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BURNS (N NAMIAS, SECTION EDITOR)

Current State of Selected Wound Regeneration Templates and Temporary Covers

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Abstract

Purpose of Review To review four wound coverage options—xenografts, allografts, Integra®, and MatriStem™—and outline considerations to help providers select the appropriate cover.

Recent Findings Xenografts were the first skin substitutes used to cover wounds. They are inexpensive but inherently less similar to native host skin than cadaveric allografts, the current gold standard for temporary wound coverage. Integra® is an established dermal matrix that provides permanent coverage by naturally integrating into the wound to create a neo-dermis. MatriStem™ urinary bladder matrices are recently available products designed to promote wound healing. They have shown promising, albeit limited, results in clinical studies.

Summary Each reviewed coverage option presents its own risk-benefit profile. The optimal choice for an individual patient depends on various wound- and patient-related factors that should be evaluated collectively. Adherence to wound management principles is paramount regardless of the coverage option. This review aims to facilitate the selection process for providers.

Keywords Wound healing · Tissue engineering · Skin substitutes · Dermal analogs · Regeneration templates · Reconstructive surgery

Introduction

The skin is the largest organ in the human body and plays a critical role as a protective barrier to the outside world and in thermoregulation [1, 2]. The skin is a bilayer with an avascular epidermis composed primarily of proliferating keratinocytes and a well-vascularized dermal layer composed mainly of collagen, glycosaminoglycans, and elastin fibers (Fig. 1a). These cells confer skin elasticity and tensile strength. The protective properties of the integument are lost when the skin's barrier function is damaged resulting in a wound (Fig. 1b).

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The reconstructive ladder provides a stepwise approach to wound closure, from simple wound healing by secondary intention to complex tissue transfer in the form of vascularized flaps [2, 3]. When primary or secondary wound closure is not possible and skin grafting is considered, wound regeneration templates and temporary covers can be valuable additions to a provider's armamentarium. Regeneration templates and temporary covers are effective skin substitutes, as they provide rapid coverage of the wound, thereby minimizing fluid loss and also potentially decreasing infection risk in the case of allografts [4]. They can also provide durable resistance to shearing forces, promote new dermal tissue synthesis, serve as a regenerative scaffold, and recruit key mediators for wound healing [3, 4].

There is a wealth of wound cover options that differ in regard to durability, the specific skin layer they replace, and the source of the material. These products can be classified as biologic, biosynthetic, or synthetic based on their material composition [5, 6]. Covers can also be categorized into epidermal, dermal, and dermo-epidermal (composite) constructs depending on the integumentary region they replace [7]. Additionally, they can be divided into temporary versus permanent covers. Temporary products are applied to induce

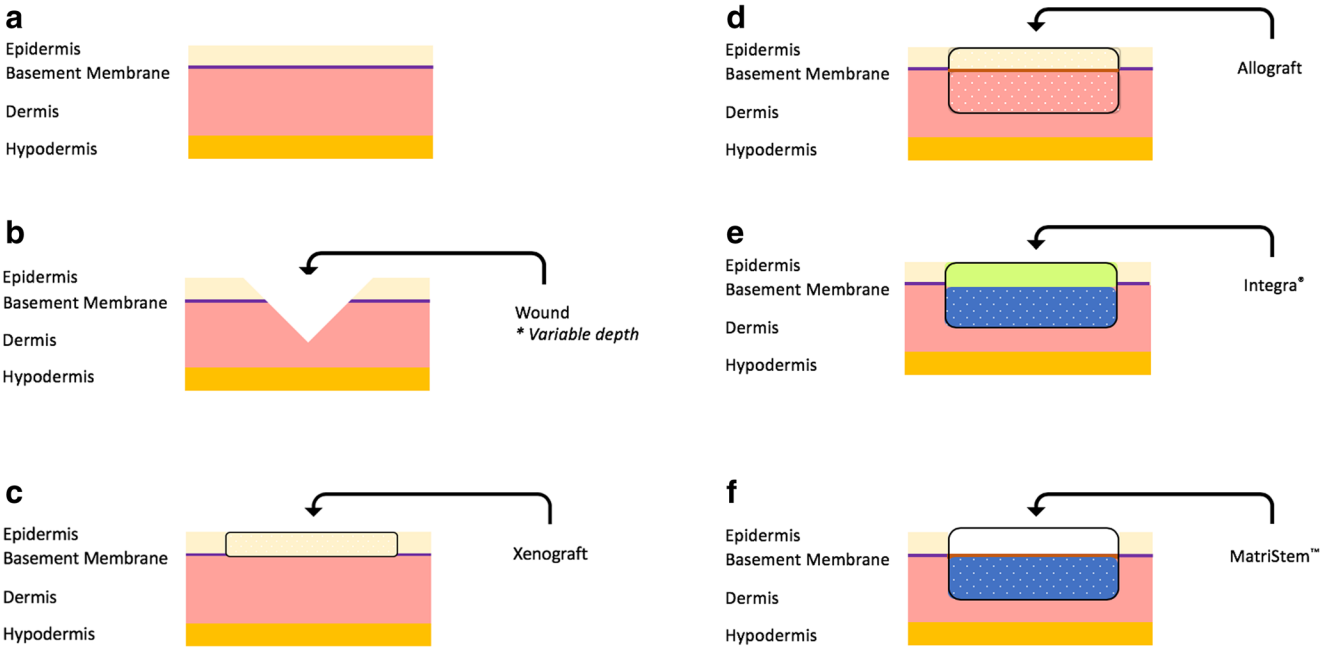

Fig. 1 Composition of wound care covers. **a** Layers of the integument. **b** Disruption of the skin layers by a wound. **c** Coverage of the wound by natural biological xenograft, which provides the epidermal component of the integumentary. **d** Coverage of the wound by natural biological allograft, which includes all elements of the native layers of the integumentary. **e** Coverage of the wound by artificial biologic Integra®, which includes an epidermal and dermal bilayer. **f** Coverage of the wound by artificial biological MatriStem™, which includes a basement membrane and a dermal component

healing in the underlying wound bed and typically do not integrate into the wound. Conversely, permanent covers act as regenerative scaffolds that are partially (i.e., Integra® Dermal Regeneration Template) or completely (i.e., Alloderm™ Regenerative Tissue Matrix) assimilated into the healed wound [8].

Three modern classification systems have been published to categorize skin substitutes [9, 10••, 11••]. In 2008, Kumar improved the former Balasubramani et al. classification by making it more comprehensive. The Kumar classification was broadly divided into Class 1 temporary impervious dressing materials, Class 2 single layer durable skin substitutes, and Class 3 composite skin substitutes [9]. In 2011, Ferreira introduced a more clinically inclined classification system which included (1) the skin layer to be replaced (epidermal, dermal, and dermal-epidermal composites); (2) the durability in the wound bed (temporary and permanent); and (3) the origin of the grafting material (biological, biosynthetic, and synthetic) [12]. In 2014, Shahrokhi et al. suggested a classification based solely on the source of the dermal substitute divided into synthetic versus biological (natural or artificial) materials [11••]. Most recently, Davison-Kolter et al. published what they claimed to be a universal classification system [10••]. It included five elements: (1) cellularity (acellular or cellular); (2) layering (single layer or bilayer); (3) replaced region (epidermis, dermis, or both); (4) materials used (natural, synthetic, or both—Table 1); and (5) permanence (temporary or permanent).

