**Technology update:**

Indications for the use of MatriDerm® in the treatment of complex wounds

Until recently, the gold standard treatment for covering full-thickness skin defects that required surgery was the use of a full-thickness skin graft in small defects and split-thickness skin grafts in larger instances. The use of full-thickness skin grafts is limited due to the size and availability of suitable donor sites. The use of split-thickness skin grafts can result in complications such as hypertrophic scarring, keloids or disabling contractures especially across joint surfaces. This has led to the development of dermal templates in order to improve the reconstruction of the dermis, which is very important for the quality and functionality of the reconstructed skin. This paper reviews the relevant aspects of wound healing and summarises the efficacy of an engineered dermal template called MatriDerm® (Medskin Solutions/Dr Suwelack) in a variety of acute and reconstructive wounds.

**Author:**
Stuart Enoch
Lars-Peter Kamolz

**References**
These multiple procedures can be stressful for the patient and are inefficient, both in terms of cost and resources[6].

To circumvent this limitation, Matriderm is an engineered dermal template specially developed to provide a one-step grafting procedure without the disadvantages of diminished take-rate.

BASIC WOUND HEALING
Superficial epidermal injuries heal by re-epithelialisation from existing keratinocytes or keratinocyte stem cells that are present in the wound bed. Scarring in such injuries is minimal.

If the injury extends to the superficial layer of the dermis, it is possible that regeneration of the epidermis will occur without surgical intervention provided there are sufficient number of keratinocyte stem cells. If epidermal keratinocytes are completely lost, repair may occur from the epithelial stem cells that are present in the hair follicles and/or sweat glands in the deep layers of the skin (dermis).

When the injury extends to the deeper layers (including the hypodermis or muscle), the injured surface is depleted of its keratinocytes, fibroblasts and any stem cells. Thus surgical excision of the involved tissue is frequently required along with reconstruction using STSGs, which contain all the epidermis and superficial parts of the dermis, thereby transferring self-renewing keratinocyte stem cells to the recipient area.

Deep dermal and full-thickness skin injuries usually require surgical excision and grafting. In such deep wounds, an ‘ideal’ skin substitute would provide immediate replacement of both these essential layers (epidermis and dermis), therefore the ideal skin substitute is defined as one that[6]:

- Resists infection
- Withstands shearing forces
- Lacks antigenicity
- Is conformable to irregular wound surfaces
- Is flexible and durable
- Closes the wound immediately
- Rejuvenates new skin
- Is synthetic and bio-acceptable.

With advances in tissue engineering and biotechnology, there are several skin substitutes — both in use at present and in development — that are employed for the replacement or reconstruction of one or both layers of the skin.

TISSUE-ENGINEERED DERMAL CONSTRUCTS
Tissue-engineered dermal constructs (TEDC) are a heterogeneous group of products that are aimed at replacing, either temporarily or permanently, the form and function of lost dermis. These products provide an alternative to the standard wound coverage in circumstances when established wound dressings are not appropriate.

TEDCs consist of a micro-engineered, biocompatible polymer matrix produced by tissue engineering. If used in combination with cellular and/or extracellular elements, such as collagen, they result in a biosynthetic product. Synthetic and biosynthetic constructs are intended to be stable, biodegradable and are aimed at providing an adequate environment for the regeneration of tissue.

MatriDerm is a class III product which works as an implant. The collagen-elastin matrix is absorbed in approximately six weeks by replacement of autologous cells and tissue. As such it acts as a scaffold for tissue reconstruction (neodermis).

Any skin substitute should maintain its three-dimensional structure for a minimum of three weeks to allow in-growth of blood vessels and fibroblasts, as well as coverage by epithelial cells. Biodegradation begins after this period and the whole process should occur without a significant ‘foreign body’ reaction, since this may lead to increased scarring.

Depending on their composition, both synthetic and biological skin substitutes can be divided into dermal, epidermal or dermo-epidermal replacements. Sustainability is an additional factor, depending on whether a skin substitute is temporary or permanent:

- **Temporary skin substitutes:** provide transient physiologic wound closure, including protection from trauma, provision of a barrier to bacteria and pathogens, and maintenance of a moist wound environment, until repair of the damaged tissue is complete.
- **Permanent skin substitutes:** as the name suggests these are designed to provide permanent wound closure, replace lost skin components (epidermis, dermis or both), and integrate with the recipient tissue.

HISTORY OF ENGINEERED DERMAL CONSTRUCTS
An allograft is a tissue or organ that is transplanted from one individual to a member...
of the same species, but with a different genotype (e.g., human to human) and contains both epidermis and dermis. Cadaver skin allografts have been used for many years, but provide only temporary coverage because of host rejection.

