

Extracellular Matrix Biomaterials for Soft Tissue Repair

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KEYWORDS

- Collagen • Extracellular matrix • Soft tissue reconstruction
- Bioscaffold • Acellular matrix • gTissue

The biological and physical augmentation provided by extracellular matrix (ECM) derived implants continues to challenge and refine the conventional wisdom of biomaterials. Human autograft and allograft ECM devices (eg, tendons, fascia, dermis, and ligaments) have been followed by bovine, porcine, and equine implants whose origins include heart valves, dermis, pericardium, and components of the intestine. Although artificial chemical crosslinking was initially thought necessary to limit the foreign body reaction to an implanted animal tissue and preserve implant integrity, it is now appreciated that different tissue-processing methodologies can produce xenogenic ECM devices with characteristic post-implantation responses ranging from the classic foreign body encapsulation of a permanent implant to one where the implant is degraded and resorbed to one where the processed ECM implant is populated by local fibroblasts and supporting vasculature to generate a new, metabolically active tissue.

ECM biomaterial technologies offer a range of device physicomaterial properties that can elicit distinct, biological responses after implantation. Reference to this class of implants as “acellular matrices” or “collagen scaffolds” can be a disservice, if the specifics of the devices and the possible impact on outcomes are not well understood. This article reviews the multiple ECM devices available for podiatric applications and highlights the impact of tissue source and processing on physicomaterial properties and host-implant interactions, with regard to surgical applications and clinical considerations.

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PRODUCT PROCESSING AND COMPOSITION

The composition of an ECM biomaterial reflects the original constituents of the source tissue and the selected processing methodology that may act to preserve, remove, or modify various components of the source tissue.

Tissue Source (Material Origin)

All ECM-based implants are derived from mammalian tissues, including dermis, pericardium, and small intestinal submucosa (SIS), although other processed tissues may enter the market in the future. These tissues are harvested at different developmental stages from various species, including human, porcine, equine, and bovine in ages ranging from fetal to adult (**Table 1**). Although the ECM of each, regardless of species, is composed primarily of fibrillar collagens, inherent source variation (tissue, species, and age) manifests in the form of different

- Microstructure
- Specific composition including the
 - Quantities and types of noncollagenous proteins, glycosaminoglycans (GAGs), or other factors
 - Ratios of collagens (Types I, III, IV)
- Mechanical properties
- Physical dimensions including available final product sizes and/or thickness

An example of the diversity in ECM microstructure as a function of tissue type and species is highlighted in **Fig. 1**. Dermis ECM is discernible by the crosshatch pattern of woven collagen fibers in contrast to the thin, laminated layers of intestinal submucosa that constitute SIS-based ECM biomaterials. The microstructure can also vary by age and location of harvest. As a calf develops through fetal stages into adulthood, the thickness of the dermis increases and the collagen fibers and cables that make up the dermal architecture grow in diameter. The biochemical composition of the ECM can also change with age. For example, fetal and neonatal dermis has between 3 and 5 times more Type III collagen than adult dermis,¹⁻³ Type III collagen is a form of fibrillar collagen associated with healing and developing tissues.⁴⁻⁶ The choice of tissue source also determines the possible width and breadth of the final product, based on the ability to harvest large pieces of uniform, continuous material.

Processing

Although the original source tissue dictates the characteristics of the device, the processing conditions under which an ECM biomaterial is prepared can equally influence characteristics of the final product. Many of the numerous materials available for clinical consideration are processed in different, often proprietary, ways. Although the specifics of the chemical or enzymatic steps and washes often remain unknown, the original goals and results can be described. Some ECM biomaterials are processed to remove cells but to retain most other ECM components. For example, Graft-Jacket (Wright Medical Technology, Arlington, TN) is a minimally processed allograft derived from human dermis and reported to retain noncollagenous components of the ECM including elastin and proteoglycans.^{7,8} Restore (DePuy, Warsaw, IN, USA) and Surgisis (Cook, Bloomington, IN, USA) are SIS-based materials that have been reported to retain fibronectin (FGF-2) and GAGs, but not vascular endothelial growth factor (VEGF).^{9,10} Alternatively, fetal bovine dermis biomaterials (SurgiMend and PriMatrix, TEI Biosciences, Boston, MA, USA; TissueMend, Stryker Orthopedics, Kalamazoo, MI, USA), have been processed using a method originally intended as

