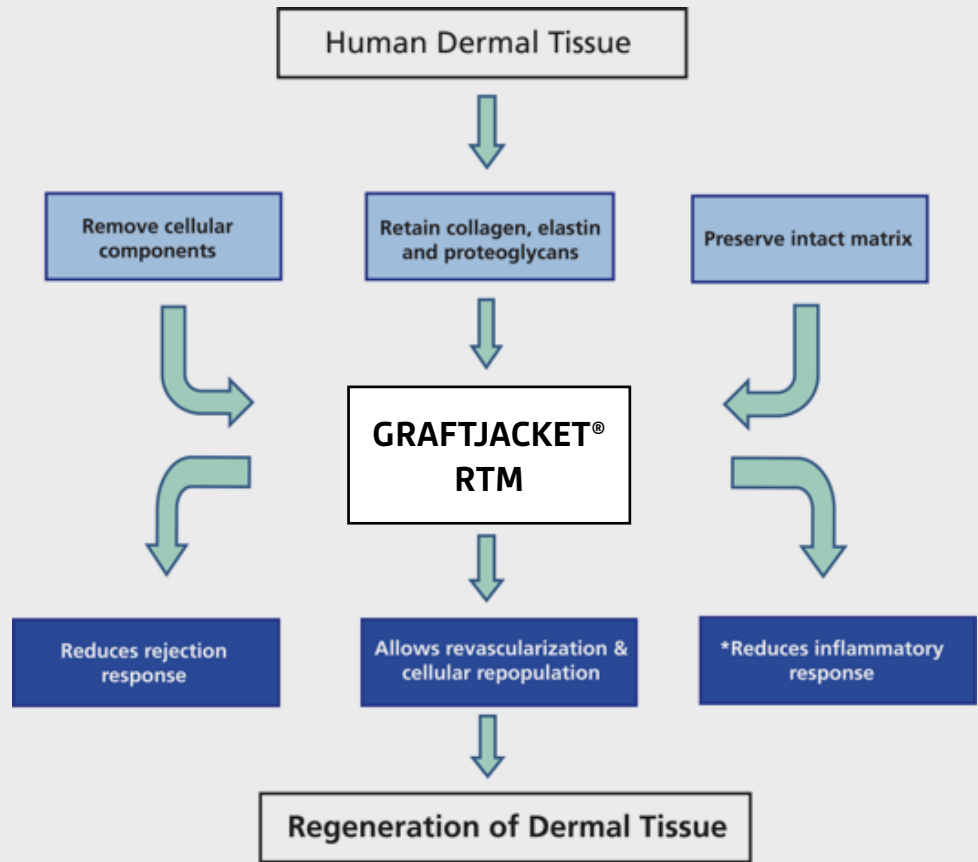
The proprietary processing methodology used to produce GRAFTJACKET® RTM results in an intact, acellular dermal matrix that retains natural biological components and allows the body to initiate its own tissue regeneration process. Derived from donated human dermis acquired with comprehensive donor screening and consent, GRAFTJACKET® RTM undergoes a proprietary aseptic process designed to remove cells and preserve matrix structure (Figure 1):

1. Epidermis and cells are removed in an aseptic process
  - Absence of cells reduces potential for host immune response
  - Structure of the matrix, including the vascular channels, is retained
2. Matrix is freeze-dried to remove moisture while preserving natural biologic composition
  - Care is taken to prevent formation of ice crystals, thus minimizing damage to the matrix which might trigger an inflammatory response
  - Preservation of the structural composition provides a scaffold for cell repopulation and revascularization

**NOTE:** Appendix 1 contains US Regulatory information for GRAFTJACKET® RTM, including Indications for Use, Contraindications, donor tissue safety testing, and regulatory classification.

**Figure 1.** GRAFTJACKET® RTM Processing Steps

\*Note: A primate study shows that the inflammatory process is reduced.<sup>4</sup> Correlation of these results to results in humans has not been demonstrated.



As demonstrated in Figure 1 the goal of this proprietary process is to remove elements that could trigger a specific rejection or non-specific inflammatory response in the patient's body and to maintain the components and structure needed to facilitate repopulation of the matrix with host cells. Findings in a preclinical primate study demonstrated that the foreign body inflammatory response was not activated by GRAFTJACKET® RTM, which resulted in tissue regeneration instead of tissue repair and scar tissue formation.<sup>4</sup>

## GRAFTJACKET® RTM Composition and Incorporation

The biological and structural components of GRAFTJACKET® RTM consist of the components of native dermis, including collagen matrix (predominantly types I and III), glycosaminoglycans (eg, hyaluronan, chondroitin sulfate, heparan sulfate) and glycoproteins. The fenestrated surface of the matrix has an intact basement membrane that contains type IV collagen, laminin and other glycoproteins, as well as less abundant nonstructural collagens (Figure 2).

Figure 2 illustrates the structural integrity of the matrix, which can be secured by sutures or staples. When placed into a sharply debrided

wound bed, the thin profile of GRAFTJACKET® RTM conforms to the wound, while fenestration allows fluid to escape.

After placement, GRAFTJACKET® RTM provides a template that facilitates incorporation into the body. The first step in wound repair is creation of the ECM, which is provided by the implanted matrix. Host fibroblasts migrate into the scaffold, multiply and deposit new collagen. Other cells (including endothelial cells) are recruited from surrounding tissue as the tissue regeneration process continues. As illustrated in the lower portion of Figure 2, the retained vascular channels in GRAFTJACKET® RTM also facilitate the inosculation process by which existing blood vessels communicate with vascular channels in the matrix, enabling initial revascularization. Over time new blood vessels also develop in the matrix through the process of angiogenesis. Because the patient's own cells repopulate the matrix, the matrix is ultimately remodeled into the patient's dermal tissue.