These classification systems attempt to organize and categorize the multitude of available options for skin substitutes. Products such as Integra® Dermal Regeneration Template (DRT) which were classified as class 3 (materials that replace both the dermal and epidermal layer) in the Kumar

Table 1 Classification of products based on materials used [11••, 13]

Classification	Product example
Epidermal	Cultured epithelial autograft (CEA)
Dermal	
Natural biological	Alloderm®
	Glyaderm®
	DermaMatrix®
	Tiscover®
	Stratice®
	Permacol®
Artificial biological	Integra®
	Matriderm®
	Biobrane®
	Terudermis®
	Apligraf®
Synthetic	Dermagraft®
	Poluactive®
Dermo-epidermal	Permaderm®
	DenovoSkin®

classification can now be described based on the Davison-Kolter classification as (1) acellular, (2) bilayer of (3) epidermis and dermis with (4) natural and synthetic (5) temporary material. Of note, Integra® DRT is considered permanent by some as its inner (dermal) component is integrated into the wound to form a neo-dermis and temporary by others as none of its components remain intact in the wound. The different classification systems help clinicians select products based on the "needs" of the wound. Clinicians should thus be aware of coverage options in each broad category.

Regeneration templates and temporary covers are a diverse group of products, each with specific applications as well as their unique set of advantages and limitations. The ideal skin substitute is permanent, inexpensive, readily and abundantly available off-the-shelf, easily stored with a long shelf life, rapidly and easily applied with one procedure, mechanically pliable yet durable, protective against moisture loss and infection, biocompatible with no risk of immunogenicity or infectious disease transmission, rich with healing factors that enhance host tissue regeneration, and both cosmetically and functionally adequate in terms of scar quality, pigmentation, and possess all native adnexal tissue [11••, 14]. Since none of the current coverage options possesses all of these qualities, providers must carefully evaluate these product-related considerations in combination with patient-related factors such as their age, comorbidities, religious or ethical reservations, and desired aesthetic and functional outcomes. Clinicians should provide personalized care for individual patients by taking each of these factors into account when selecting a wound cover.

When discussing skin substitutes, it is important to remember the long history of wound cover options. Although to date there exists no perfect product, there have been significant advances in the development of wound covers since the first mention of xenograft, a temporary biological epidermal replacement. From 1500 B.C. to the recent introduction of three-dimensional (3D) skin printing, each new product developed over the years has served to help in the advancement of the field of skin substitutes. We begin this review by describing the first skin substitute introduced, xenograft.

Historic Skin Substitute

Xenograft—Temporary Biological Epidermal Replacement

History

Xenografts have served as wound covers as early as 1500 B.C., with frog skin coverings having been documented in the Papyrus of Ebers. Zoografting, as the practice was then termed, was also attempted with the skin of various other animals including water lizards, sheep, rats, and chicken [3, 15]. Despite the failure of early attempts, xenografts were observed to confer wound healing benefits through protection, hydration, and pain relief, which popularized their use as temporary dressings. Since the 1960s, pig dermis remains the mainstay of xenografts for humans [16]. Its benefits include affordability, accessibility, and histologic similarity to human skin. In countries such as Brazil, bovine and sheep skin options also exist in addition to the ever-present frog skin covers [17].

Product Description

Porcine xenografts consist of de-epithelialized pig dermis (Fig. 1c). Commercially available brands include EZ-Derm®, MediSkin®, Permacol®, Strattice®, and Xenoderm®. Of these products, EZ-Derm® and Permacol® have the greatest tensile strength due to cross-linking, which confers resistance to enzymatic breakdown by collagenase [18]. Xenografts can be used fresh or off-the-shelf after storage at ambient temperature, although some institutions freeze-dry or preserve them with glycerol to prolong shelf life and diminish antigenicity [15, 19]. Following standard preparation of the wound bed and direct application of the xenograft, wound adherence occurs in approximately 1 to 2 days without any surgical intervention [15]. While antigenicity poses a logical concern, xenografts do not form vascular connections with the host tissue, thus rejection does not occur. Instead, they slough away either due to slow vascular necrosis or by formation of the epithelium across the underlying wound bed [3, 15]. The benefits of porcine xenografts are well documented: decreased healing time and pain; retained fluids, proteins, and electrolytes; and reduced bacterial overgrowth [15, 16, 19]. In addition to their use as wound dressings for partial-thickness burn injuries in mostly developing countries [20, 21], xenografts have been employed in a wide range of surgical procedures such as rhinoplasty [22, 23], facial contouring [24], rotator cuff repair [25], and abdominal wall reconstruction [26] and hernia repair [27, 28].

Advantages and Disadvantages

Compared to other dermal substitutes, porcine xenografts possess a long shelf life, and are both inexpensive and abundantly available. They are indicated when human skin is not an option due to limited access or patient refusal on religious, ethical, or sociocultural grounds. In terms of disadvantages, xenografts are inherently less similar to native dermis than allografts, limited to temporary coverage, and contraindicated in patients with allergies to porcine materials. There is also a theoretical risk of transmission of zoonoses [15]. Moreover, they have yielded disappointing results, in part due to cross-linking, which confers durability but also theoretically impairs wound healing [11••]. Indeed, the clinical utility of xenografts

has been brought into question by studies revealing that neither Permacol® [29] nor EZ-Derm® [20] demonstrates significant benefits over split-thickness skin grafting alone.

Skin Substitute Options

Xenografts have largely been replaced by allograft when wounds require temporary wound cover. Cadaveric allograft is considered the gold standard for temporary wound coverage. Allografts are natural epidermal substitutes that promote wound healing while acting as a temporary wound cover. If permanent wound coverage is sought, many options are available (Table 1) including Integra® DRT, the longest standing biological wound coverage option available. We discuss in detail the history, product composition as well as advantages/disadvantages of allograft and Integra® DRT in order to provide clinicians with detailed knowledge of these two options.

Allografts—Temporary Biologic Composite Skin Substitute

History

The 1503 manuscript of Branca of Sicily is commonly cited as the first known attempt to use human-to-human skin grafts [30, 31]. George David Pollock, the pioneer of skin grafts, notably used a piece of his own skin for a surgical procedure in 1871 [32]. The development of modern allografts underwent rapid acceleration in the wake of World War II, during which the number of burn victims increased dramatically [33]. In response, the first modern skin bank was created by the United States Navy in 1949 [34]. Modern lypophilization technology has allowed cadaveric tissue to be stored indefinitely as allograft material [35, 36]. To date, donated skin from non-profit skin banks remains the primary source of allografts [3, 30].