Table 1

Overview of the diverse set of clinically available ECM biomaterials by tissue source, manufacturer, specifications, and applications

Trade Name	Animal Source	Tissue Source	Cross-linker	Terminal Sterilization	Thickness*	Cleared Indications**	Marketer	Manufacturer	
TissueMend	Fetal Bovine	Dermis	None	Low Temperature Ethylene Oxide	~ 1 mm	Tendon reinforcement	Stryker Orthopaedics	TEI Biosciences	
SurgiMend					~ 2.3, or 4 mm	Hernia repair Plastic & reconstructive surgery			
SurgiMend 2.0, 3.0, 4.0	~ 1 mm								Skin and wound healing
PriMatrix			Fetal Bovine	HMDI	Gamma irradiation	0.5 - 1.5 mm	Hernia repair Plastic & reconstructive surgery		
Permacol	Adult Porcine		EDC			Ethylene Oxide	~ 1.5 mm		Tendon reinforcement
Zimmer Collagen Patch				0.8 - 1.2 mm	Hernia repair Plastic & reconstructive surgery				
CollaMend	None	E-beam	1.5 - 2.0 mm			Tendon reinforcement Hernia repair		Davol (Bard)	
Conexa				Adult Human	None		None	0.8 - 3.3 mm	By US law, tissue transplants intended only for homologous use
Strattice	0.5 - 2.0 mm	Wright Medical Ethicon (J&J)							
Alloderm			Gamma irradiation	0.8 - 1.8	Musculoskeletal Transplant Foundation	Davol (Bard) Mentor	RTI Biologics		
GraftJacket	E-Beam Radiation	0.3 - 1.0 mm						Tendon reinforcement	DePuy
FlexHD			Adult Porcine	Small Intestinal Submucosa (SIS)	Ethylene Oxide	0.3 - 1.0 mm	Reconstructive surgery Hernia repair		Cook
AlloPatch	~ 0.1 mm	Skin and wound healing				Healthpoint			
AlloMax			None	Gamma irradiation	~ 1mm		Tendon reinforcement	Biome/ Organogenesis	Organogenesis
NeoForm	Adult Equine	Pericardium				EDC			
Restora			0.3 - 0.6 mm	Skin and wound healing					
Surgisil	Adult Bovine	None			E-Beam Radiation	0.2 - 1.2 mm	Hernia repair Muscle flap reinforcement Staple-line reinforcement	Synovis	
Biodesign Oasis			Peri-Strips						

*Total range of product thickness, but versions may be sold with tighter range subsets

**see Instructions For Use for individual products for detailed and complete indications.

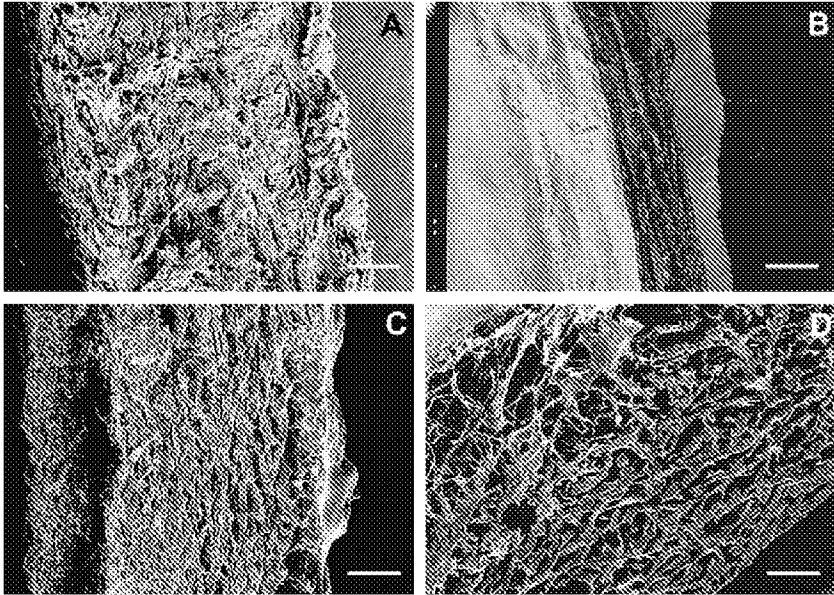


Fig. 1. Scanning electron micrographs of cross-sections of (A) Permacol, (B) Surgisil, (C) Allo-derm, and (D) SurgiMend. The woven collagen fiber architecture of porcine dermis (A) is similar to that of human dermis (C) and bovine dermis (D), and the thin laminated layers of SIS (B) are apparent. Differences in the porosity of the 3 dermis-based tissues and SIS are also apparent. (Scale bar = 200 μm).

