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Skin Substitutes and Dermatology: A Review

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Abstract Death from large burn wounds has pushed the development of life-saving techniques to cover and heal these wounds as rapidly as possible, resulting in a variety of tissue engineered skin substitutes available on the market. There remains a paucity of good quality RCTs evaluating the efficacy of skin substitutes, and even fewer studies comparing products to each other. While some products have been used successfully for dermatologic applications and published in the literature, a vast majority of data that we do have on skin substitutes relates to chronic wound management and care of burn patients. Though not specific to our specialty, the use of skin substitutes for these indications can be extrapolated to dermatology. Understanding the composition, advantages/disadvantages, and risk/benefit of each product, as well as the indications for each product's use, facilitates the selection of the appropriate substitute. This review will hopefully provide the information that makes the use of these products feasible for the appropriate defect.

Keywords Allograft · Autograft · Dermatology · Dermatologic surgery · Mohs surgery · Reconstruction · Skin substitute · Wound · Xenograft

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Introduction

Death from large burn wounds has pushed the development of life-saving techniques to cover and heal these wounds as rapidly as possible. Full-thickness and split-thickness autologus grafts were many times not large enough to cover wounds, and this lead to cultured autologous skin grafts, which while they took several weeks to grow, offered unlimited amounts of epidermis for grafting. While autografting provides the best engraftment, these grafts may not solve all the cosmetic and functional issues. Full-thickness skin grafts may not correct contour distortion, while split-thickness grafts (meshed or unmeshed) may lead to poor cosmesis or even deformity secondary to contracture. The new skin substitutes, whether they are biologic or synthetic, offer new options that have improved outcomes with appearance and function. While outcomes have been improving for burn patients, the use of all of the products and techniques has offered new opportunities for large difficult surgical wounds. This paper will review the new products available for dermatologic surgeons managing complex wounds (Table 1).

Skin substitutes are primarily categorized by the type of tissue used for grafting. Products are broadly classified as xenografts, allografts, and autografts. There can be some overlap among categories when an individual product contains both animal and synthetic components or both human and animal components. For the purpose of this paper, products with any human tissue, regardless of the presence of concomitant animal tissue, are classified as allografts. Products with animal tissue and no human component, regardless of whether they have synthetic components, are classified as xenografts.

Table 1 Select skin substitute characteristics by tissue type

Type of skin substitute	Examples	Preparation Time	Shelf life/storage	Antigenicity	Cost*
Allogenic acellular dermis	Alloderm, Allopatch DermaMatrix	Rehydration (3-40 min)	2–3 yrs room temp	Low	$$$$
Allogenic cellular dermis	Dermagraft	~30 min	Frozen	Moderate	$$$
Allogenic composite tissue	Apligraf	Ready to use	Short (5 days)	Moderate	$$$
Xenografts	Mediskin	Ready to use to short thaw/rehydration time	18 mos–5 yrs based on product	High	$
	Integra				$$$
Autologous cultured skin	Epicel	30 min to 21 days	N/A	None	N/A
Synthetic	BioBrane	Ready to use	3 yrs	High	$

*Relative cost comparison based on negotiated contracts at a single institution

Xenografts

Xenografts are tissues from one species used for wound repair in another species. Porcine and bovine products are most commonly used. They are usually dermis from which the epidermis has been removed, although some products also have epidermis attached. Sterilization of the products is achieved by treatment with antibiotics, chemical antiseptics, and radiation. Xenografts have been successfully used to biologically dress and enhance healing of a variety of wounds, including full-thickness and partial burns, vascular, diabetic, trauma and pressure-induced ulcers. Xenografts have also been successfully used in dermatologic surgery reconstruction. They may provide an advantage to primary repair in a variety of instances, such as exposed bone, tendon or cartilage, or in cases of significant wound depth, where they can stimulate dermal regeneration and contour restoration prior to definitive repair, preventing contraction or binding down of any graft and preserving mobility when reconstructing defects overlying joints. Xenografts may be appealing to the dermatologic surgeon due to their long shelf life and relatively low cost.

A variety of commercially available xenografts exist. They are typically found as a 2x2 inch square in sterile package that must be stored refrigerated or frozen to prevent dessication of the isolated dermis. However, new products have been developed that can be stored at room temperature. The frozen or refrigerated xenografts quickly thaw upon room temperature exposure. In those products with an epidermal component, it is essential to identify the dermal side of the graft, which will curl toward this side when suspended from a corner. Xenografts are easily and rapidly applied by placing the dermal side down onto the wound and trimming the overhanging edges as needed. The perimeter is then sutured into place and an overlying dressing applied, with care to ensure the center of the graft is making good contact with the wound base. This is accomplished with either basting sutures or a bolster dressing. Wound check is performed in 5–7 days. At this time, the graft may be removed. If further dermal regeneration is needed before allowing reepithelialization or performing definitive repair, another xenograft can be applied. Alternatively, the graft may be left in place as a biologic dressing, in which case necrosis and slough over time is to be expected [1]. Occasionally there is what appears to be a "take" of the xenograft, although, over time, all donor cells are replaced with host cells.

Some examples of porcine derived acellular xenografts with applications for dermatologic surgery include EZ-Derm, Mediskin, Oasis tissue matrix, and Matristem.