The GRAFTJACKET® RTM scaffold supports relatively quick revascularization.<sup>5</sup> In a study of full-thickness burns, GRAFTJACKET® RTM was incorporated in 5–7 days.<sup>5</sup>

## Benefits of GRAFTJACKET® RTM

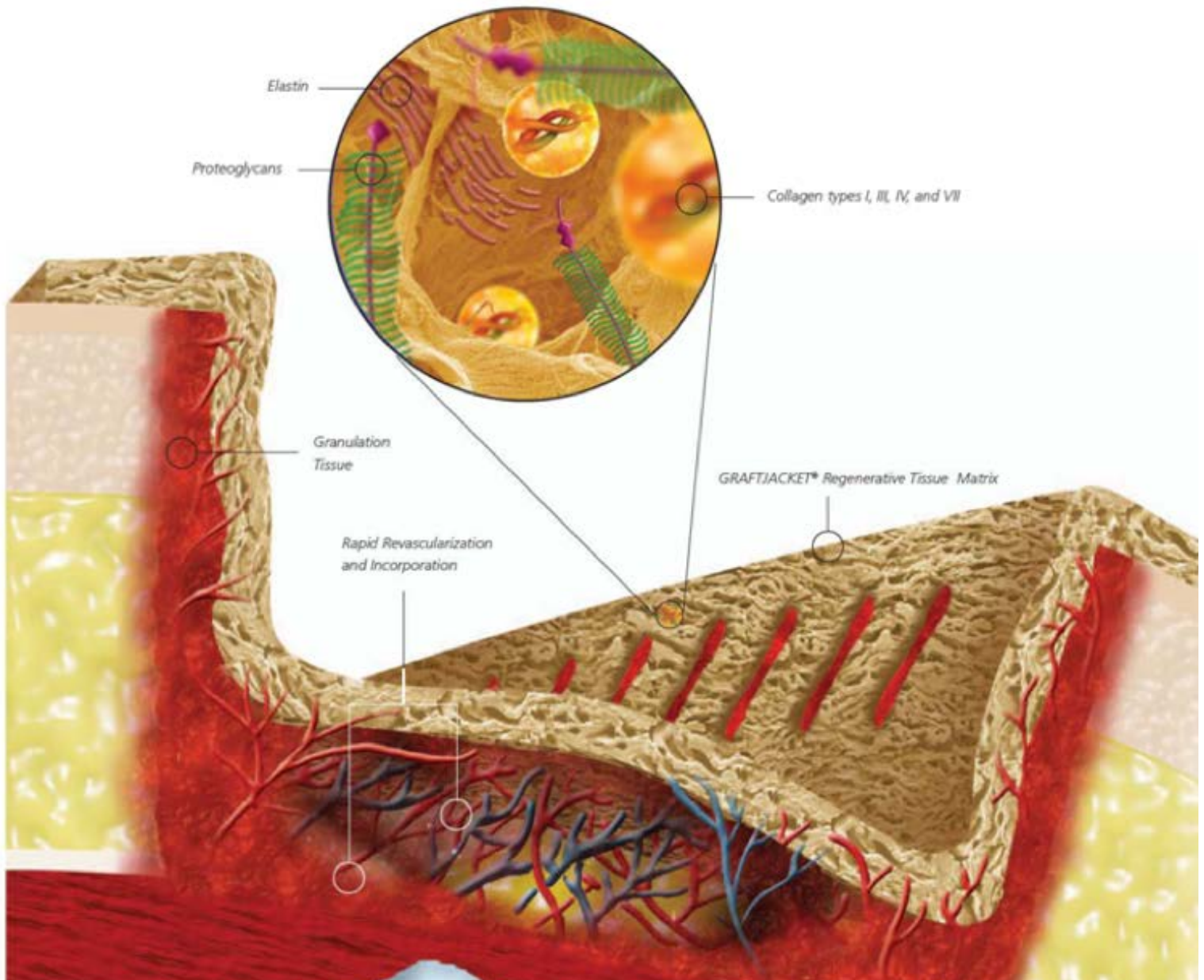
Unlike scar formation, use of GRAFTJACKET® RTM results in like-for-like replacement of missing dermal tissue.<sup>1,4</sup> The body populates the scaffold with its own cells and ultimately transforms into tissue that closely resembles what was lost.<sup>4</sup>

Other advantages include:

- No donor-site wound.
- Potential reduction in the use of autograft skin and need for flap repair.<sup>6</sup>
- In most cases, a single application of GRAFTJACKET® RTM has been reported in studies to be effective on diabetic foot wounds classified by UT Grading System 1 - 3, including partial-thickness and full-thickness wounds penetrating into tendon or bone.<sup>7,8</sup>
- Favorable outcomes have been shown in patients with significant co-morbidities such as diabetes, neuropathy, infection, and obesity.<sup>8</sup>
- Antibiotics may be added to GRAFTJACKET® RTM during rehydration.<sup>9</sup>

**Figure 2.** GRAFTJACKET® RTM Schematic

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## GRAFTJACKET® Xpress FSTS

GRAFTJACKET® Xpress FSTS is micronized (powdered) human dermis (GRAFTJACKET® RTM) that is rehydrated prior to use.

### Proprietary Processing Technology

Processing GRAFTJACKET® Xpress FSTS starts with the two steps used to produce GRAFTJACKET® RTM then adds a third step:

1. Epidermis and cells are removed in an aseptic process
2. Matrix is freeze-dried to remove moisture while preserving natural biologic composition
3. Matrix is then cryofractured to produce the micronized GRAFTJACKET® Xpress FSTS

**NOTE:** Appendix 1 contains US Regulatory information for GRAFTJACKET® Xpress FSTS, including Indications for Use, Contraindications, donor tissue safety testing, and regulatory classification.