a matrix preservation technique for scientific investigations of the collagen fiber architecture¹¹ where all lipids, fats, carbohydrates, and noncollagenous proteins are removed. Thus the composition of this material is primarily Type I and Type III collagen, conserved in a native and undamaged state. Final device manufacturing steps for some products include lyophilization or solvent evaporation to remove water before sterilization, and others are sold in their final rinse solution. Materials that are dried or lyophilized can be shipped and stored dry for extended periods. Using lyophilization, the pore size (see Fig. 1), rehydration rate, and ability of blood and cells to penetrate the matrix can be modulated.

Processing: Artificial Crosslinking

“Crosslinking” is a term borrowed from polymer chemistry that describes chemical bonds between polymer chains. The collagen fiber architecture of the ECM is a polymer network, and over time a natural mechanism to stabilize the fiber matrix through intermolecular bonds by lysyl oxidase has evolved.¹² Historically, artificial crosslinking was first employed to mask the antigenic response of xenograft heart valves using glutaraldehyde. Subsequent scientific investigations into this and other similar methods determined that crosslinking chemistry could be used to stabilize artificially collagen materials reconstituted from homogenized sources, reducing the otherwise rapid degradation of these biomaterials *in vivo*.¹² More recently, some ECM biomaterials have adopted these different chemical crosslinking methodologies to achieve intended effects by altering cell-matrix interactions and mechanical properties. For example, Permacol (Covidien, Mansfield, MA) is crosslinked with hexamethylene diisocyanate (HMDI) to make a permanent collagen implant, hence the titular

conjunction. Others have used 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC), because of its ability to add crosslinks without retaining the crosslinking molecule,¹³ while surreptitiously being investigated as a conjugation method for adding other desirable molecules and growth factors that could be incorporated into future devices. As a result, addition of these nonnative crosslinks alters the host response at a cellular level. One resulting change is a decrease in the susceptibility of the collagen molecule to enzymatic degradation, namely by matrix metalloproteinases (MMPs),^{14,15} thereby increasing in vivo persistence. However, these artificial modifications can also affect growth factor binding to collagen, cell attachment, and migration,^{16,17} and lead to recognition as a foreign body by the host (see section on Host-implant interactions later in this article). Many ECM biomaterials are now not intentionally crosslinked, as new processing methodologies have achieved clinically acceptable persistence without the need for artificial stabilization.

Processing: Sterilization

Most ECM biomaterials are terminally sterilized to ensure that the final product has no infectious bacteria or viruses. These methods include the use of ethylene oxide (EO) gas, gamma irradiation, or electron-beam (e-beam) irradiation. EO sterilization requires a porous and dry final product to allow the gas into and exhaust out of the matrix; irradiation need not be dry, but may crosslink or denature the final product.¹⁸⁻²¹ Allografts are the exception, as most are aseptically processed and treated with antibiotics.

Product Processing and Composition: Summary

In summary, ECM biomaterial processing varies between soft tissue substitutes. Different chemical washes and rinses are used in processing and manufacturing; some are crosslinked; some are dried or lyophilized; a variety of sterilizing methodologies are used. Any or all of these steps can alter the composition of the resulting ECM biomaterial. The individual parameters of the same methods may differ among products. For example, freezing times and temperatures during lyophilization can alter ice-crystal formation, resulting in different size crystals, and subsequent material porosity. Differences must be evaluated by investigating the final product composition, physical/mechanical properties, and the host-implant interactions.

PHYSICAL-MECHANICAL PROPERTIES

The physical and mechanical properties of an ECM biomaterial are a function of the tissue source, processing, crosslinking, and sterilization. The physical dimensions of the device can be strongly correlated with those of the source material. For example, the size of the tissue available for harvest from the host determines the sizes available for processing into final product. Currently, Permacol and SurgiMend, derived from porcine and bovine dermis, respectively, are available in sheets up to 25 by 40 cm, while most human autografts are limited to smaller sizes related to the ability to harvest tissue using dermatomes. Within this subset of dermal ECM biomaterials, the thickness can range from approximately 0.5 mm to 4 mm, although most products are available in an average thickness of 1 mm. In contrast, SIS devices are typically thin; the thickest, 10-layer laminated version of Surgis is less than 1 mm thick on average.