In 1981, Integra® (LifeSciences), a collagen-based dermal substitute with a silicone top layer, was engineered to serve as a dermal template. Although promising results have been obtained, Integra requires a two-step approach where the top layer, which serves as a temporary epidermal replacement, is removed when the artificial dermis appears macroscopically revascularised[7]. This is generally performed 2–3 weeks post-application.

Subsequently in 1994, AlloDerm® (LifeCell), a chemically treated ‘decellularised’ allograft, was developed to be used alone or in combination with cultured autologous keratinocytes for the closure of burns and chronic wounds.

Another acellular product TransCyte® (Advanced BioHealing), consists of an inner nylon mesh, in which human foreskin fibroblasts are embedded, and an outer silicone layer designed to limit evaporation. It has been successfully used as temporary wound coverage after the excision of burn wounds and other complex ulcers.

A cellular composite, Dermagraft® (Advanced BioHealing), has also been designed to treat diabetic foot ulcers and again uses human foreskin fibroblasts but has been cultured in a biodegradable polygelatin mesh and then cryopreserved so that they remain viable. However, such meshes die a few weeks after implantation, therefore, the product probably acts as a delivery vehicle for growth factors and ECM produced by fibroblasts.

A porcine small intestinal submucosa acellular collagen matrix (Oasis® [Cook Biotech]) and an acellular xenogeneic collagen matrix (EZ-DermTM [AM Scientifics]) are also available and have relatively long shelf lives. However, evidence of their efficacy is limited. The Unite® Biomatrix collagen wound dressing (Synovis) is another crosslinked native collagen structure that is designed to provide a biologic solution for chronic wounds, such as diabetic foot ulcers, venous ulcers, pressure ulcers and vasculitic ulcers.

THE ROLE OF COLLAGEN IN DERMAL CONSTRUCTS

Collagen is the most effective biocompatible material for dermal substitution in full-thickness wounds. It is normally present in large quantities in the skin and is vital for normal wound healing. Reconstituted collagen is made of soluble collagen fragments, whereas native collagen is built up from insoluble collagen fibres.

It is important that any dermal matrix does not degrade too quickly in the wound. Reconstituted collagen matrices disintegrate within a week and do not contribute to dermal regeneration. However, native collagen matrices composed of intact collagen fibres survive for longer and contribute to dermal regeneration. The addition of extracellular matrix proteins further delay disintegration for up to four weeks[8].

Elastin is a protein made of simple amino acids such as glycine and proline. It is elastic and allows tissues, including skin, to return to their original shape after stretching or contracting.

Dermal substitution of full-thickness skin defects with a native collagen matrix incorporating elastin contributes to skin regeneration. The native collagen fibres form a scaffold that guides fibroblasts and possibly other cells toward dermal regeneration, while the presence of elastin particles in the collagen matrix diminishes the formation of granulation tissue in the early phase of wound healing. As a result, a high-quality neodermis with randomly organised collagen bundles is regenerated. Also, by diminishing the expression of myofibroblasts, the presence of elastin reduces wound contraction.

MATRIDERMA

MatriDerm is a dermal substitute suitable for one-step repair of full-thickness skin defects in combination with STSG. MatriDerm is a scaffold consisting of a native bovine type I, III and V collagen fibre template incorporating elastin hydrolysate that is converted into native host collagen within weeks following application. The matrix can be stored at room temperature and comes in 1mm and 2mm thick sheets.

Application

MatriDerm can be applied directly from the pack onto the wound bed following the debridement of any slough, exudate or unhealthy tissue, and after careful haemostasis. The matrix can easily be rehydrated in the wound bed by 0.9% physiological saline solution.
Sheets of 2mm thickness are recommended for two-step repairs, with a time interval of seven days to allow for vascularisation of the matrix before the transplantation of STSG. However, a one-step procedure is feasible in the acute and reconstruction phases, for example following burn injuries.

Approximately 10 days after dressing removal, physiotherapy can be initiated. The skin graft take rate does not differ significantly compared with a normally applied STSG and the quality of the resulting scars is reported to be superior compared with skin grafting alone.39

There are reports claiming that dermal substitutes using one-step grafting procedures might affect the survival of the overlying epidermal transplant, and it has been postulated that the increased diffusion distance for nutrients and oxygen to the autograft after inter-positioning of the substitute can reduce chances of the graft’s survival.40 However, in many studies employing MatriDerm and sheet autografts, this problem was not encountered.41 MatriDerm is also a feasible one-stage procedure in critical care patients.