Product Description

Cadaveric allografts are dermo-epidermal (composite) skin substitutes that provide temporary coverage and promote wound healing before they are rejected 2 to 3 weeks post-transplantation (Fig. 1d). While Alloderm RTM has been used in breast surgery [37–39], cleft palate repair [40], and even neurosurgery [41, 42], allograft is primarily indicated for large full-thickness burn injuries wherein donor sites are limited and a temporizing coverage is required following excision [19, 43–47]. Clinical examples of allograft use by our group are shown in Fig. 2.

Advantages and Disadvantages

Consistent with the plastic surgery tenet of substituting like tissue for like tissue, cadaveric allografts are more similar to native skin in their anatomy and physiology when compared to xenografts and bioengineered covers [48]. As a result, they effectively restore several important functions of the skin for the duration of their application: mechanical protection against shearing forces, decrease microbial contamination, and loss of fluids, electrolytes, proteins, and heat [19]. Other advantages of cadaveric allograft include their prolonged storage time, and ability to test the viability of a wound bed prior to autografting. Allograft has a relatively inexpensive product cost (since they are donated), but remains expensive to harvest, prepare, and store.

In spite of its advantages, cadaveric skin carries a theoretical risk of transmission of infectious diseases, though there has not been a documented case of allograft-transmitted HIV in over 30 years [49]. Commercially available allograft (GammaGraft®) is sterilized with gamma rays to eliminate this risk, but these products are more costly than donated tissue and it is unknown whether gamma irradiation compromises the structural integrity of the integumentary system or causes long-term harm [1]. Another issue with cadaveric allografts is the hidden cost associated with their processing and storage, as their natural shelf life without lypophilization is merely 7 to 10 days [36]. They can also take a significant amount of time to apply and must be held in sufficient supply to enable full coverage of large percent total body surface area (%TBSA) wounds [14]. Indeed, a recent study conducted by our group revealed that cadaveric allografts do not compare favorably to Biobrane®, a popular synthetic dressing, in relation to operative cost and time [14]. Finally, two surgical procedures must be performed in order to avoid the inevitable rejection of cadaveric allografts: temporary application of the allograft followed by replacement with an autograft.

Beyond donated cadaveric skin, there are several acellular covers derived from human dermis that will be discussed briefly in this review. Commercially available examples include Alloderm®, Glyaderm®, GraftJacket®, and Dermamatrix®. These products undergo various decellularization treatments to remove both the epidermis and the cellular components of the dermis in order to obtain an acellular scaffold for dermal regeneration. In terms of advantages, the resulting skin substitutes are immunologically inert and can be stored for prolonged periods [36] while preserving the micro-architecture and porosity of native dermis [48]. However, they are more expensive than cadaveric allograft and typically still require two surgical procedures, as epidermal or thin split-thickness autografts must additionally be applied to provide a complete set of new skin.

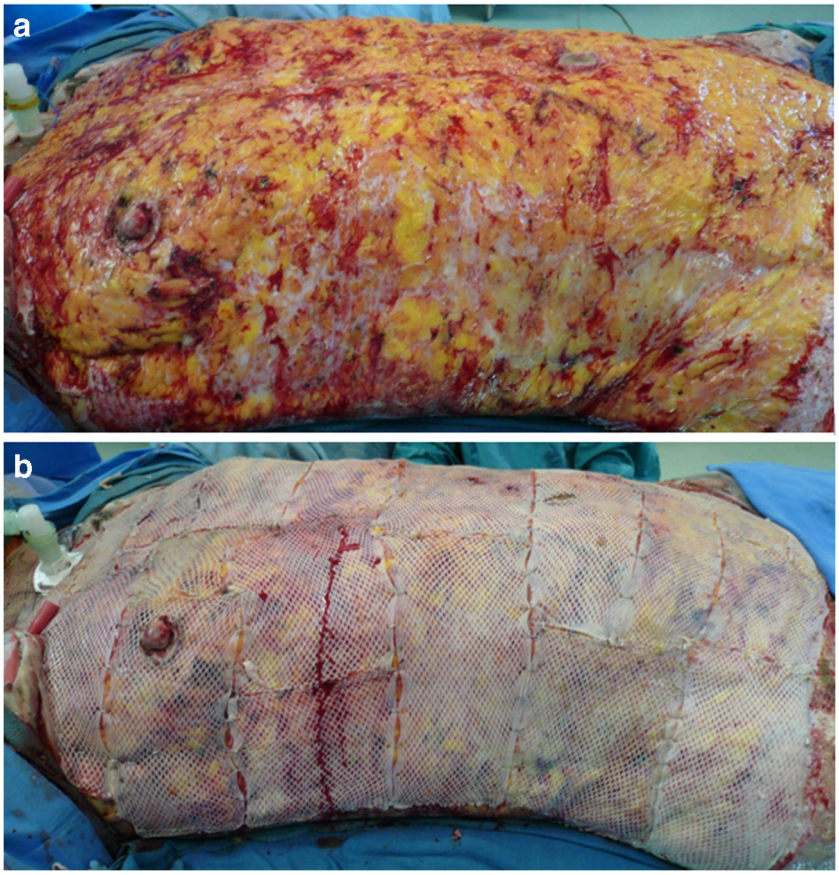

Fig. 2 A 36-year-old female with 70% TBSA full-thickness seen burn post debridement (**a**) and post allograft to torso and anterior abdomen (**b**)

Integra® Dermal Regenerative Template—Biosynthetic Temporary Epidermal and Permanent Dermal Replacement

History

Drs. Ioannis Yannas and John Burke developed the first regenerative skin scaffold Dermal Regenerative Template (DRT) in 1976 [50]. Designed with burn victims at the Boston Shriners Hospitals in mind, this dermal analog was first tested with deep skin wounds in guinea pig models. DRT was initially deemed to be a failure, as it delayed healing time [51]. However, this extended healing time delayed wound contraction to allow for wound closure by dermis-like tissue, termed neo-dermis [52–54]. This discovery led to the patenting of the "medical device" Integra®DRT in 1983 [55]. In 1996, the FDA approved Integra® DRT for use in deep partial-thickness and full-thickness burns and, subsequently, for unstable scar replacement [11••].

Product Description

The Integra® Dermal Regenerative Template (IDRT) represents a scaffold analog of the extracellular matrix (ECM) (Fig. 1e). IDRT is a bilayer product comprised of a type 1 collagen-glycosaminoglycan scaffold (CGS) base layer and a silicone top layer [52]. In a debrided deep skin wound, the CGS layer sits over the hypodermis, acting as the dermal ECM template, while the silicone serves as a temporary epidermal covering [56]. In physiological wound repair, fibroblasts invade the damaged skin and contract the wound edges to form a scar. The collagen type 1 fibers in the IDRT slow this process by binding fibroblasts via integrin-ligand interactions and preventing the macroscopic contractile forces [57]. This delay allows for proper synthesis of a dermal stroma in place of scar, which gradually replaces the IDRT, leading to formation of a neo-dermis. After the dermis matures over a period of 2 to 3 weeks during which limited donor sites can heal in time for re-harvesting, the superficial silicone layer can be removed and replaced with an epidermal autograft [56].