### GRAFTJACKET® Xpress FSTS Composition and Incorporation

Micronized GRAFTJACKET® Xpress FSTS contains the same biologic components as GRAFTJACKET® RTM. When rehydrated according to manufacturer's instructions with sterile normal saline (0.9% sodium chloride), the flowable nature of GRAFTJACKET® Xpress FSTS makes it suited for placement into wounds that are deep or have areas where tunnels and/or undermining is present (Figure 3).<sup>10</sup>



(Image courtesy of Steven Brigido, DPM and David Armstrong, DPM)

**Figure 3.** Placement of GRAFTJACKET® Xpress FSTS into a Tunneling Wound

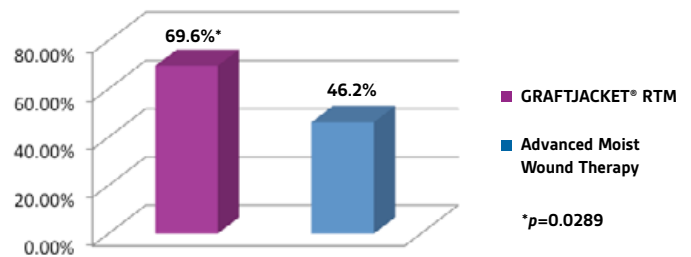
### Benefits of GRAFTJACKET® Xpress FSTS

- Easy to prepare and apply.<sup>11</sup>
- Conforms to and has maximum contact with difficult wound surface areas.<sup>11</sup>
- Has resulted in successful closure of deep wounds and wounds with sinus tracts and undermining.<sup>11</sup>

## GRAFTJACKET® RTM and GRAFTJACKET® Xpress FSTS Clinical Evidence Summary

Randomized controlled trials (RCTs) and retrospective studies (summarized below and in Table 1) support positive clinical outcomes using a single application of GRAFTJACKET® RTM to treat full-thickness lower extremity wounds. Results from a retrospective study of GRAFTJACKET® Xpress FSTS used to treat complex tunneling diabetic foot ulcers also showed that a single application in conjunction with off-loading was sufficient to achieve complete healing.

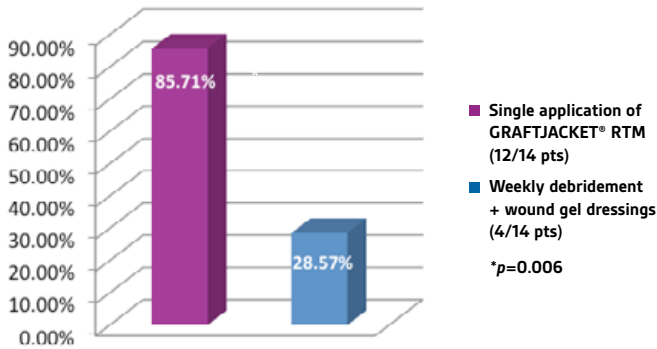
- In a multicenter RCT, the researchers reported prospective data from 11 sites that compared GRAFTJACKET® RTM to advanced moist wound care (control group treatments included: alginates, foams, hydrocolloids, and hydrogels) in treating DFUs.<sup>7</sup> Forty-six patients randomized to the study group received a single GRAFTJACKET® RTM application. Thirty-nine patients in the control group were treated with advanced moist wound therapy. Significantly more patients achieved complete healing, defined as 100% epithelialization without drainage, by the end of the study period in the GRAFTJACKET® RTM group (32/46 patients; 69.6%) versus the control group (18/39 patients; 46.2%,  $p=0.0289$ ) (Figure 4).



**Figure 4.** Percent of Patients With Complete Wound Closure in 12 Weeks<sup>7</sup>

The Kaplan-Meier survivorship analysis reported a significantly higher ( $p=0.015$ ) non-healing rate for the control group. After adjusting for baseline ulcer size as a significant covariate ( $p=0.0194$ ), the authors reported that the non-healing rate was still significantly higher ( $p=0.0233$ ) for the control group while the odds of healing was approximately two times higher for GRAFTJACKET® RTM patients. There was no significant difference between groups for mean time to complete healing (GRAFTJACKET® RTM =5.7 weeks v. control= 6.8 weeks). According to the authors, the study supports the use of a single GRAFTJACKET® RTM application "as an effective treatment of diabetic, neuropathic ulcers."<sup>7</sup>

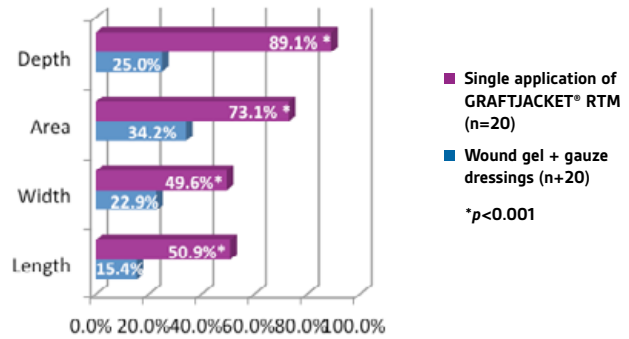
- In a single-site RCT, the study evaluated the effectiveness of a single GRAFTJACKET® RTM application compared to weekly sharp debridement with wound gel dressings (control group).<sup>12</sup> All 28 patients had non-infected, full-thickness (Wagner Grade 2), lower extremity wounds of > 6 weeks duration and completed the 16-week study. Significantly more GRAFTJACKET® RTM-treated patients achieved complete wound healing compared to control patients: GRAFTJACKET® RTM, 12/14 (85.71%) vs. Control, 4/14 (28.57%),  $p=0.006$  (Figure 5).



**Figure 5.** Percent of Patients With Complete Wound Closure in 16 Weeks<sup>12</sup>

Statistical significance ( $p \leq 0.001$ ) favoring GRAFTJACKET® RTM was achieved for final ulcer area, depth, and volume reduction as well as for number of wounds healed. On average, GRAFTJACKET® RTM wounds also healed sooner than control group wounds: 11.92 vs. 13.5 weeks, respectively, although the difference was not significant. The author concluded that GRAFTJACKET® RTM is a safe and effective treatment for lower extremity wounds, regardless of location or depth.<sup>12</sup>

- In a single site RCT, 40 diabetic patients with full-thickness lower extremity wounds were randomized to receive debridement followed by either a single application of GRAFTJACKET® RTM (with mineral oil-soaked fluff compressive dressings) or control therapy (Curasol® wound gel with gauze dressings).<sup>13</sup> All wounds had persisted without epithelialization for at least six weeks and were > 1cm<sup>2</sup> in size. Both groups had weekly evaluations for four weeks after treatment. At four weeks, wounds treated with GRAFTJACKET® RTM (n=20), compared to those treated with Control (n=20), showed significantly greater reductions in length, width, area, and depth, respectively (Length: 3.4mm vs 1.0mm,  $p < 0.001$ ; Width: 2.3mm vs 1.0mm,  $p < 0.001$ ; Area: 1.5cm<sup>2</sup> vs 0.5cm<sup>2</sup>,  $p = 0.006$ ; and Depth: 1.9mm vs 0.4mm,  $p < 0.001$ ). Consequently, percent of wound closure at four weeks also significantly favored wounds treated by GRAFTJACKET® RTM compared to the Control, respectively (Length: 50.9% vs 15.4%,  $p < 0.001$ ; Width: 49.6% vs 22.9%,  $p < 0.001$ ; Area: 73.1% vs 34.2%,  $p < 0.001$ ; Depth: 89.1% vs 25.0%,  $p < 0.001$ ) (Figure 6).<sup>13</sup>