Moreover, MatriDerm has haemostatic properties that reduce the risk of split-skin subgraft haematoma.42 The fact that MatriDerm does not contain any chemical crosslinking results in a matrix that can provide effective biocompatibility.42

EVIDENCE

There is evidence for the use of MatriDerm in a broad range of indications, eg full-thickness wounds, trauma and skin cancer excisions.11,13

MatriDerm has also been found to be effective in both the acute and reconstructive phases of hand and joint injuries due to flame burns. The first clinical reports were published by Haslik et al who performed early debridement and immediate grafting of unmeshed STSG with MatriDerm on 10 patients as a one-step procedure.

An overall skin graft take rate of 97% was observed 14 days postoperatively and after three months pliability of the grafted area was found to be excellent with a mean Vancouver Skin Score (VSS) of 3.2+/-1.2. A full range of motion was achieved in all hands and no blisters or hypertrophic scars were noticed in any of these wounds. This pilot study provided the initial evidence for the effectiveness of MatriDerm in hand burns and consequently resulted in MatriDerm being considered as an effective treatment modality in such injuries.

More recently, Haslik et al reported the long-term results of applying unmeshed STSG with MatriDerm in 17 patients. A skin graft take rate of 96% was observed and long-term follow-up revealed an overall VSS of 1.7. No limitations in hand function were observed and DASH-score (disability of arm, shoulder and hand) analysis revealed excellent hand function in patients who underwent debridement and reconstruction following burn injury (15.6 DASH score). Good hand function (27.2 DASH score) and minimal donor site morbidity was also found in the forearms of patients who underwent a radial forearm flap harvest.

Bloemen et al reported the results of a 12-year prospective randomised follow-up on 46 patients who were treated with STSG or STSG plus MatriDerm for acute burns and reconstructive surgery. Intra-individual comparison was also carried out between scars from patients treated with STSG alone and those treated with STSG and MatriDerm. In reconstructive sites, the surface roughness parameter was significantly improved in the MatriDerm group.

Subjective assessment in acute and reconstructive burn scars showed several statistically significant differences in favour of the MatriDerm group, such as pliability, relief, pigmentation and the quality of the healed wound. Elasticity measurements in acute burn patients showed higher scores for substituted scars, although the difference was not statistically significant. For the subcategory of scars treated with a largely expanded meshed skin graft, a significantly higher elasticity was found for the substituted site.

In a prospective intra-individual comparative study by Ryssel et al comprising 10 patients with severe burns (age 49.5 ± 16.2 years; TBSA 45.6 ± 14.5%), 20 wounds were treated with either STSG alone or simultaneous application of MatriDerm and STSG after appropriate excision of the burn wound. Results showed that the take rate of the graft was not altered by simultaneous application of the dermal matrix (p = 0.015). After three to four months the VSS demonstrated a significant increase in elasticity in the MatriDerm group (p = 0.04) as compared with the non-substituted group who received unmeshed autograft. However, a significant difference was not found between this and the meshed autograft group (p = 0.24).

Subsequently, Ryssel et al evaluated the effectiveness of MatriDerm in burns on the

References

In this prospective study, 18 patients (age 45.1±17.4 years, 43.8±11.8% TBSA) with extensive burn wounds on the dorsum of both hands received an STSG sheet alone on one hand or an STSG sheet with MatriDerm on the other as a one-step procedure. Simultaneous application of STSG and MatriDerm did not have any detrimental effect in the graft take compared to STSG alone (p>0.05). In addition, VSS analysis demonstrated a significant increase in skin quality in the group with MatriDerm (p=0.02) compared to the control group. The range of motion measured by Finger-Tip-Palmar-Crease-Distance (FFPD) was found to be significantly improved in the substituted group (p=0.04).

### Case Studies

Despite successful defect coverage by complex skin flaps, large and deep wounds are particularly susceptible to surgical revision because of contour and scar deformities. The application of the dermal template MatriDerm in patients with problematic wounds represents an innovative reconstruction method, from initial coverage to scar development.

**Case 1**

A 70-year-old male pensioner suffered an ischaemic stroke at home. He was found four days later lying on the floor unable to move and had developed large pressure ulcers of the left thorax and the lateral side of the left knee. After cardiopulmonary stabilisation at the intensive care unit, operative debridement of the necrotic tissue exposed both knee capsule and rib cartilage.

Figs 1 and 2 show the left knee and left side of the thorax one week after the use of initial debridement and NPWT to obtain proper granulation of the wound beds. Defect coverage was performed with 1mm MatriDerm and unmeshed split skin grafts. Negative pressure wound therapy (NPWT) was then used to encourage optimum fixation of the MatriDerm and the split-thickness skin grafts and this was discontinued after one further week.