Currently, Integra® DRT is a well-established product in the acute burn care [11••] and reconstruction [58–60] of patients with limited donor sites, exposure of important structures such as tendons, unstable scar replacement [61], and the surgical treatment of soft tissue defects [62–65]. In our experience, IDRT can be applied to a wide variety of anatomical sites and may be particularly useful in head and neck burns, as its dermal equivalent prevents contracture and improves cosmetic outcomes (Fig. 3); as well as in hand burns, as its dermal scaffold is resistant to shearing forces (Fig. 4).

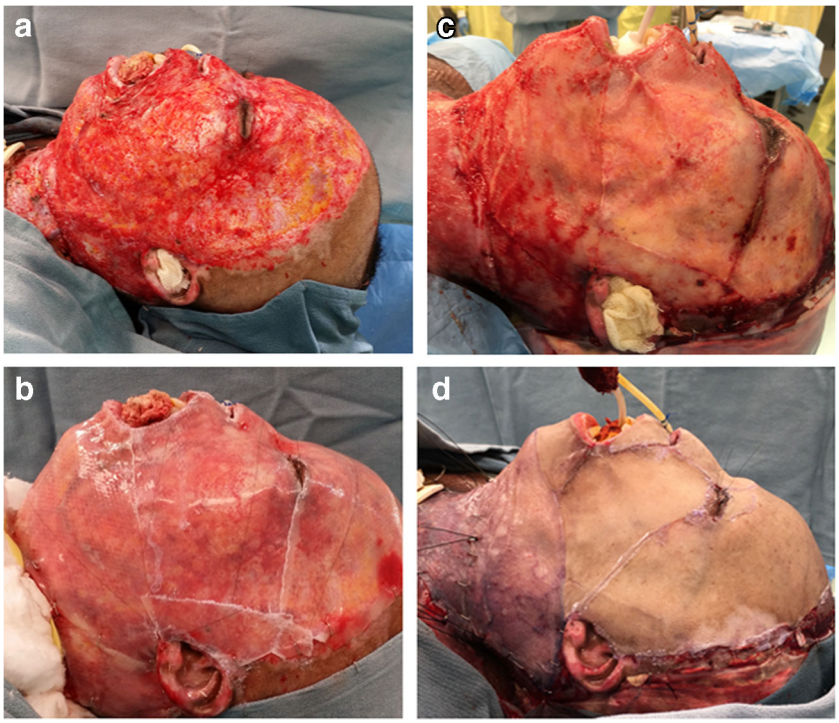

Fig. 3 A 26-year-old female with 65% TBSA full-thickness burn post self-immolation. After the burnt head and neck skin was carefully debrided (**a**), Integra® was applied in accordance with aesthetic subunits of the face (**b**). The cover was allowed to integrate for approximately 3 weeks (**c**) and then the superficial silicone layer was replaced by a sheet autograft (**d**)

Advantages and Disadvantages

Integra® DRT boasts a number of advantageous features. Other than being contraindicated for those with allergic reactions to bovine products [66], it circumvents the issue of immunogenicity that limits xenografts and allografts to temporary coverage. IDRT is also widely accessible off-the-shelf, where it can be stored for up to 2 years [36]. Its neo-dermis allows for thinner autografts, thereby minimizing donor site morbidity. Importantly, IDRT has also demonstrated improved long-term elasticity and cosmesis compared to split-thickness skin grafting alone [67]. Finally, the product is additionally offered in single layer form (IntegraSL®), which allows for simultaneous application of the dermal matrix together with an overlying epidermal or thin split-thickness autograft in patients with

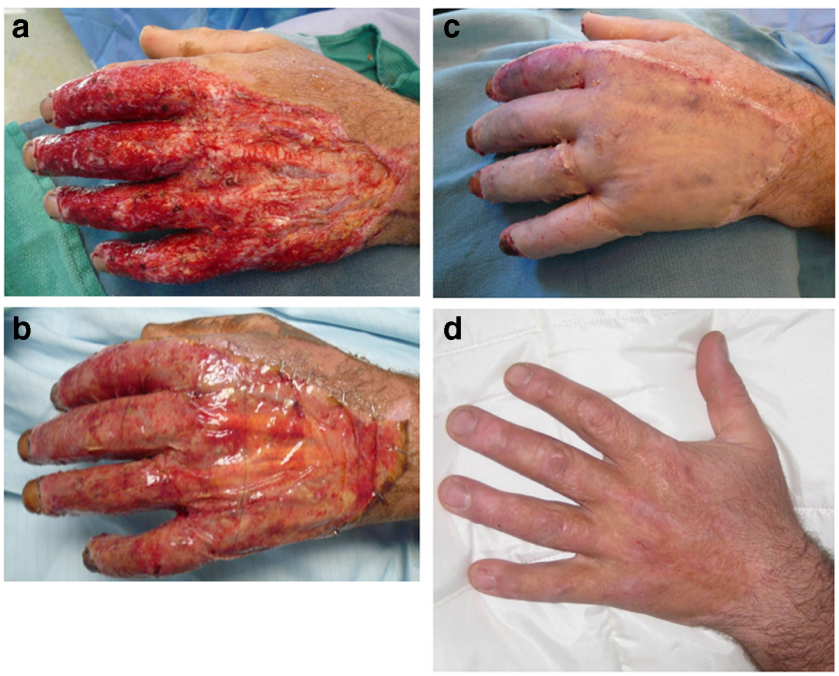

Fig. 4 A 42-year-old left hand dominant male with full-thickness tar burn to the left hand. The burnt dorsal skin was carefully debrided (**a**) before Integra® was applied on the clean wound bed (**b**). The cover was allowed to integrate for 3 weeks and then the epidermal layer was replaced by a sheet autograft (**c**). The long-term aesthetic results are depicted in (**d**)

Table 2 Comparison of reviewed wound covers in relation to the ideal skin substitute characteristics

Characteristics	Xenografts	Allografts	Integra®	MatriStem™ UBM
Inexpensive	✓	✓ relatively	✗	✗
Off-the-shelf	✓	✗ (other than fresh)	✓	✓
Long shelf life	✓	✓ if cryopreserved or lyophilized	✓	✓
Durable	✓	✓	✓	✓
Pliable	Product-dependent	✓	✓	✓
Ease of handling (1 procedure)	✗	✗	✗	✗
Non-antigenic	✗	✗	✓	✓
No disease transmission risk	✗ theoretical risk	✗ theoretical risk	✓	✓
Permanent (integrated in wound)	✗	✗	✓	✓
Minimal donor site morbidity	–	–	✓	–
Resembles native skin anatomy	✗	✓	✗	✗
Barrier to fluid loss and shear	✓	✓	✓	✓
Resistance to local infection	✗	✓	✗	
Produces stable scar			✓	

adequate donor site availability. Integra™ Matrix Wound Dressing is another available product which can be used single stage or in conjunction with a thin skin autograft. Integra™ Matrix is a collagen-glycosaminoglycan biodegradable matrix that provides a scaffold for dermal regeneration.