Mediskin requires freezer storage, while EZ-Derm has been chemically treated with an aldehyde to increase strength and allow for extended storage at ambient temperature. According to the manufacturer, these two products are designed for permanent grafting in partial thickness wounds or as a temporary dressing for full thickness wounds (http://www.brennenmed.com/) (Fig. 1).

Matristem comes in both sheet and particle form, both of which are intended for single use. According to the manufacturer, Matristem products are indicated for the management of a variety of wounds including, but not limited to, partial and full thickness wounds, pressure ulcers, diabetic ulcers, vascular ulcers, donor sites/grafts, post-Mohs surgery, dehisced wounds, traumatic wounds, and draining wounds (http://www.acell.com/acell-products.html) (Fig. 2).

Oasis tissue matrix is a porcine derived collagen scaffold and it is also indicated for a variety of wounds, similar to Matristem, including post-Mohs defects and graft/donor sites.

Data is limited on the specific use of these products in dermatology. Anecdotally, the authors have successfully used Mediskin and Matristem following Mohs surgery for select patients and defects.

Not yet reported for use in dermatologic surgery, additional porcine dermis xenografts exist {e.g., DermMatrix (formerly InteXen,) and Permacol] and have applications for soft tissue repairs in urological, gynecological , and gastrointestinal surgery, as well as facial suspension for post paralysis reconstructive surgery [2, 3]. Enduragen is another acellular porcine derived dermal matrix which is designed for "soft tissue reinforcement and repair," according to the

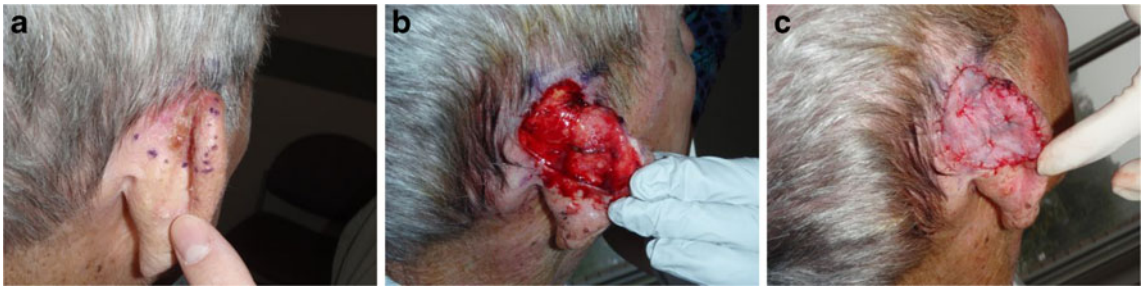

Fig. 1 **a** Large SCC of the posterior helix; **b** Post-Mohs defect on the posterior helix; **c** Immediate repair with porcine xenograft (Mediskin)

manufacturer's website (http://www.stryker.com/en-us/products/Craniomaxillofacial/MEDPOR/ENDURAGenDermalCollagenMatrix/index.htm). Reports for use in facial plastic and oculoplastic surgery exist, but not for use in dermatologic surgery repair.

Two bovine derived dermal templates, Integra and Matriderm, are successfully used as xenografts in dermatology and published reports on specific product use exist. Integra first emerged as a bilayer substitute composed of bovine tendon collagen and glycosaminoglycans with a top layer comprised of a synthetic semipermeable silicone membrane. The silicon membrane mimics epidermal function by creating a semipermeable barrier. Matriderm is a single layer dermal template comprised of bovine collagen and elastin. Both products are indicated for management of full thickness or deep dermal burn wounds, chronic wounds, traumatic wounds, and following cutaneous surgery for skin cancer removal. The collagen–glycosaminoglycan and collagen–elastin xenografts are placed into the wound permanently and provide a matrix for ingrowth of surrounding cells forming a neo-dermis. The dermal templates are resorbed as healing ensues. For deep wounds, the dermal template can be stacked two or even three layers thick.

Integra Bilayer is intended for two-stage repair. It is designed to stimulate neodermis formation for 3–4 weeks, at which time the silicon top sheet is removed and definitive wound repair with a thin epidermal, full-thickness, or split-thickness skin graft is performed. In the case of smaller wounds, including post-Mohs defects, the wound may be successfully allowed to re-epithelialize on its own in lieu of placing an autograft without significant contraction or contour deformity (Fig. 3). Integra has been shown to work well in deep wounds and over exposed bone, tendon, cartilage, and joints.

Matriderm is intended for one-step repair in combination with STSG of full thickness wounds and skin defects. The product comes in 1-and 2-mm-thick sheets. While both thicknesses are listed for one-step repair, when using the 2-mm sheets, it has been recommended for staged repair, waiting 7 days for matrix vascularization before applying STSG [4]. Both Integra and Matriderm are stored at room temperature. The templates can be applied straight from the packaging after rehydration achieved by submersion in sterile physiologic saline.

More recently, Integra Single Layer, which lacks the silicon membrane, is being developed. Prior to this formulation, physicians reported using Integra as a single-layer sheet by carefully peeling the collagen matrix away from the silicon membrane (Fig. 4). A recent comparison study of Matriderm 1-mm and Integra single layer 1.3-mm for one-step closure of full-thickness skin defects in a rat model showed no major differences between the two and concluded that both are efficacious for one-step reconstruction [5].