**Figure 6.** Percent of Wound Closure in 4 Weeks<sup>13</sup>

- In a multicenter retrospective study of outcomes with GRAFTJACKET® RTM on DFUs,<sup>8</sup> the authors reviewed records at four sites and evaluated 75 diabetic patients with 100 chronic, full-thickness lower extremity wounds. Patients had multiple co-morbidities, and 47 of 100 wounds were classified as Grade 3 (having exposed bone or joint) according to the University of Texas (UT) Wound Classification System.<sup>14</sup> In addition, 72% of the Grade 3 wounds were both infected and ischemic. The overall healing rate was 91%. For all wounds, mean times to matrix incorporation, 100% granulation, and complete healing were  $1.5 \pm 0.90$ ,  $5.1 \pm 3.5$ , and  $13.8 \pm 8.8$  weeks, respectively. The safety profile (no matrix-related adverse events) and high healing rate in this retrospective study support use of a single application of GRAFTJACKET® RTM to treat these complicated wounds.<sup>8</sup>

- An early retrospective study evaluated the effectiveness of GRAFTJACKET® RTM for the treatment of diabetic patients with UT grade 2A foot wounds.<sup>15</sup> Data from 17 consecutive patients treated at a wound care center were analyzed to determine time to complete wound closure and proportion of wounds healed within the 20-week evaluation period. Treatment consisted of debridement, a single application of GRAFTJACKET® RTM, and use of moisture-retentive dressings until complete epithelialization. Average wound size was  $4.5 \pm 3.2$ cm<sup>2</sup> and average duration prior to treatment was  $29.8 \pm 22.4$  weeks. During the study period, 14 of 17 (82.4%) wounds healed in a mean time of  $8.9 \pm 2.7$  weeks. There were no product-related complications during the study. The authors concluded that the acellular matrix dressing “may be a useful adjunct to appropriate DFU care for deep, non-infected, non-ischemic wounds.”<sup>15</sup>

- A single-site retrospective study reported the use of GRAFTJACKET® Xpress FSTS in treatment of 12 patients with complex tunneling diabetic foot ulcers for a 12-week period.<sup>11</sup> Patients had full-thickness, non-infected sinus tract wounds (defined as those with a depth greater than length and width) and received a single 2cc placement of GRAFTJACKET® Xpress FSTS post wound debridement. All patients

also received offloading via an instant total contact cast until the wound was considered healed for 2 weeks. Initial average baseline wound area was  $342.7 \pm 234.0\text{mm}^2$  with wound depth of  $13.8 \pm 5.9\text{mm}$ . At the end of 12 weeks 10/12 pts (83.3%) achieved complete wound healing (100% epithelialization without drainage). The average time to complete healing was  $8.5 \pm 2.0$  weeks (slowest healing time was 11 weeks). The average time to 100% depth reduction for complete healers was  $7.8 \pm 2.2$  weeks. At the end of the study period two patients (who were non compliant with offloading) had 95% and 98% closure rates with 99% reduction of volume. All patients had 50% reduction in wound depth within first 14 days. The authors noted that compliance with offloading until graft incorporation is necessary, since ambulation pressure can extrude the graft from the sinus tract. Based on study results they conclude that use of GRAFTJACKET® Xpress FSTS "supports neo-subcutaneous tissue formation and allows the body to rapidly repair these wounds."<sup>11</sup>

The following summarizes literature associated with use of GRAFTJACKET® RTM and GRAFTJACKET® Xpress FSTS since their inception.

- A case series reported the use of GRAFTJACKET® regenerative tissue matrix (RTM) in conjunction with negative pressure wound therapy (NPWT) on 11 patients with lower extremity and trunk wounds.<sup>16</sup> Treatment consisted of sharp debridement and placement of GRAFTJACKET® RTM with the reticular layer facing the wound bed and secured with staples to the wound margin. Bacitracin and a nonadherent layer (ADAPTIC™, Systagenix Wound Management, Gatwick UK) covered the GRAFTJACKET® RTM and NPWT was applied as a bolster at -125mmHg continuous for 1-2 weeks. After NPWT discontinuation, gauze dressings moistened with mineral oil were used to cover the GRAFTJACKET® RTM, with dressing changes occurring every 1-2 days. Patient treatments were successful with follow up ranging from 1 week to 6 months. Two patients developed an infection, one of which resulted in partial graft loss and required reapplication of GRAFTJACKET® RTM and NPWT. All wounds achieved complete healing, and all but one patient received a single application of GRAFTJACKET® RTM.<sup>16</sup>
- A 3-patient case series evaluated the use of GRAFTJACKET® Xpress FSTS in conjunction with GRAFTJACKET® RTM on lower extremity wounds.<sup>17</sup> Patients received antibiotics and underwent debridement prior to treatment. Treatment consisted of application of 10cc of GRAFTJACKET® Xpress FSTS into the deep tunneling wound and subsequent placement GRAFTJACKET® RTM, which was either sutured or stapled in place. A non-adherent dressing was placed over the GRAFTJACKET® RTM covering the entire wound bed. No complications were reported throughout the course of treatment. Follow up ranged from 2 weeks to 3 months. Two of the three patients achieved wound healing within 6 weeks and the remaining patient achieved wound healing within 3 months.<sup>17</sup>