Despite its advantages, Integra® DRT is not without shortcomings. It has been associated with a greater risk of hematoma and seroma formation that predispose to infection and total loss of the product, particularly given its lack of inherent antibacterial qualities [3, 67]. Nonetheless, it can be meshed at a 1:1 ratio to help avoid hematomas and seromas while optimizing the bioavailability of antimicrobial dressings. This countermeasure illustrates another drawback of IDRT: it requires skilled surgeons who have overcome a significant learning curve to use it properly [11••]. Additionally, IDRT is cross-linked with glycosaminoglycans, which have anti-angiogenic properties, albeit no clinical studies corroborating their theoretical impairment in wound healing [68]. Another issue is that IDRT cannot provide a full dermo-epidermal replacement despite its substantial cost [69]. Lastly, the evidence for its use remains modest and should be expanded [67, 70].

Table 3 Advantages and disadvantages of reviewed wound coverage options

Reviewed cover	Advantages	Disadvantages
Porcine xenografts	•Inexpensive •Long shelf life •No surgical intervention required •Full dermo-epidermal skin substitute	•Less similar to host skin than allografts •Limited to temporary coverage •Contraindicated in allergies to porcine materials. Cross-linking may compromise wound healing
Cadaveric allografts	•More similar to host skin than xenografts •Test wound bed viability prior to autografting •Long shelf life if lypophilized or cryopreserved (but otherwise short)	•Limited to temporary coverage •Theoretical risk of infectious disease transmission •Application requires two surgical procedures •Significant operative time and cost •Must be held in sufficient supply to enable full coverage
Integra®	•Non-antigenic •Naturally integrates into wound •Long shelf life •Off-the-shelf availability •Better elasticity and cosmesis than split-thickness skin grafting alone •Minimal donor site morbidity	•Expensive •Contraindicated in allergies to bovine materials •Risk of hematoma and seroma formation •Risk of infection and loss of product •Significant learning curve for use •Cross-linking may compromise wound healing •Only substitutes dermis
MatriStem™	•Naturally integrates into wound •Long shelf life •Off-the-shelf availability	•Relatively expensive •Extremely limited research on its use as yet

Alternative Skin Substitutes

Interestingly, several skin substitutes have been developed and have promising results as wound covers yet are poorly integrated into clinical practice. We discuss one product, MatriStem™, in this review in order to generate discussion about this promising product. MatriStem™ is a natural single layer dermal substitute.

MatriStem™—Temporary Biologic Dermal Replacement

History

As early as 1966, experiments with submucosal autografts of veins were successful in dogs [71]. The ECM of submucosal grafts provided a matrix for tissue regeneration after the tissue was devitalized and rendered acellular [72, 73]. By the advent of the twenty-first century, small intestine submucosa of pigs was being used successfully as xenograft material in humans [74]. The use of porcine urinary bladder, as opposed to intestine, as an ECM scaffold was patented in 1999 by Dr. Alan Spievack, who founded ACell® [72, 75]. The FDA approved the first ACell® products in 2002 for use in trauma wounds including partial-thickness burns [76].

Product Description

ACell's MatriStem™ Urinary Bladder Matrix (UBM) is a porcine-derived ECM scaffold (Fig. 1f). The UBM is obtained by harvesting bladder tissue from a pig and then de-epithelializing it with a hypertonic solution. The epithelial cells are hence separated from their basement membrane and the remaining abluminal tissue can be removed by mechanical or chemical (enzymatic) means [72]. Porcine UBM is unique in that it retains its basement membrane following enzymatic treatment [77]. The intact basement membrane ECM can then be placed on damaged tissue. This provides a medium that encourages cell growth, migration, and development. Over the first 14 days, mononuclear cells infiltrate the ECM matrix while its scaffold degrades. Site-specific endothelial cells provide remodeling in the wound bed thereafter. Additionally, the basement membrane complex prevents invasion of fibroblasts, effectively reducing scar formation. The result is well-formed, functional tissue [77–79]. According to a growing number of studies conducted from 2010 onward, MatriStem™ UBM has been successfully used in deep partial-thickness burn injuries [80•], ulcers [81–84], and gastroenterological [85–87], genitourinary [88–91], and other reconstructive [84, 92–94] surgeries. It was also recently reported to be used in the treatment of a right atrial sarcoma [95] and a left atrial hemangioma [96].

Advantages and Disadvantages

The advantages of MatriStem™ UBM include its immediate availability as an off-the-shelf product and its ability to be stored at room temperature (Table 2). While it appears to have performed favorably thus far in terms of important parameters including wound healing time and surgical site infection rates [97], the published evidence for its use remains extremely limited, particularly with respect to burns [80•]. Furthermore, it is a relatively expensive product whose cost falls between that of synthetic grafts and most comparable biological grafts [88].

Conclusions

This brief review describes and appraises four wound coverage options: xenografts, allografts, Integra®, and MatriStem™ (Table 2). The review highlights the first wound cover described (xenograft), provides comprehensive information for two commonly used products (Integra® and allograft), and highlights a promising yet infrequently utilized product, MatriStem™. The advantages and disadvantages of each wound cover are summarized in Table 3 to facilitate comparison. Various other wound cover options are available to providers caring for wounds, each with their own risk-benefit profile. When considering wound covers, clinicians should compare and contrast options in order to select the most appropriate wound coverage options with regard to cellularity, layering, replaced region, material, and permanence.

Due to the characteristic deficiencies of each currently available skin substitute, new technology is being aggressively pursued to expand the burn care provider's armamentarium. Skin bioprinting or 3D printing of the skin is a novel technology that was first developed in 1984 by Charles W. Hull [98•, 99•, 100]. Due to the substantial advances in engineering, industrial design, biotechnology, and medicine of the last decade, there has been significant progress in the in vitro development of this new technology. Three-dimensional printing offers the distinct advantage of reproducibly allowing for precise layering of extracellular matrix, growth factors, and epidermal cells [98•, 99•, 100]. It also provides an alternative when faced with a shortage of donor sites. 3D printing is a promising novel skin substitute option owing to these advantageous features. Another interesting area of research is the use of stem cells in the treatment of dermatological conditions such as wound regeneration. Compared to the traditional skin substitutes, stem cells are advantageous in that they have the potential to differentiate into various cells types, thus creating integumentary components that are missing (for example, hair follicles or elastin) in currently available skin substitutes [101, 102]. As each patient possesses adult stem cells, this tissue engineering technology will profoundly impact wound care if it succeeds in offering a full dermo-epidermal replacement without the risk of immune rejection.

Despite promising novel technology such as 3D skin printing and stem cells, no perfect wound cover is presently available. The optimal choice for a given patient is context-dependent and rests on a number of factors that should be collectively taken into consideration. These include cost, availability, shelf life, ease of use, permanence, anatomic extent of the wound, inflammatory response elicited by the product, and resistance to fluid loss, infection, and shearing forces. Regardless of the cover, the importance of properly applying the principles of wound management—early and adequate debridement, infection control, and perfusion restoration—cannot be overstated. Therefore, characteristics of a specific wound as well as careful evaluation of these parameters should guide healthcare providers toward selecting the most appropriate cover for an individual patient.