Allografts

Allografts are tissue transplanted between two genetically distinct individuals of the same species. Allogenic skin transplantation is thought to provide vascular linkage within

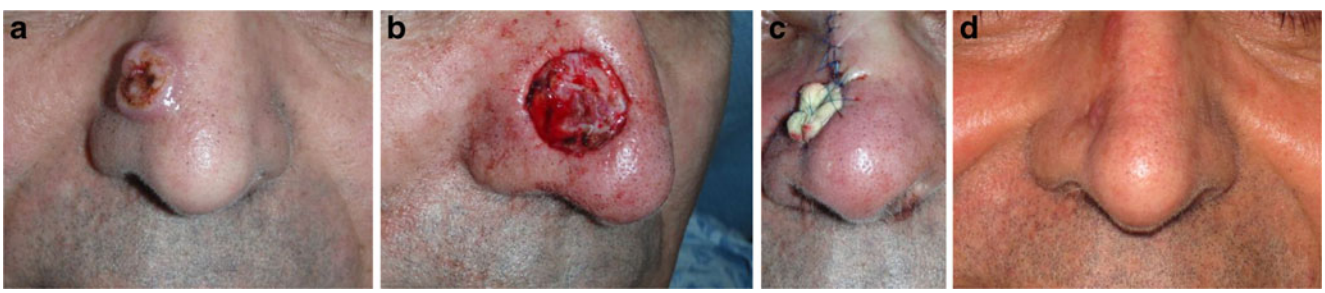

Fig. 2 **a** Large BCC of the nose; **b** Mohs defect with exposed muscle; **c** Combined complex closure and porcine xenograft (Matristem) wound sheet to alar defect with tie-down bolster in place; **d** 5 months post operatively with good contour and symmetry

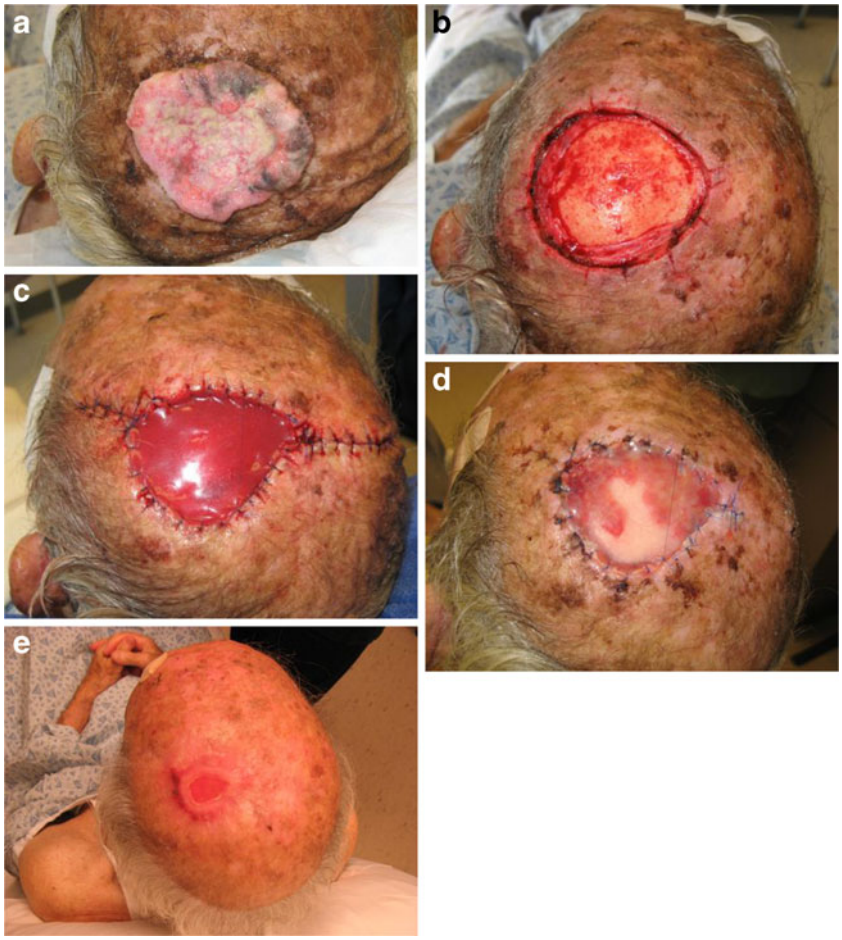

Fig. 3 **a** Large SCC of the scalp; **b** Defect with large amount of exposed bone; **c** Immediately after application of bilayer wound matrix (Integra) with its silicone sheet intact; **d** 4 weeks postoperatively with extensive vascularized neodermis evident; **e** The wound 9 weeks later almost fully epithelialized

3 days of transplantation, versus 2 to 3 weeks observed with xenografts. Allografts can be divided into three categories: (1) epithelial/epidermal; (2) dermal; (3) composite. Within these categories, the allograft may be acellular or cellular. Amongst cellular allografts one further distinction between living and nonliving can be made.