**Table 1.** Literature Review of GRAFTJACKET® RTM and GRAFTJACKET® Xpress FSTS Studies

| Author   | Study Type  | Patients  | Results/Conclusions  |
|--|---|---|--|
| Reyzelman A et al <sup>7</sup> (International Wound Journal, 2009)<br><br>According to the authors, "This study supports the use of single-application AM therapy [GRAFTJACKET® RTM] as an effective treatment of diabetic, neuropathic ulcers." | Multicenter RCT (12 weeks) comparing single application of Acellular Matrix (AM) (GRAFTJACKET® RTM) to Standard of Care therapies (Control) | 86 patients with DFUs (41/46 patients in AM group completed the study; 37/39 patients in the control group completed the study) | <ul style="list-style-type: none"> <li>• Significantly more AM patients achieved complete healing*: AM, 32 of 46 pts (69.6%) vs. Control, 18 of 39 pts (46.2%); <math>p=0.0289</math>. *Complete healing defined as 100% epithelialization without drainage</li> <li>• Odds of healing in AM group were 2.7 times higher than in control group</li> <li>• Mean healing time: AM, 5.7 weeks vs. Control, 6.8 weeks</li> <li>• Non-healing rates for patients completing the study: AM, 14 of 46 pts (30.4%) vs. Control, 21 of 39 pts (53.9%)</li> <li>• Kaplan-Meier survivorship analysis presented a significantly higher non-healing rate for the control group (<math>p=0.0075</math>)</li> <li>• After adjusting for initial ulcer size, the non-healing rate between groups was significantly higher for the control group (<math>p=0.0233</math>) and odds of healing was 2 times higher in AM group</li> </ul> |



**Table 1. (cont.)** Literature Review of GRAFTJACKET® RTM and GRAFTJACKET® Xpress FSTS Studies cont.

| Author   | Study Type   | Patients  | Results/Conclusions   |
|--|--|---|---|
| Brigido SA <sup>12</sup><br>(International Wound Journal, 2006)  | Prospective, single-site, RCT (16 weeks) to evaluate effectiveness of GRAFTJACKET® RTM on chronic, non-healing lower extremity wounds  | 28 patients with full-thickness, non-infected wounds of at least six weeks' duration were treated with sharp debridement and randomized to: <ul style="list-style-type: none"> <li>• Single application of GRAFTJACKET® RTM plus mineral-oil-soaked fluff compression dressing (n=14)</li> <li>• Control treatment of wound gel with gauze dressings (n=14)</li> </ul>  | <ul style="list-style-type: none"> <li>• All patients had Wagner Grade 2 wounds and completed the 16-week study</li> <li>• By end of study significantly more GRAFTJACKET® RTM patients (12 of 14, 85.71%) achieved complete wound closure compared to Control patients (4 of 14, 28.57%) (<math>p=0.006</math>)</li> <li>• Statistical significance (<math>p \leq 0.001</math>) was reported favoring GRAFTJACKET® RTM for final ulcer area, depth, volume and number of wounds healed</li> <li>• On average GRAFTJACKET® RTM wounds healed sooner than Control wounds: 11.92 vs. 13.5 weeks</li> </ul>  |
| Brigido SA et al <sup>13</sup><br>(Orthopedics, 2004)<br>The authors state that<br><br>"After 1 month of treatment, preliminary results demonstrate that this novel tissue matrix promotes faster healing at a statistically significant rate over conventional treatment."  | Prospective, single-site, RCT (4 weeks) to evaluate effectiveness of one application of GRAFTJACKET® RTM vs conventional therapy<br><br>Endpoints included average wound reduction per week (millimeters), percent closure at four weeks, and average number of applications   | 40 diabetic patients with full-thickness, non-infected wounds of at least six weeks' duration and $>1\text{cm}^2$ were debrided and randomized to: <ul style="list-style-type: none"> <li>• One application of GRAFTJACKET® RTM (n=20) or</li> <li>• Control (n=20) (conventional therapy using Curasol® wound gel with gauze dressings and standardized off-loading)</li> </ul>  | <ul style="list-style-type: none"> <li>• Average starting wound area was <math>9.7\text{cm}^2</math></li> <li>• Average reduction in wound measurements per week significantly favored GRAFTJACKET® RTM vs. Control (respectively) <ul style="list-style-type: none"> <li>- Length: 3.4mm vs 1.0mm, <math>p&lt;0.001</math></li> <li>- Width: 2.3mm vs 1.0mm, <math>p&lt;0.001</math></li> <li>- Area: <math>1.5\text{cm}^2</math> vs <math>0.5\text{cm}^2</math>, <math>p=0.006</math></li> <li>- Depth: 1.9mm vs 0.4mm, <math>p&lt;0.001</math></li> </ul> </li> <li>• The percent of wound closure at four weeks significantly favored GRAFTJACKET® RTM <ul style="list-style-type: none"> <li>- Length: 50.9% vs 15.4% (<math>p&lt;0.001</math>)</li> <li>- Width: 49.6% vs 22.9% (<math>p&lt;0.001</math>)</li> <li>- Area: 73.1% vs 34.2% (<math>p&lt;0.001</math>)</li> <li>- Depth: 89.1% vs 25.0% (<math>p&lt;0.001</math>)</li> </ul> </li> </ul> |
| Winters C et al <sup>8</sup> (Advances in Skin and Wound Care, 2008)<br><br>The authors concluded that "the absence of matrix-related complications, in addition to the relatively high rate of wound healing in this complex patient population, indicates that the matrix is a safe treatment option for more complicated, diabetic lower extremity wounds." | Multicenter (4 sites) Retrospective Study using acellular dermal matrix (GRAFTJACKET® RTM) to treat 100 chronic, full-thickness lower extremity wounds   | 75 diabetic patients with 100 wounds on: <ul style="list-style-type: none"> <li>• Foot (86)</li> <li>• Ankle (8)</li> <li>• Lower extremity (6)</li> </ul>  | <ul style="list-style-type: none"> <li>• First multicenter study of GRAFTJACKET® RTM and first to include UT Grade 3 wounds with exposed bone or joint (72% of these were both infected and ischemic)</li> <li>• Overall healing rate was 91%</li> <li>• For all wounds, the mean times to matrix incorporation, 100% granulation, and complete healing* were <math>1.5 \pm 0.90</math> weeks, <math>5.1 \pm 3.5</math> weeks, and <math>13.8 \pm 8.8</math> weeks, respectively</li> <li>*Complete healing defined as 100% epithelialization without drainage</li> </ul>   |
| Martin BR et al <sup>15</sup> (International Wound Journal, 2005)  | Single-site Retrospective Study evaluating use of an acellular matrix (GRAFTJACKET® RTM) to treat diabetic foot wounds. Endpoints included time to closure and number of diabetic foot wounds achieving complete closure in 20 weeks   | 7 consecutive diabetic patients with UT grade 2A neuropathic foot wounds treated with surgical debridement and a single application of the acellular matrix   | <ul style="list-style-type: none"> <li>• Average wound size was <math>4.6 \pm 3.2\text{cm}^2</math></li> <li>• Mean wound duration prior to treatment was <math>29.8 \pm 22.4</math> weeks</li> <li>• During the 20-week study period, 14 of 17 (82.4%) wounds healed in a mean <math>8.9 \pm 2.7</math> weeks</li> </ul>   |
| Brigido SA et al <sup>11</sup><br>(Foot & Ankle Specialist, 2009)<br><br>The authors state that "The material is easy to prepare and inject into the wound, thereby preventing the necessity of extensive surgical exposure. The matrix supports neo-subcutaneous tissue formation and allows the body to rapidly repair these wounds."                        | Single-site Retrospective Study evaluating use of an acellular flowable soft tissue scaffold (GRAFTJACKET® Xpress FSTS) to treat complex tunneling diabetic foot ulcers<br><br>Endpoints included time to complete healing (complete epithelialization without drainage and time to depth healing (wound base at skin level) | 12 diabetic patients with full-thickness, non-infected sinus tract wounds treated with 1 application of GRAFTJACKET® Xpress FSTS and followed for 12 weeks <ul style="list-style-type: none"> <li>• Sinus tract wounds were defined as those with a depth greater than length and width</li> <li>• 2cc of GRAFTJACKET® Xpress FSTS were placed post full-thickness wound debridement</li> <li>• All patients received offloading via an instant total contact cast until the wound was considered healed for 2 weeks</li> </ul> | <ul style="list-style-type: none"> <li>• Initial average baseline wound area was <math>342.7 \pm 234.0\text{mm}^2</math> with wound depth of <math>13.8 \pm 5.9\text{mm}</math>.</li> <li>• Performance of GRAFTJACKET® Xpress FSTS: <ul style="list-style-type: none"> <li>- 10/12 pts (83.3%) achieved complete wound healing</li> <li>- <math>8.5 \pm 2.0</math> wks was average time for complete healing; (longest healing time was 11 wks)</li> <li>- <math>7.8 \text{ wks} \pm 2.2 \text{ wks}</math> was average time to 100% depth reduction for complete healers</li> <li>- 2/12 pts had 95% and 98% closure rates with 99% reduction of volume in 12 wks (they were non-compliant with offloading)</li> <li>- All pts had 50% decrease in wound depth within first 14 days</li> </ul> </li> </ul>  |