Compliance with Ethical Standards

Conflict of Interest Dr. Adibfar has nothing to disclose. Dr. Retrouvey has nothing to disclose. Dr. Padeanu has nothing to disclose. Dr. Shahrokhi reports personal fees from Integra LifeSciences, personal fees from UpToDate, personal fees from Acelity, outside the submitted work. Dr. Jeschke has nothing to disclose.

Human and Animal Rights and Informed Consent All patients have given consent for their pictures to be included in publications.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Nyame TT, Chiang HA, Orgill DP. Clinical applications of skin substitutes. Surg Clin North Am. 2014;94(4):839–50.
2. Janis JE, Kwon RK, Attinger CE. The new reconstructive ladder: modifications to the traditional model. Plast Reconstr Surg. 2011;127(Suppl 1):205S–12S.
3. Shores TJ, Gabriel TA, Gupta TS. Skin substitutes and alternatives: a review. Adv Skin Wound Care. 2007;20(9):493–508.
4. van der Veen VC, van der Wal MB, van Leeuwen MC, Ulrich MM, Middelkoop E. Biological background of dermal substitutes. Burns. 2010;36(3):305–21.
5. Banes AJ, Compton DW, Bornhoeft J, Hicks H, Link GW, Bevin AG, et al. Biologic, biosynthetic, and synthetic dressings as temporary wound covers: a biochemical comparison. J Burn Care Rehabil. 1986;7(2):96–104.
6. Jones I, Currie L, Martin R. A guide to biological skin substitutes. Br J Plast Surg. 2002;55(3):185–93.
7. Yildirimer L, Thanh NT, Seifalian AM. Skin regeneration scaffolds: a multimodal bottom-up approach. Trends Biotechnol. 2012;30(12):638–48.
8. Simman R. Wound closure and the reconstructive ladder in plastic surgery. J Am Col Certif Wound Spec. 2009;1(1):6–11.
9. Kumar P. Classification of skin substitutes. Burns. 2008;34(1):148–9.
10. •• Davison-Kotler E, Sharma V, Kang NV, García-Gareta E. A universal classification system of skin substitutes inspired by factorial design. Tissue Eng Part B Rev. 2018;24(4):279–88 **(This paper provides the most recently-proposed classification system for and skin substitutes nearly a decade following the work of Kumar and Ferreira et al.).**
11. •• Shahrokhi S, Arno A, Jeschke MG. The use of dermal substitutes in burn surgery: acute phase. Wound Repair Regen. 2014;22(1):14–22 **(The above reference provides a detailed review of numerous dermal substitutes and their classifications. It also describes the functional requirements of dermal substitutes.)**.
12. Ferreira MC, Paggiaro AO, Isaac C, Neto NT, dos Santos GB. Skin substitutes: current concepts and a new classification system. Rev Bras Cir Plást. 2011;26(4):696–702.
13. Chua AW, Khoo YC, Tan BK, Tan KC, Foo CL, Chong SJ. Skin tissue engineering advances in severe burns: review and therapeutic applications. Burns Trauma. 2016;4:3.
14. Austin RE, Merchant N, Shahrokhi S, Jeschke MG. A comparison of Biobrane™ and cadaveric allograft for temporizing the acute burn wound: cost and procedural time. Burns. 2015;41(4):749–53.
15. Chiu T, Burd A. "Xenograft" dressing in the treatment of burns. Clin Dermatol. 2005;23(4):419–23.
16. Bromberg BE, Song IC, Mohn MP. The use of pig skin as a temporary biological dressing. Plast Reconstr Surg. 1965;36:80.
17. Sarto Piccolo N, Sarto Piccolo M, Sarto Piccolo MT. The use of frogskin as a biological dressing for temporary cover of burn wounds. In: Eisenmann-Klein M, Neuhann-Lorenz C, editors. Innovations in plastic and aesthetic surgery. Berlin: Springer Berlin Heidelberg; 2008. p. 129–37.
18. Mulier KE, Nguyen AH, Delaney JP, Marquez S. Comparison of Permacol™ and Strattice™ for the repair of abdominal wall defects. Hernia. 2011;15(3):315–9.
19. Pruitt BA, Levine NS. Characteristics and uses of biologic dressings and skin substitutes. Arch Surg. 1984;119(3):312–22.
20. Troy J, Karlnoski R, Downes K, Brown KS, Cruse CW, Smith DJ, et al. The use of EZ Derm® in partial-thickness burns: an institutional review of 157 patients. Eplasty. 2013;13:e14.
21. Burkey B, Davis W, Glat PM. Porcine xenograft treatment of superficial partial-thickness burns in paediatric patients. J Wound Care. 2016;25(2):S10–5.
22. Pitkin L, Rimmer J, Lo S, Hosni A. Aesthetic augmentation rhinoplasty with Permacol: how we do it. Clin Otolaryngol. 2008;33(6):615–8.
23. Chang C, Kong WK. Clinical effectiveness and safety of collagen sheet for dorsal augmentation in rhinoplasty. J Craniofac Surg. 2014;25(5):1852–4.
24. Saray A. Porcine dermal collagen (Permacol) for facial contour augmentation: preliminary report. Aesthetic Plast Surg. 2003;27(5):368–75.
25. Cheung EV, Silverio L, Sperling JW. Strategies in biologic augmentation of rotator cuff repair: a review. Clin Orthop Relat Res. 2010;468(6):1476–84.
26. Doussot A, Abo-Alhassan F, Derbal S, Fournel I, Kasereka-Kisenge F, Codjia T, et al. Indications and outcomes of a cross-linked porcine dermal collagen mesh (Permacol) for complex abdominal wall reconstruction: a multicenter audit. World J Surg 2018.
27. Cheng AW, Abbas MA, Tejirian T. Outcome of abdominal wall hernia repair with biologic mesh: Permacol™ versus Strattice™. Am Surg. 2014;80(10):999–1002.
28. Warwick AM, Velineni R, Smart NJ, Daniels IR. Onlay parastomal hernia repair with cross-linked porcine dermal collagen biologic mesh: long-term results. Hernia. 2016;20(2):321–5.
29. MacLeod TM, Cambrey A, Williams G, Sanders R, Green CJ. Evaluation of Permacol as a cultured skin equivalent. Burns. 2008;34(8):1169–75.