Epidermal Allografts

Epidermal allografts were initially developed as an alternative to the widely used cultured epithelial autografting that requires several weeks for tissue expansion. Keratinocytes are harvested from donor skin which may be cadaveric or from elective plastic surgical intervention. Donors are screened for infectious disease and malignancy. Keratinocytes are expanded in vitro and prepared for transplantation. Cultured allogenic keratinocytes have been used successfully to improve epidermal coverage in burns, donor sites, and chronic ulcers, but do have limitations [6–8]. Survival of cultured allogenic keratinocytes is generally limited to 10–20 days [9, 10]. As this type of graft is not permanent, the wound healing benefit gained from cultured epidermal allografts is

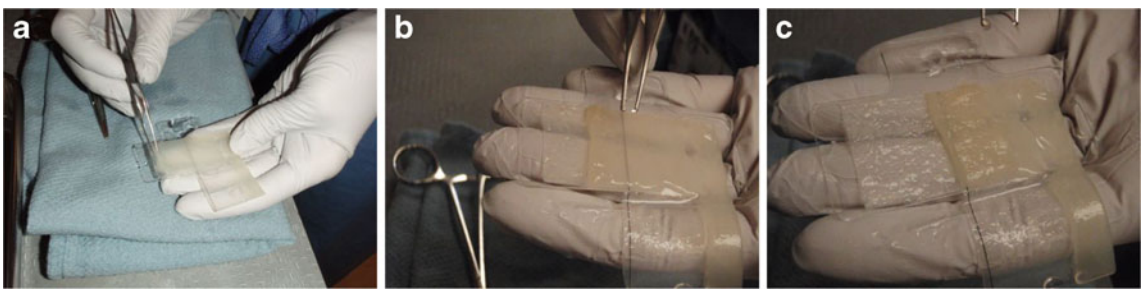

Fig. 4 **a** Bilayer wound matrix. The hard plastic backing is still in place. To provide a thicker product, the matrix is being gently teased from the silicone layer and folded on itself in **b** and **c**

attributed to the stimulation of host growth factors by the grafted keratinocytes. Other barriers to use of allogenic cultured cells include cost and availability of donor tissue [11]. In the 1980s and early 1990s, allogenic keratinocytes were used fresh, limiting their use to availability of fresh donor tissue. However, in 1996, Madden et al. demonstrated the viability of cryopreserved allogenic cultured epidermis [12]. The main advantages to using a cultured epidermal allograft are: immediate availability and elimination of the need for biopsy or harvesting from a donor site on the recipient. A major disadvantage is a theoretic risk for transmission of infectious disease.

Lyphoderm is a commercially available cultured epidermal allograft. It is a nonliving lysate of freeze-dried, sterilized keratinocytes derived from neonatal foreskin. It is formulated into a gel to be applied topically. Nonliving keratinocyte lysates such as this have been shown to have mitogenic activity and to be similarly effective as living allogenic keratinocyte cultures in stimulating closure of split-thickness autograft-covered burn wounds [11]. Lyphoderm is not FDA approved and as of 2005 was still in development for topical treatment of chronic venous ulcers [13]. Advantages are that it is ready to use and can be stored at room temperature.

Dermal Allografts

Extracellular matrix (ECM) is the major component of the dermis and is made up of collagen, proteoglycans, elastin, hyaluronic acid, and fibronectin. The ECM has a complex role in wound healing, releasing and binding to important growth factors [14]. Dermal matrix allografts can be combined with split-thickness skin grafts to provide a cosmetically appealing result due to the preservation of skin structure and texture. In our experience, they can also be used alone and the wound allowed to re-epithelialize secondarily with good cosmetic result in cutaneous surgery defects. Both cellular and acellular grafts provide a barrier from the environment, protection against infection, and reduced wound pain. However, acellular grafts are typically better incorporated into the host tissue due to their decreased antigenicity.

There are no randomized controlled studies directly comparing cellular dermal products to acellular dermal substitutes. An ongoing randomized controlled trial by Lev-Tov et al. aims to compare the two types of grafts in diabetic foot ulcers. The study has three treatment arms: standard of care (SOC), SOC plus cellular dermal matrix (Dermagraft) and SOC plus acellular xenograft (Oasis). They have not yet published results [15].

Acellular Dermal Allografts

Acellular dermal allografts provide a scaffold into which host tissue integrates and revascularizes. Transplantation of cellular allograft skin takes initially, but is ultimately rejected by the host tissue due to the antigenicity of the grafted endothelial cells [16]. Acellular dermal grafts consist of the critical structural organic components of the dermis, without the antigenic cellular components. Several acellular dermal allografts produced from donated human skin exist, including Alloderm, Allomax (formerly marketed as Neoform), DermaMatrix, GraftJacket, Flex HD, and DermACELL.

AlloDerm is made from human skin donated from US tissue banks and processed into acellular dermis. The donated dermal tissue is stripped of cells then freeze-dried to remove moisture [17]. In the Mohs literature, AlloDerm has been used as an intermediate step for split- or full-thickness grafting in patients with both small and large defects [18–20]. It has also been used to successfully repair scalp and periocular defects and is an appealing option for large cutaneous defects, especially in patients that are unable to tolerate a flap reconstruction [21•, 22]. AlloDerm has also been described for use in treatment of aplasia cutis congenita [23].