**Table 1. (cont.)** Literature Review of GRAFTJACKET® RTM and GRAFTJACKET®Xpress FSTS Studies cont.

| Author  | Study Type   | Patients  | Results/Conclusions  |
|---|--|---|--|
| <p>Stacey DH<sup>16</sup><br/>(Eplasty, 2013)</p> <p>Author concluded that "skin grafts, such as HADWM used in conjunction with NPWT, are effective treatment options for lower extremity wounds."</p>                            | <p>Case series evaluating the use of GRAFTJACKET® RTM in conjunction with NPWT to treat lower extremity and trunk wounds</p>     | <p>11 patients (6 male, 5 female; ages 31-83) with lower extremity and trunk wounds were included in this study</p>   | <ul style="list-style-type: none"> <li>• Patient treatments were successful with follow up ranging from 1 week to 6 months.</li> <li>• Two patients developed an infection, one of which resulted in partial graft loss and required reapplication of GRAFTJACKET® RTM and NPWT.</li> <li>• All wounds achieved complete healing with no reported complications related to GRAFTJACKET® RTM</li> <li>• All but one patient received a single application of GRAFTJACKET® RTM.</li> </ul> |
| <p>Williams et al<sup>17</sup><br/>(Journal of Diabetic Foot Complications, 2013)</p> <p>Authors concluded that FSTS applied to this patient population was an effective adjunctive treatment used in conjunction with HADWM.</p> | <p>Case series evaluating the use of GRAFTJACKET® Xpress FSTS in conjunction with GRAFTJACKET® RTM on lower extremity wounds</p> | <p>Three diabetic patients (2 male, 1 female, age range: 53-65) were included in this case series</p> <ul style="list-style-type: none"> <li>• Patients received 10cc of FSTS into their deep tunneling wounds followed by application of a 4cm x 4cm sheet of HADWM</li> <li>• A non-adherent dressing was placed over the HADWM covering the entire wound bed.</li> </ul> | <ul style="list-style-type: none"> <li>• No complications were reported throughout the course of treatment.</li> <li>• Follow up ranged from 2 weeks to 3 months.</li> <li>• Two of the 3 patients achieved wound healing within 6 weeks and the remaining patient achieved wound healing within 3 months.</li> </ul>  |

A recent review by Kirsner et al<sup>18</sup> discussed clinical experiences using GRAFTJACKET® RTM and GRAFTJACKET® Xpress FSTS and outlined application tips for the inexperienced user. Authors recommended the use of GRAFTJACKET® RTM for superficial and deep ulcers as an adjunct to standard care and the use of GRAFTJACKET® Xpress FSTS for tunneling wounds. Prior to application, it is critical to establish adequate blood flow to the wound, removing all necrotic tissue through debridement. Upon placing the dermal side of the GRAFTJACKET® RTM on the wound bed, the matrix can be held using sutures or skin staples; Nexcare™ Steri-Strip™ Skin Closures (3M Company, St. Paul, MN) are not recommended. The authors further recommended protecting the matrix using a non-adherent layer with mineral oil-soaked gauze, which would also serve in maintaining a moist wound healing environment and managing exudate. NPWT can be used as a bolster to human acellular dermal wound matrix (HADWM), with immediate application post-operatively.