30. Halim AS, Khoo TL, Mohd Yussof SJ. Biologic and synthetic skin substitutes: an overview. Indian J Plast Surg. 2010;43(S):S23–8.
31. Vig K, Chaudhari A, Tripathi S, Dixit S, Sahu R, Pillai S, et al. Advances in skin regeneration using tissue engineering. Int J Mol Sci. 2017;18(4):789.
32. Freshwater MF, Krizek TJ. Skin grafting of burns: a centennial. A tribute to George David Pollock. J Trauma. 1971;11(10):862–5.
33. Lee KC, Joory K, Moiemen NS. History of burns: the past, present and the future. Burns Trauma. 2014;2(4):169–80.
34. Herndon DN. Total burn care: expert consult—online and print: Elsevier Health Sciences; 2012.
35. Bondoc CC, Burke JF. Clinical experience with viable frozen human skin and a frozen skin bank. Ann Surg. 1971;174(3):371–82.
36. Shevchenko RV, James SL, James SE. A review of tissue-engineered skin bioconstructs available for skin reconstruction. J R Soc Interface. 2010;7(43):229–58.
37. Jones G, Yoo A, King V, Jao B, Wang H, Rammos C, et al. Prepectoral immediate direct-to-implant breast reconstruction with anterior AlloDerm coverage. Plast Reconstr Surg. 2017;140(6S Prepectoral Breast Reconstruction):31S–8S.
38. Parikh RP, Brown G, Sharma K, Yan Y, Myckatyn TM. Immediate implant-based breast reconstruction with acellular dermal matrix: a comparison of sterile and aseptic AlloDerm in 2039 consecutive cases. Plast Reconstr Surg 2018.
39. Gabriel A, Maxwell GP. AlloDerm RTU integration and clinical outcomes when used for reconstructive breast surgery. Plast Reconstr Surg Glob Open. 2018;6(5):e1744.
40. Simpson A, Samargandi OA, Wong A, Graham ME, Bezuhly M. Repair of primary cleft palate and oronasal fistula with acellular dermal matrix: a systematic review and surgeon survey. Cleft Palate Craniofac J 2018:1055665618774028.
41. Bowers CA, Brimley C, Cole C, Gluf W, Schmidt RH. AlloDerm for duraplasty in Chiari malformation: superior outcomes. Acta Neurochir. 2015;157(3):507–11.
42. Cobb MIH, Crowson M, Mintz-Cole R, Husain AM, Berger M, Jang D, et al. Transnasal transsphenoidal elevation of optic chiasm in secondary empty sella syndrome following prolactinoma treatment. World Neurosurg. 2018;112:250–3.
43. Yim H, Cho YS, Seo CH, Lee BC, Ko JH, Kim D, et al. The use of AlloDerm on major burn patients: AlloDerm prevents post-burn joint contracture. Burns. 2010;36(3):322–8.
44. Callcut RA, Schurr MJ, Sloan M, Faucher LD. Clinical experience with Alloderm: a one-staged composite dermal/epidermal replacement utilizing processed cadaver dermis and thin autografts. Burns. 2006;32(5):583–8.
45. Wainwright DJ, Bury SB. Acellular dermal matrix in the management of the burn patient. Aesthet Surg J. 2011;31(7S):13S–23S.
46. Pirayesh A, Hoeksema H, Richters C, Verbelen J, Monstrey S. Glyaderm(®) dermal substitute: clinical application and long-term results in 55 patients. Burns. 2015;41(1):132–44.
47. Verbelen J, Hoeksema H, Pirayesh A, Van Landuyt K, Monstrey S. Exposed tibial bone after burns: flap reconstruction versus dermal substitute. Burns. 2016;42(2):e31–7.
48. Leclerc T, Thepenier C, Jault P, Bey E, Peltzer J, Trouillas M, et al. Cell therapy of burns. Cell Prolif. 2011;44(S1):48–54.
49. Clarke JA. HIV transmission and skin grafts. Lancet. 1987;1(8539):983.
50. **Professor Ioannis Yannas: MITMECHE; [Available from**: http://meche.mit.edu/people/faculty/YANNAS@MIT.EDU].
51. Freidah J. Hope regenerated (a life-saving discovery at MIT MechE). USA: Massachusetts Institute of Technology; 2016. p. 16:56.
52. Yannas IV, Burke JF, Orgill DP, Skrabut EM. Wound tissue can utilize a polymeric template to synthesize a functional extension of skin. Science. 1982;215(4529):174–6.
53. Orgill DP. The effects of an artificial skin on scarring and contraction in open wounds 1983 **[Available from: https://scholar.google.com/citations?hl=en&user=p5HtZOAAAAAJ&view_op=list_works&sortby=pubdate]**.
54. Yannas IV, Burke JF, Warpehoski M, Stasikelis P, Skrabut EM, Orgill D, et al. Prompt, long-term functional replacement of skin. Trans Am Soc Artif Intern Organs. 1981;27:19.
55. Yannas IV, Burke JF, Orgill DP, Skrabut EM, inventors. Method of promoting the regeneration of tissue at a wound. USA1983 1983-12-06.
56. Burke JF, Yannas IV, Quinby WC Jr, Bondoc CC, Jung WK. Successful use of a physiologically acceptable artificial skin in the treatment of extensive burn injury. Ann Surg. 1981;194(4):413–28.
57. Yannas IV, Tzeranis DS, Harley BA, So PTC. Biologically active collagen-based scaffolds: advances in processing and characterization. Phil Trans R Soc A. 2010;368(1917):2123.
58. Moiemen N, Yarrow J, Hodgson E, Constantinides J, Chipp E, Oakley H, et al. Long-term clinical and histological analysis of Integra dermal regeneration template. Plast Reconstr Surg. 2011;127(3):1149–54.
59. Moiemen NS, Vlachou E, Staiano JJ, Thawy Y, Frame JD. Reconstructive surgery with Integra dermal regeneration template: histologic study, clinical evaluation, and current practice. Plast Reconstr Surg. 2006;117(7S):160S–74S.
60. Stiefel D, Schiestl C, Meuli M. Integra artificial skin for burn scar revision in adolescents and children. Burns. 2010;36(1):114–20.
61. Zajíček R, Grossová I, Šuca H, Kubok R, Pafčuga I. Experience with Integra® at the Prague Burns Centre 2002-2016. Acta Chir Plast. 2017;59(1):18–26.
62. Khan MA, Ali SN, Farid M, Pancholi M, Rayatt S, Yap LH. Use of dermal regeneration template (Integra) for reconstruction of full-thickness complex oncologic scalp defects. J Craniofac Surg. 2010;21(3):905–9.
63. Watts V, Attie MD, McClure S. Reconstruction of complex full-thickness scalp defects after dog-bite injuries using dermal regeneration template (Integra): case report and literature review. J Oral Maxillofac Surg 2018.
64. Chen TA, Ayala-Haedo JA, Blessing NW, Topping K, Alabiad CR, Erickson BP. Bioengineered dermal substitutes for the management of traumatic periocular tissue loss. Orbit. 2018;37(2):115–20.
65. Belek KA, Alkureishi LW, Dunn AA, Devcic Z, Kuri M, Lee CK, et al. Single-stage reconstruction of a devastating antebrachial injury with brachial artery, median nerve, and soft tissue deficit: a case report and review of the literature. Eplasty. 2010;10:e33.
66. Clark RA, Ghosh K, Tonnesen MG. Tissue engineering for cutaneous wounds. J Invest Dermatol. 2007;127(5):1018–29.
67. Nguyen DQ, Potokar TS, Price P. An objective long-term evaluation of Integra (a dermal skin substitute) and split thickness skin grafts, in acute burns and reconstructive surgery. Burns. 2010;36(1):23–8.
68. Yannas IV, Burke JF, Gordon PL, Huang C, Rubenstein RH. Design of an artificial skin. II. Control of chemical composition. J Biomed Mater Res. 1980;14(2):107–32.
69. Greenhalgh DG. The use of dermal substitutes in burn surgery: acute phase. Wound Repair Regen. 2014;22(1):1–2.
70. Fette A. Integra artificial skin in use for full-thickness burn surgery: benefits or harms on patient outcome. Technol Health Care. 2005;13(6):463–8.
71. Matsumoto T, Holmes RH, Burdick CO, Heisterkamp CA, O'Connell TJ. Replacement of large veins with free inverted segments of small bowel: autografts of submucosal membrane in dogs and clinical use. Ann Surg. 1966;164(5):845.