Contraindications to using AlloDerm include allergy to polysorbate 20 or to one of the antibiotics listed on the package. The product can be stored at room temperature for up to 2 years and must be rehydrated prior to use. Rehydration takes 10–40 minutes. It has a basement membrane and dermal surface that should be correctly oriented with the dermal surface facing down. A dressing must be kept in place until the patient's native keratinocytes re-epithelialize the graft to provide a protective cornified layer. AlloDerm serves as a scaffold for host fibroblasts, capillaries, and keratinocytes.

AlloDerm is FDA approved for treatment of burns and marketed for abdominal wall reconstruction, breast reconstruction, and head and neck plastic reconstruction. Several studies in deep-partial and full-thickness burns have shown that use of AlloDerm as a dermal substitute leads to thinner, widely meshed STSGs and less scarring [24–26]. This is likely due to the preservation of skin texture and elasticity with the application of a dermal substitute upon which to apply the epidermal split-thickness graft. Repliform is another commercially available variant of Alloderm. Cymetra is an injectable formulation of the product.

DermaMatrix, also a human derived acellular allograft, differs from AlloDerm and another acellular dermal matrix, Allomax (formerly marketed as Neoform) in its processing. DermaMatrix is processed using a detergent and acid washes then freeze dried. It can be stored for 3 years at room temperature. DermaMatrix is similar in its applications to other acellular dermal substitutes, and has been used successfully in oculoplastic reconstruction, head and neck reconstruction,

and breast reconstruction [27, 28]. Oculoplastic uses of DermaMatrix as well as Alloderm have included reconstruction of the eyelid and periocular unit following resection of cutaneous malignancy [29, 30]. In one retrospective analysis of complications among head and neck parotidectomy reconstructions with either AlloDerm or DermaMatrix, DermaMatrix was associated with a greater number of postoperative complications [31]. However, this data is not generalizable to all surgical defect locations, especially since the presence of salivary tissue in the wound bed may create a very different environment than other non-salivary head and neck reconstruction locations. Advantages of DermaMatrix over other acellular dermal matrix products include its long shelf life at room temperature and rapid rehydration. DermaMatrix can be stored for 3 years at room temperature and rehydrates in 3 minutes compared to AlloDerm, which is stored refrigerated for 2 years and requires 30 minutes of rehydration.

Histologic and immunohistologic evaluation of cellular infiltration and revascularization were performed comparing 4 different acellular dermal matrices (AlloDerm, DermACELL, DermaMatrix, and Integra) in a rat model. Cellular infiltration was greatest in DermACELL and lowest in AlloDerm. Angiogenesis was observed in all four products by day seven. The clinical implications for these differences remain unclear [32•]. A similar study by Gordley and Cole compared AlloDerm, Enduragen (acellular dermal matrix of porcine derivation,) and DermaMatrix implants in mice. On histologic examination, there was little difference in the inflammatory infiltrate between the three products. However, they observed significant clinical differences. DermaMatrix maintained its original shape and consistency while AlloDerm lost some of its original shape and became softer. Enduragen the porcine dermal substitute, maintained its original shape but became more firm. These findings require further study, but suggest that Enduragen may be better for cartilaginous structure repair, such as the nasal ala, while AlloDerm may be less well suited to the face due to its tendency to lose its structural integrity [33].

Additional acellular dermal matrix products derived from human skin include Allopatch HD, Flex HD, and GraftJacket. These products, in addition to Allomax, referred to above, have not yet been reported for use in dermatology or dermatologic surgery to our knowledge. Allopatch HD is specifically marketed as a biologic matrix for tendon augmentation. Flex HD is indicated for breast reconstruction and hernia repair. GraftJacket is indicated for "repair or replacement of damaged or inadequate integumental tissue [34]." GraftJacket has also been studied in chronic wounds. Brigido et al. conducted a pilot study demonstrating the efficacy of GraftJacket in 40 patients with chronic lower-extremity diabetic ulcers. A single application of GraftJacket resulted in significant reduction in ulcer size at four weeks compared with standard wound care [35]. The physical properties of Allopatch were compared to several other soft tissue augmentation products (Allograft, SportMesh, GraftJacket, Orthadapt). Allopatch and GraftJacket had greatest suture retention strength. These two acellular dermal substitutes showed greater strength and stiffness compared with SportMesh and Orthadapt [36].

Cellular Dermal Allografts

Cellular dermal allografts are composed of a structural dermal scaffold as well as donor fibroblasts. Examples of cellular dermal substitutes include ICX-SKN, TransCyte, and Dermagraft. The cellular components synthesize proteins of the extracellular matrix to stimulate wound healing, but also cause an immunologic host response.

ICX-SKN is a synthetic dermal allograft. A matrix of fibrin is synthesized then seeded with human dermal fibroblasts. The resulting tissue is then freeze-dried and irradiated. Phase I trial data in six healthy subjects who underwent full thickness excisions and immediate application of ICX-SKN showed graft persistence and re-epithelialization at 28-days post operatively [37]. No further trials have been published to our knowledge.