The authors did not comment on post-operative dressing of GRAFTJACKET® Xpress FSTS, but did state that patient compliance with off-loading was crucial for good healing. Post application, it is important that clinicians do not remove the matrix to assess wound healing progression as this may interrupt incorporation of the matrix. Lastly, the authors emphasize the importance of monitoring the progress of matrix incorporation and wound healing. The cases below illustrate the use of GRAFTJACKET® RTM on specific wound types.

# CASE STUDY 1: VENOUS LEG ULCER TREATED WITH GRAFTJACKET® RTM

## Patient/Diagnosis

A 72-year-old male presented to the hospital with a large, chronic, right lower extremity wound. Patient had a previous renal and liver transplant and was currently on chronic immunosuppression medications. Patient had a history of venous ulcers on both legs with the ulcer on the right leg being present for over a year. After initial presentation, the wound was debrided (Figure 1) and sheets of GRAFTJACKET® RTM were pieced over the 330cm<sup>2</sup> wound (Figure 2). A nonadherent layer (ADAPTIC™) in conjunction with bacitracin was placed over the GRAFTJACKET® RTM, then bolstered by V.A.C.® Therapy using GRANUFOAM™ Dressing. Pressure was set continuously at -125mmHg. V.A.C.® Therapy was applied for 2 weeks and dressings were changed once a week. The patient developed an infection resulting in partial loss of GRAFTJACKET® RTM. Patient required readmission to the operating room for replacement of GRAFTJACKET® RTM, which was bolstered with V.A.C.® Therapy. After discontinuation of V.A.C.® Therapy, mineral oil, ADAPTIC™, and KERLIX™ gauze were used over GRAFTJACKET® RTM and changed daily. Patient remained at a long-term acute care hospital for close monitoring. At last follow-up (1 month post GRAFTJACKET® RTM placement) the wound was healed (Figure 3).



**Figure 1.** Wound after initial debridement



**Figure 2.** GRAFTJACKET® RTM: initial placement



**Figure 3.** 30 days after GRAFTJACKET® RTM

*Patient data and photos courtesy of Dr. D. Heath Stacey (NWA Center for Plastic Surgery, Fayetteville, AR)*

# CASE STUDY 2: PRESSURE ULCERS TREATED WITH GRAFTJACKET® RTM

## Patient/Diagnosis

A 50-year-old paraplegic male presented with a fever and three pressure ulcers (PrUs): two Stage 3 ischial PrUs and one Stage 4 sacral PrU (Figure 1). The patient's medical history included tobacco use, hypertension and chronic pain. On admission, pre-albumin levels were at 9.



**Figure 1.** PrUs at initial presentation.

For seven days all wounds were treated with V.A.C. VERAFO™ Therapy using V.A.C. VERAFO™ Dressings. Dakin's Solution was instilled until the foam was filled, followed by a soak time of 3 minutes. Instillation was repeated every hour followed by continuous negative pressure at -125mmHg (Figure 2). The following week V.A.C.® Therapy using V.A.C.® GRANUFOAM SILVER™ Dressing was used at continuous pressure set to -125mmHg. Dressings were changed every Monday, Wednesday, and Friday for 4 weeks.



**Figure 2.** PrUs after seven days of V.A.C. Veralo™ Therapy.

A sheet of 4cm X 8cm GRAFTJACKET® RTM was placed over each PrU in the operating room (OR). A nonadherent layer in conjunction with VASOLINE™ gauze (Covidien, Mansfield MA) was placed over the GRAFTJACKET® RTM, which was then bolstered with V.A.C.® Therapy using GRANUFOAM™ Dressing. Pressure was set continuously at -125mmHg, and dressings were changed every Monday and Friday.

Two weeks after the placement of GRAFTJACKET® RTM (Figure 3), the healthcare facility changed the therapy unit to an alternate negative pressure unit, which resulted in the loss of a graft. The patient required readmission to the OR for replacement of GRAFTJACKET® RTM on the left ischial PrU. V.A.C.® Therapy was re-initiated as the bolster using GRANUFOAM™ Dressing with pressure set continuously at 125mmHg for 2 more weeks.



**Figure 3.** PrUs two weeks after GRAFTJACKET® RTM application.

A second application of GRAFTJACKET® RTM was used as a final covering for both the left and sacral PrUs (Figure 4), and dermal skin buds began forming within 5 days of second application. Figures 5 and 6 show the healing progression of each PrU.



**Figure 4.** Second application of GRAFTJACKET® RTM for left and sacral PrUs.



**Figure 5.** Nine days after second GRAFTJACKET® RTM application for left and sacral PrUs.



**Figure 6.** Three weeks after second GRAFTJACKET® RTM application for left and sacral PrUs.

At last follow-up visit (Figure 7), all PrUs were healed. Within two weeks of hospitalization, patient's pre-albumin levels were up to 22 and continued to normalize throughout treatment.



**Figure 7.** Seven weeks after GRAFTJACKET® RTM placement

This patient previously had a rotational flap done for Stage 4 decubitus ulcers two years prior. We were left with the only option of using GRAFTJACKET® RTM, a human acellular dermal matrix. What happened in the subsequent months was remarkable as the skin started to grow not only as wound bed matrix but also began covering the wound.

*Patient data and photos courtesy of J. Douglas Duke II, DO, Ft. Smith, AR*

# CASE STUDY 3: CHRONIC HAND WOUND TREATED WITH GRAFTJACKET® XPRESS FSTS

## Patient/Diagnosis

A 58-year-old male with diabetes mellitus presented with a non-healing wound following traumatic injury to the right hand (Figures A and B) post multiple debridements and attempted closures. On Day 1, after debridement (Figure C), 2cc of GRAFTJACKET® Xpress FSTS were expressed into the deep soft tissue defect (Figure D). A split-thickness skin graft (STSG) was then placed over the wound (Figure E) and bolstered with V.A.C.® Therapy, using a bridge dressing made out of V.A.C.® GRANUFOAM SILVER™ Dressing (Figure F). Pressure was set continuously at 125mmHg. V.A.C.® Therapy was applied for 1 week then removed. At Week 1 the STSG showed 100% take (Figure G) and was covered by a non-adherent layer. By Week 6, wound depth had reduced to zero, and there was maturation of the STSG with no evidence of wound recurrence. Comparison of Figures H and I demonstrates the progression in wound healing. Despite difficulty with compliance, this patient was able to achieve a successful outcome with complete wound healing with the assistance of GRAFTJACKET® Xpress FSTS, thereby avoiding the need for more complicated flap reconstruction.