72. Spievack AR, ACell Inc, inventors. Tissue regenerative composition, method of making, and method of use thereof. **USA2003 2003-06-10**.
73. Gilbert TW, Sellaro TL, Badylak SF. Decellularization of tissues and organs. Biomaterials. 2006;27(19):3675–83.
74. Lindberg K, Badylak SF. Porcine small intestinal submucosa (SIS): a bioscaffold supporting in vitro primary human epidermal cell differentiation and synthesis of basement membrane proteins. Burns. 2001;27(3):254–66.
75. Our Story: ACell Inc; 2018 [**Available from:** https://acell.com/our-story/].
76. 510(k) Summary—ACell UBM lyophilized wound dressing. In: Services DoHaH, editor.: Food and Drug Administration; 2002.
77. Brown B, Lindberg K, Reing J, Badylak S. The basement membrane component of biologic scaffolds derived from extracellular matrix. Tissue Eng. 2006;12(3):519–26.
78. Badylak SF. The extracellular matrix as a scaffold for tissue reconstruction. Semin Cell Dev Biol. 2002;13(5):377–83.
79. Lanteri Parcells A, Abernathie B, Datiashvili R. The use of urinary bladder matrix in the treatment of complicated open wounds. Wounds. 2014;26(7):189.
80.• Kim JS, Kaminsky AJ, Summitt JB, Thayer WP. New innovations for deep partial-thickness burn treatment with ACell MatriStem matrix. Adv Wound Care (New Rochelle). 2016;5(12):546–52 **(This recent publication provides insight into how ACell® products are increasingly being studied in spite of the currently-limited research on their clinical uses)**.
81. Martinson M, Martinson N. A comparative analysis of skin substitutes used in the management of diabetic foot ulcers. J Wound Care. 2016;25(Sup10):S8–S17.
82. Frykberg RG, Cazzell SM, Arroyo-Rivera J, Tallis A, Reyzelman AM, Saba F, et al. Evaluation of tissue engineering products for the management of neuropathic diabetic foot ulcers: an interim analysis. J Wound Care. 2016;25(Suppl 7):S18–25.
83. Liu YC, Chhabra N, Houser SM. Novel treatment of a septal ulceration using an extracellular matrix scaffold (septal ulceration treatment using ECM). Am J Otolaryngol. 2016;37(3):195–8.
84. Rommer EA, Peric M, Wong A. Urinary bladder matrix for the treatment of recalcitrant nonhealing radiation wounds. Adv Skin Wound Care. 2013;26(10):450–5.
85. Iorio T, Blumberg D. Short-term results of treating primary and recurrent anal fistulas with a novel extracellular matrix derived from porcine urinary bladder. Am Surg. 2015;81(5):498–502.
86. Afaneh C, Abelson J, Schattner M, Janjigian YY, Ilson D, Yoon SS, et al. Esophageal reinforcement with an extracellular scaffold during total gastrectomy for gastric cancer. Ann Surg Oncol. 2015;22(4):1252–7.
87. Cairo SB, Tabak B, Harmon CM, Bass KD. Novel use of porcine extracellular matrix in recurrent stricture following repair of tracheoesophageal fistula. Pediatr Surg Int. 2017;33(9):1027–33.
88. Sasse KC, Warner DL, Ackerman E, Brandt J. Hiatal hernia repair with novel biological graft reinforcement. JSLS. 2016;20(2).
89. Gupta A, Francis S, Stewart R, Hobson D, Meriwether KV. Repair of colonic neovaginal stenosis using a biological graft in a male-to-female transgender patient. Int Urogynecol J 2018.
90. Pearlman AM, Mujumdar V, McAbee KE, Terlecki RP. Outcomes of adult urethroplasty with commercially available acellular matrix. Ther Adv Urol. 2018;10(11):351–5.
91. Liang R, Knight K, Easley D, Palcsey S, Abramowitch S, Moalli PA. Towards rebuilding vaginal support utilizing an extracellular matrix bioscaffold. Acta Biomater. 2017;57:324–33.
92. Shanti RM, Smart RJ, Meram A, Kim D. Porcine urinary bladder extracellular matrix for the salvage of fibula free flap skin paddle: technical note and description of a case. Craniomaxillofac Trauma Reconstr. 2017;10(4):318–22.
93. Dorman RM, Bass KD. Novel use of porcine urinary bladder matrix for pediatric pilonidal wound care: preliminary experience. Pediatr Surg Int. 2016;32(10):997–1002.
94. Flavill E, Gilmore JE. Septal perforation repair without intraoperative mucosal closure. Laryngoscope. 2014;124(5):1112–7.
95. Abu Saleh WK, Al Jabbari O, Ramlawi B, Bruckner BA, Loebe M, Reardon MJ. Right atrial tumor resection and reconstruction with use of an acellular porcine bladder membrane. Tex Heart Inst J. 2016;43(2):175–7.
96. Abu Saleh WK, Al Jabbari O, Bruckner BA, Reardon MJ. Case report: a rare case of left atrial hemangioma: surgical resection and reconstruction. Methodist Debakey Cardiovasc J. 2016;12(1):51–4.
97. Sasse KC, Brandt J, Lim DC, Ackerman E. Accelerated healing of complex open pilonidal wounds using MatriStem extracellular matrix xenograft: nine cases. J Surg Case Rep 2013;2013(4).
98. Algzlan H, Varada S. Three-dimensional printing of the skin. JAMA Dermatol. 2015;151(2):207.
99.• Augustine R. Skin bioprinting: a novel approach for creating artificial skin from synthetic and natural building blocks. Prog Biomater 2018. **(A recent report that provides an introduction to 3D skin printing, a promising future option for the future of skin reconstruction)**.
100. He P, Zhao J, Zhang J, Li B, Gou Z, Gou M, et al. Bioprinting of skin constructs for wound healing. Burns Trauma. 2018;6:5.
101. Chen M, Przyborowski M, Berthiaume F. Stem cells for skin tissue engineering and wound healing. Crit Rev Biomed Eng. 2009;37(4–5):399–421.
102. Niezgoda A, Niezgoda P, Nowowiejska L, Białecka A, Męcińska-Jundziłł K, Adamska U, et al. Properties of skin stem cells and their potential clinical applications in modern dermatology. Eur J Dermatol. 2017;27(3):227–36.