TransCyte is cellular dermal allograft (neonatal fibroblast components) that also has xenograft properties (porcine dermal collagen.) Bovine products are used in the growth medium, therefore, contraindications include hypersensitivity to both bovine and porcine material. The product consists of a nylon mesh covered with porcine dermal collagen (similar to Biobrane.) Neonatal fibroblasts are then added and allowed to proliferate and synthesize extracellular matrix (ECM) components for 17 days. The ECM and growth factors are then cryopreserved. TransCyte is FDA approved for temporary coverage of deep wounds before grafting at a later date. It is also used for coverage of superficial partial thickness wounds not in need of grafting. In a retrospective review, Lukish et al. found that TransCyte decreased the length of stay for pediatric burn patients compared with standard burn therapy [38]. No published studies for use of TransCyte in dermatology specifically were found by PubMed search.

Dermagraft is a dermal substitute created from human donor fibroblasts. It is composed of fibroblasts, an extracellular matrix, and scaffold. It is supplied frozen and must be thawed then rinsed prior to use. A prospective RCT documented greater complete wound closure in diabetic foot ulcers treated with Dermagraft than with standard care [39]. A smaller pilot study of 18 patients demonstrated efficacy of Dermagraft in venous ulcers as well [40]. No published studies for the use of Dermagraft in dermatology specifically were found by PubMed search.

Composite Allografts

Composite allografts more closely recreate the natural tissue with both dermal and epidermal layers. However, it is unclear from the literature that this is a significant advantage [41]. Composite grafts that combine allogenic dermis with autografted epidermal keratinocytes allow for the structural advantages of dermal substitutes as well as rapid reepithelialization with a non-immunogenic cellular epidermis [42]. Examples of composite allografts include: Apligraf and Orcell. One advantage to the composite grafts is more complete barrier function without the need for a second surgical procedure. For example, Apligraf contains a cornified epidermal layer composed of neonatal keratinocytes, eliminating the need for STSG over the dermal scaffold.

Alloskin is a composite allograft made from cadaveric tissue containing epidermis and dermis. This product is indicated for both acute and chronic wounds, and can be applied to exposed substructures. It has a 5 year shelf life (http://www.altrux.com/Products). PubMed search on this product revealed no published reports or studies.

Apligraf is a composite skin substitute derived from both human (allograft) and animal tissues (xenograft), though it is typically included in the allograft category. Bovine type 1 collagen is used to create a dermal matrix upon which human fibroblasts can infiltrate. Human keratinocytes comprise an epidermal layer. The fibroblasts and keratinocytes are harvested from neonatal foreskin. Apligraf does not contain other skin structures such as appendages, vasculature, Langerhans cells, macrophages, lymphocytes, or melanocytes. It is approved for use on chronic venous ulcers and diabetic ulcers. Contraindications include wound infection and bovine protein allergy.

While the majority of studies on Apligraf are for use in chronic ulcer management, there are some recent case reports and series on Apligraf related to cutaneous surgery and dermatology. In one series of 15 patients repaired with Apligraf following skin cancer excision, 12 of the 15 showed clinical take of the product without adverse effects at one week [43]. Gohari et al. compared Apligraf with secondary intent healing in 14 patients for use following Mohs surgery or skin cancer excision. Twelve patients were ultimately observed and patients in the Apligraf group were found to have more pliable and less vascular scars compared with the group allowed to heal secondarily at six months follow-up. There were no differences in time to heal, pain, hematoma formation, infection, erythema, edema or exudate between the two groups [44]. In a prospective, multicenter, single-arm, open study Eaglstein et al. followed 107 patients repaired with Apligraf following excisional surgery usually for skin cancer. The patients would reportedly have otherwise been repaired by graft or allowed to heal secondarily. They observed no rejection of the product and concluded that their results suggested the product may be safe and useful for repair following cutaneous surgery [45]. In a randomized controlled trial of 20 patients, Apligraf was compared with autografts and polyurethane film for use in acute wounds. The study demonstrated Apligraf equivalence with autograft for these wounds [46].

Other dermatologic diseases in which Apligraf has been used and reported include epidermolysis bullosa [47, 48], post carbon dioxide treatment for hypertrophic scar [49], aplasia cutis congenita of the trunk [50], bullous morphea [51], and for ectropion in a patient with harlequin ichthyosis [52].

Apligraf has proven to improve wound healing in both diabetic foot ulcers and venous ulcers and the majority of studies of the product revolve around these conditions. A few will be discussed here. In 2001, a randomized controlled trial compared Apligraf to moist gauze dressings in diabetic foot ulcers. Complete wound healing was achieved in 56 % of the Apligraf treated patients compared with 38 % in controls at 12 weeks. Osteomyelitis and amputation were lower in the Apligraf group. Study patients were re-evaluated at six months for re-ulceration with no differences in the treatment groups [53]. Another randomized controlled trial comparing Apligraf plus standard ulcer care with standard care alone in diabetic patients with full-thickness neuropathic ulcers found that Apligraf resulted in a higher incidence of wound closure at 12 weeks (51.5 % vs. 26. 3 %) [54]. In 1998, Falanga et al. demonstrated, in a prospective RCT, Apligraf superiority to standard compression therapy with an Unna boot with no evidence of graft rejection [55]. Later, in 2000, Falanga published a multicenter randomized trial showing better wound healing of venous ulcers treated with compression plus Apligraf compared with compression alone [56]. Cost analysis of Apligraf plus compression compared with compression alone based on Falanga's data, demonstrated an overall cost savings in the Apligraf arm. The computer modeled cost analysis estimated annual treatment costs of $20,041 for the Apligraf group and $27,493 for the compression only group.