Beside optimal graft take, MatriDerm provided reliable defect coverage [Figs 3 and 4].

**Case 2**

This 71-year-old pensioner suffered a degloving injury of the left lower leg and foot [Fig 1]. After operative debridement, there was significant soft tissue loss with visible tendons and periostal structures of the medial ankle [Fig 2]. Angiography showed that the lower leg and foot were only being nourished by a arteriosclerotic tibialis posterior artery.

Defect coverage was performed using 1mm MatriDerm and unmeshed split skin grafts in combination with one week of NPWT to fix the grafts [Fig 3]. Two years after the accident the patient was able to wear normal shoes and clinical gait analysis demonstrated a perfect functional outcome [Fig 4].

These case studies were prepared by M Öhlbauer and B Wallner of the Department of Plastic, Hand and Reconstructive Microsurgery, and Ph Rapp and M Militz of the Department of Septic Surgery, BG Trauma Center, Murnau, Germany.
In a case reported by Cervelli et al.,[11] concurrent application of STSG and MatriDerm was found to be a simple, safe and economical in the treatment of diabetic foot ulcers. The report presented a 65-year-old male with a three-year history of infected diabetic ulcer (25 x 35mm; 10mm deep) in his foot. The patient was treated with MatriDerm and STSG as a one-step procedure on the wound bed following surgical debridement, complemented by antibiotic therapy. After a single treatment, the investigators found a reduction in the size of the ulcer 15 days postoperatively. Pain and exudate were also found to be reduced.

In another case report, Wetzig et al.[12] demonstrated the possibility of using STSG with MatriDerm on deep wounds with exposed tendons to achieve acceptable functional and cosmetic outcome. The report presented an 80-year-old male who had multiple co-morbidities (including diabetes) with a tendon-exposing defect on the dorsum of the foot resulting from micrographic-controlled tumour excision. The defect was closed by applying MatriDerm and STSG in a one-step procedure following surgical debridement and haemostasis. The wound achieved complete closure with a normal skin appearance six months postoperatively.

The properties of MatriDerm were further investigated by Ryssel et al.[14] in more complex cases such as necrotising fasciitis (NF). In their study, five patients who had full-thickness skin defects with exposed tendons or joint capsules due to NF were treated with a single-step application of MatriDerm and STSG. These patients, who would normally have undergone complex reconstructive surgery that might have included a free-flap, were either not keen on extensive flap surgery, or had unfavourable vascular preconditions. The investigators reported no reduction in the skin graft take rate. The healing time, however, might be considered to be prolonged compared to reconstructive flap surgery.

More recently, Goutos and Ghosh[17] have demonstrated the potential use of gauze-based negative pressure wound therapy (NPWT) as an adjunct to MatriDerm resurfacing. In the 10 patients studied (seven males and three females), vacuum therapy (as opposed to foam-based NPWT) was found to be effective in all cases for bolstering the one-step MatriDerm templates onto wounds, and contributed to excellent rates of epithelialisation (mean: 94%; range: 70–100%). Additionally, patient concordance with the device was reported to be excellent and the costs associated with its use were found to be lower compared with foam-based NPWT.

FUTURE RESEARCH
In common with many other similar products, randomised controlled trials examining the effectiveness of MatriDerm are currently lacking, making it difficult to safely recommend its widespread use in clinical practice. The current evidence is mostly based on non-randomised prospective trials, retrospective reviews, small case series and isolated case reports. No trials are available at present that evaluate MatriDerm with an existing TEDC or a similar dressing/device. In addition to evaluating clinical components such as rate of healing and skin graft take, a carefully designed study to ascertain the clinical effectiveness of dermal templates in terms of the sensory recovery of the field, pigmentation and long-term skin quality will provide more robust information to recommend its use in a variety of challenging wounds.

Tissue-engineered skin substitutes and TEDC are seldom effective in sloughy and exudative wounds with unhealthy wound beds. Efficient wound care (wound debridement and exudate management), adequate rest, compression, pressure relief and skin care must be provided as clinically indicated. Novel treatment modalities such as TEDC should complement rather than replace the tenets of good, basic wound care.

ACKNOWLEDGEMENTS
This article was prepared with the aid of sponsorship from Medskin Solutions/Dr Suwelack.

AUTHOR DETAILS
Stuart Enoch, MBBS, PhD, PGCert (Med Sci), MRCSEd, MRCS (Eng), Programme Director – Education and Research, Doctors Academy; Honorary Tutor in Wound Healing – University of Cardiff
Lars-Peter Kamolz, MD, PhD, Msc, Professor and Head, Division of Plastic, Aesthetic and Reconstructive Surgery, Department of Surgery, Medical University of Graz, Austria

References