**A.** Initial presentation of wound



**B.** Deep defect at base of wound



**C.** Wound post debridement



**D.** Placement of GRAFTJACKET® Xpress FSTS



**E.** Application of split-thickness skin graft



**F.** Placement of V.A.C.® Therapy



**G.** Wound at Week 1



**H.** Wound at Week 6



**I.** Close-up of wound at Week 6

*Patient data and photos courtesy of Dr. Michael N. Desvigne (Peoria, AZ)*

## CONCLUSION

As an acellular dermal matrix replacement scaffold from donor human cadaver tissue, GRAFTJACKET® RTM retains its natural biological components. It also preserves structural integrity of the complex, 3-dimensional (3-D) dermal matrix, including intact vascular channels. Findings from a preclinical primate study<sup>4</sup> demonstrated that GRAFTJACKET® RTM integrates into host tissue with a reduced likelihood of inflammatory response. The clinical study by Winters and colleagues has shown that a single application of GRAFTJACKET® RTM has been effective in the treatment of partial- and full-thickness lower extremity wounds in diabetic patients (a challenging patient population).<sup>8</sup>

GRAFTJACKET® Xpress FSTS is a micronized (powdered) version of the GRAFTJACKET® RTM that is rehydrated prior to placement. GRAFTJACKET® Xpress FSTS retains the native extracellular proteins that stimulate cell migration and proliferation in a formulation that can be placed into deep wounds and tunneling.

Unlike the fibrotic scar tissue that forms as a result of the reparative process, both GRAFTJACKET® RTM and GRAFTJACKET® Xpress FSTS are regenerative tissue matrices that are infiltrated by host cells and transformed into host tissue. Because scar tissue lacks the strength and flexibility of native tissue, these acellular dermal matrices provide a favorable end result to the healing process.

# Appendix 1:

## US Regulatory Considerations

### Indications for Use

GRAFTJACKET® RTM for wounds provides a scaffold for the body's repair or replacement of damaged or inadequate integumental tissue, such as diabetic foot ulcers, venous leg ulcers, pressure ulcers, or for other homologous uses of human integument.<sup>9</sup>

GRAFTJACKET® Xpress FSTS supports the body's repair of damaged or inadequate integumental tissue, such as deep dermal wounds or diabetic ulcers.<sup>10</sup>

Each package of GRAFTJACKET® RTM or GRAFTJACKET® Xpress FSTS is intended for use in 1 patient, on a single occasion.<sup>9,10</sup>

### Contraindications

GRAFTJACKET® RTM and GRAFTJACKET® Xpress FSTS are contraindicated for use in any patient who is sensitive to polysorbate 20 or to any of the antibiotics listed on each product's Instructions for Use (IFU) package.<sup>9,10</sup>

Also, GRAFTJACKET® Xpress FSTS should not be used in the periocular, forehead or glabellar areas because of the particle size.<sup>10</sup>

### Donor Tissue Safety Testing

Donor tissue undergoes several levels of testing and screening to assure its safety. Blood samples from each potential GRAFTJACKET® RTM/GRAFTJACKET® Xpress FSTS skin donor are screened by Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories and must be negative when tested for:

- Hepatitis B surface antigen (HBsAg)
- Antibody to hepatitis C (HCV)
- Nucleic Acid Testing (NAT) for HIV, HBV, HCV
- Antibody to Hepatitis B core (HBcAb)
- Antibody to human immunodeficiency virus (HIV) types 1 and 2
- Antibody to human T-lymphotropic virus (HTLV) types I and II, if sent to the EU
- Syphilis<sup>16</sup>

All tests are licensed approved, or cleared by the Food and Drug Administration (FDA). A licensed physician further determines donor suitability after review of all donor screening and testing records. Donor screening includes history (medical and social) and physical examination, serology and microbiology, and cause of death. Samples of the donor skin are tested for, and shown to be free of, bacterial and fungal pathogens; however, normal nonpathogenic skin bacteria may be present.<sup>16</sup>

**NOTE:** Existing tests cannot provide absolute assurance that human source material will not transmit disease.<sup>16</sup>

### Regulatory Classification

GRAFTJACKET® RTM and GRAFTJACKET® Xpress FSTS are derived from donated human skin from US tissue banks and regulated by the FDA Center for Biologics Evaluation and Research (CBER) as human tissue for transplantation. CBER protects and advances the public health by ensuring that biological products are safe and available to those who need them. Additionally, CBER provides the public with information to promote the safe and appropriate use of these biological products.<sup>17</sup>

GRAFTJACKET® RTM and GRAFTJACKET® Xpress FSTS are regulated by the FDA under the category of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), which are defined as articles "containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion or transfer into a human recipient." For an HCT/P to be regulated under section 361 of Public Health Service Act (PHSA) and 21 CFR Part 1271, the product must meet the following criteria:

- Is minimally manipulated
- Is intended for homologous use
- Is not combined with another article
- Does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function

GRAFTJACKET® RTM meets all four of these criteria for regulation as an HCT/P.

GRAFTJACKET® RTM and GRAFTJACKET® Xpress FSTS are processed and marketed in accordance with FDA requirements for banked human tissue (21 CFR, Part 1271) and *Standards for Tissue Banking* of the American Association of Tissue Banks (AATB). GRAFTJACKET® RTM and GRAFTJACKET® Xpress FSTS are compliant with the AATB *Standards for Tissue Banking* and state guidelines, including California, Florida, New York, Maryland, and Illinois.



# GRAFTJACKET®

regenerative tissue matrix (RTM)

# GRAFTJACKET® Xpress

flowable soft tissue scaffold (FSTS)

## Product Monograph

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**NOTE: Every patient is different and patient results may vary. Before use, physicians must review all risk information and essential prescribing information which can be found in the GRAFTJACKET® regenerative tissue matrix and GRAFTJACKET® Xpress FSTS Instructions for Use. Rx only.**

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