Human amniotic membrane has been used for wound coverage since the early 20th century. It became less popular with the advent of porcine grafts in the 1960s, but is still used in ocular and skin reconstruction. Newer applications include genitourinary reconstruction and creation of a barrier around potentially invasive tumors. It has some as yet incompletely understood anti-inflammatory, antibacterial, and anti-viral properties. These, as well as the tissue transparency, minimal adherence to underlying structures, reduction of pain, and production of growth factors that stimulate epithelialization make it an effective skin substitute. However, it is difficult to obtain prepare and store, as it must be obtained by elective cesarean section [57•]. A prospective study of amniotic membrane applied to 15 patients with chronic venous leg ulcers showed significantly decreased

pain after transplantation as well as a significant decrease in ulcer size with suppression of excessive fibrosis [58].

Epifix is a commercially prepared amniotic membrane. It is marketed for use in burns, chronic wounds, and plastic surgery reconstruction. Human amniotic membrane tissue is donated then sterilized. It serves as a multilayer collagen matrix. It is comprised of a single layer of epithelial cells, a basement membrane, and a connective tissue matrix that can be engrafted by the patient's skin stem cells. It can be stored at room temperature.

GammaGraft is irradiated human skin with a dermal and epidermal component. It is used as a temporary skin graft on chronic wounds, surgical wounds, and burns. It can be stored at room temperature, which is an advantage over other allografts. It is typically left on until the underlying wound has re-epithelialized [59••].

Orcel is a composite allograft formed by culturing neonatal keratinocytes onto a type I bovine collagen sponge with porous and nonporous sides. It is then cryopreserved. Therefore, like AlloDerm, this cryopreserved cultured dermal substitute contains both human and animal components but is typically considered allograft rather than xenograft. The sponge forms a matrix with cytokines and growth factors, which becomes vascularized and absorbed as healing ensues. Orcel is FDA approved for reconstruction after hand release surgery in epidermolysis bullosa patients as well as graft donor sites in these patients. Sibbald et al. reviewed charts of six patients with recessive dystrophic epidermolysis bullosa (RDEB) in whom Orcel was used serially on nonsurgical erosions/ulcers as well as for wound coverage following hand release surgery [60]. They found the substitute advantageous for wound protection, healing, and symptom relief, though no control group was used for comparison. Hasegawa et al. treated three patients with RDEB and intractable ulcers with twice weekly applications of Orcel for six weeks. They noted wound bed granulation at one week and re-epithelialization from the wound edges by four weeks, suggesting the substitute might be promising in this group of patients [61]. Again, no controls were observed for comparison.

Theraskin is a composite allograft derived from donated human skin and is comprised of keratinocytes, fibroblasts, and extracellular matrix components. It is used in the management of chronic wounds including diabetic foot ulcers, venous stasis ulcers, arterial insufficiency ulcers, and pressure sores. Theraskin can be used overlying exposed bone, muscle or tendon. A retrospective clinical study of 188 patients evaluated Theraskin for the management of diabetic foot ulcers and venous leg ulcers. The authors found the product to be effective and safe for these indications [62•]. No control group was studied for comparison.

StrataGraft is a cellular composite allograft consisting of a dermal equivalent and a *unique* biologically active epidermal layer generated from NIKS human keratinocyte progenitor cells (http://www.stratatechcorp.com/products/index). A proof of concept clinical trial showed that the skin substitute was well tolerated in traumatic wounds. There was no evidence of acute immunogenic response against the NIKS keratinocytes or increased sensitivity to the cells following exposure [63•]. This product is not yet available for use in the United States.

Autografts

Autografts are grafts that are transplanted from one location to another on the same individual. These can be subdivided into split-thickness skin grafts, full-thickness skin grafts, and cultured autologous skin. Due to the straightforward nature of STSGs and FTSGs, only cultured autologous skin will be discussed here. Cultured autologous grafts allow for expansion of a patient's own tissue from a small biopsy sample. These cultured epidermal grafts have not yet been reported for use in wounds related to cutaneous surgery. One application being studied and published in the literature is the use of autologous melanocyte grafts for transplantation in patients with stable vitiligo, though no specific product appears to be on the market [64, 65]. Cultured autografts have been successfully used in management of severe second degree burns and chronic lower extremity ulcers and the literature focuses on these applications.

BioSeed-S is a cultured keratinocyte graft requiring two weeks to expand, after which the cells are applied to the wound bed in a fibrin glue vehicle via syringe. The cultured keratinocytes continue to divide and re-epithelialize. A similar product, BioSeed-M, is available for mucosal surfaces. A multicenter RCT comparing BioSeed-S plus compression with standard care plus compression for therapy resistant chronic leg ulcers demonstrated more complete resolution of ulcers and faster healing time with BioSeed-S [66]. MySkin is another commercially available cultured autologous graft similar to Bioseed-S.

CellSpray, a unique cultured autologous graft is produced when stem cells are isolated from the basal layer of skin biopsy and formulated into a solution which can then be sprayed over the wound bed. CellSpray is appropriate for patients with >30 % BSA affected and can be ready within seven days of initial biopsy. CellSpray XP is used for patients with 10–30 % BSA affected and can be ready within 48 hours of biopsy. A third similar product, ReCell, can be used for areas 20×20 cm and comes with a tissue processing kit to perform the cell preparation in about 30 minutes at the bedside (http://www.avitamedical.com/index.php).

Epicel is a cultured epidermal autograft comprised of cultured keratinocytes grown into sheets of skin about 50 cm^2 and 2–8 layers thick. The graft production usually takes 16–21 days. The resultant sheets are then returned for application in the operating room. Residual murine and bovine proteins

may be present during tissue processing, therefore, patients who receive Epicel are considered to have undergone xenotransplantation and cannot donate blood or other body parts. There are no randomized controlled trials to confirm efficacy, however, efficacy of Epicel is supported by a single center case series of 30 patients with severe burns and poor prognosis. A total of 26 % +/- 15 % BSA was covered by Epicel with 9 % survival. Fragility of the grafted skin with blistering during maturation was the major disadvantage to the product [67]. Epicel is expensive and time consuming to produce, but may provide a valuable option for burn patients with extensive body surface area affected.

Cultured Skin Substitute is another form of cultured epidermal autograft but that also has a cultured autologous dermal layer. Autologous human keratinocytes and fibroblasts are cultured in a medium of collagen and glycosaminoglycans. Uneven pigmentation of the final graft can occur due to melanocytes that are unpredictably present in the cell culture. Boyce et al. compared cultured skin substitute to split thickness autograft and found no significant difference between the two modalities at one year. The authors concluded that cultured skin substitute may be an effective skin substitute in patients when donor skin is limited [68].

Synthetic Substitutes

Synthetic skin substitutes are comprised of nonbiologic materials. Advantages are that they can be synthesized on demand without need for biologic tissue and there is greater control over scaffold components. Additionally, the products can be modified for specific use by adding different growth factors and do not carry a risk for disease transmission [69••].

Suprathel is a synthetic monolayer acellular synthetic wound dressing produced from copolymers DL-lactide, trimethylcarbonate, and alpha-caprolactone. Indications for use include split-thickness skin graft donor site coverage and dressing of partial-thickness burns. Uhlig et al. found Suprathel to be superior to paraffin gauze alone in managing burns [70]. Schwarze et al. found the synthetic substitute to be no better than petrolatum gauze in management of burns but there was decreased pain and cost [71]. No studies specifically relating to dermatology were found by PubMed search.

Biobrane is a temporary synthetic dressing composed of a semipermeable silicone film bonded to nylon fabric. The fabric serves as a scaffold into which porcine dermal collagen has been bound. The patient's blood and sera form a clot within the nylon matrix, thereby adhering the tissue to the wound bed. The Biobrane dressing is removed once the underlying tissue has re-epithelialized, typically in 7–14 days. Biobrane was initially developed in 1979 as an alternative to allograft skin, but has become the standard skin substitute in burn patients. Two more refined products, Biobrane-L, a less adherent mesh, and Biobrane gloves, for use on hand injuries, are now also available.

Biobrane is recommended for use in partial-thickness burns and donor sites. Biobrane has also been used postoperatively in patients undergoing axillary resection of hidradenitis suppurativa [72]. A recent review of the literature on Biobrane in the Annals of Plastic Surgery reported that grade A evidence supports the use of Biobrane for partial thickness burns; Grade B evidence supports its use in conditions resulting in loss of the epidermis such as toxic epidermal necrolysis (TEN) or pemphigus; and grade B to C evidence is available to support the application of Biobrane in dermabrasion, skin graft donor sites, laser resurfacing, and chronic wounds [73]. There is one published report of allergic contact dermatitis with confirmed positive patch testing to the product [74].

Comparison of Biobrane to DuoDERM (a hydrocolloid dressing,) in pediatric partial thickness burns showed no difference in pain or healing time between the treatments [75]. A prospective randomized trial of partial burns in pediatric patients comparing Biobrane, TransCyte, and silver sulfadiazine cream, found that Biobrane and TransCyte were associated with decreased pain. The Biobrane-treated patients required more skin grafts than the TransCyte group and fewer than the silver sulfadiazine arm [76].

Conclusion

A multitude of skin substitute products have been developed. Their availability has expanded the options for the dermatologist and dermatologic surgeon when faced with managing complex wounds. In spite of their clinical efficacy, there remains a paucity of good quality RCTs contributing to the evidence based use of skin substitutes and even fewer studies comparing products to each other. While some products have been used successfully for dermatologic applications and reports of this use have been published in the literature, a vast majority of data that we have on skin substitutes relates to chronic wound management and care of burn patients. Though not specific to our specialty, the use of skin substitutes for these indications can be extrapolated to dermatology. Understanding the composition, advantages/disadvantages, and risk/benefit of each product, as well as the indications for each product's use facilitates the selection of the appropriate substitute. This review will hopefully provide the information that makes the use of these products feasible for the appropriate defect.

Conflict of Interest E Foley declares no conflicts of interest.
A Robinson declares no conflicts of interest.
M Maloney declares no conflicts of interest.

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- • Of importance
- •• Of major importance

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