The initial mechanical properties of ECM biomaterials have been widely investigated,²²⁻²⁵ and are dictated by the microstructure of the material. Thicker materials have an increased load-carrying capacity, and the properties of any ECM biomaterial can be altered with chemical crosslinking methodologies. However, the stress-strain

characteristics of acellular dermal materials are similar to those of the native tissue from which they were derived (**Fig. 2**). As a result of comparing elastic modulus measurements (taken without prestretching and in the low modulus region) with native tendon, some studies have suggested that these materials “may not be capable of providing appreciable mechanical reinforcement” to tendon repair.²⁶ Although these data can be refuted when ECM biomaterials are tested in clinically relevant models,^{22,27} the goal in using the materials stems from their ability to reinforce without the conventional stress-shielding or material property mismatch problems associated with synthetics that are orders of magnitude stiffer than native tendon. In addition, these studies of initial mechanical properties ignore that the properties of the implanted ECM biomaterial change with time, making the initial mechanical strength a poor indicator of ultimate clinical success.

HOST-IMPLANT INTERACTIONS

Conventional wound healing is a highly coordinated cellular response to injury, reviewed in other studies specifically for skin^{28,29} and tendon.^{30,31} Normal wound healing following surgical intervention results in limited acute inflammation lasting approximately 2 weeks, followed by a remodeling phase lasting from weeks to years, as the repaired tissue is slowly reorganized. How the addition of an ECM biomaterial affects this process, and conversely, how this process affects the implanted device, can vary within this subset of products. A limited number of comparative studies or clinical trials are available for many devices. However, for some products there is a solid foundation of literature and experience that identifies at least five possible biological responses, including:

- ECM nonincorporating responses
 - (1) Encapsulation
 - (2) Rejection
- ECM incorporating responses
 - (3) Resorption
 - (4) Integration with progressive degradation
 - (5) Adoption and adaptation

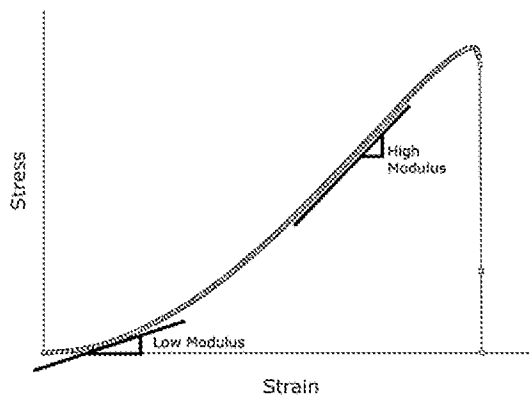


Fig. 2. Characteristic stress-strain curve for SurgiMend under uniaxial tension. An initial low modulus region, a function of collagen fiber reorientation and alignment, is followed by a linear high modulus region.

Nonincorporating

Encapsulation

The subset of host-implant interactions most familiar to those accustomed to using polymer meshes or sutures is crosslinked materials. The acute and chronic inflammatory profile of Permacol, HMDI crosslinked porcine dermis, is consistent with that of the classic foreign body response to nonresorbable biomaterials ending without incorporation, but rather in fibrous encapsulation.^{32,33} Initially the response includes a heavy collection of macrophages and neutrophils at the periphery of the implant (**Fig. 3G, I**). With time, macrophages fuse together to form foreign body giant cells as the host attempts to wall off the foreign object with a layer of dense connective tissue, that is, fibrous encapsulation (see **Fig. 3J**). In a study compared with Permacol, the reported response to Collamend (Davol, Warwick, RI, USA), an EDC crosslinked porcine dermis product, found similar results between the two materials, including moderate chronic inflammation, limited to the periphery of the implant at 6 months with no cellular or vascular infiltration.⁷ This response can be desirable if the expected clinical outcomes are congruous with those typified by nondegradable polymers or metals, used in many products, including hip implants and surgical meshes. However, encapsulated ECM biomaterials can be prone to many of the same complications as other permanent implants that react following the classic foreign body response,³⁴ such as migration or transcutaneous extrusion.^{33,35}

Rejection

Other interactions have been described for crosslinked ECM biomaterials that deviate from the permanent implant, foreign body response. For example, CuffPatch (Organogenesis, Canton, MA, USA), an EDC crosslinked SIS patch indicated for tendon repair, initially demonstrated a host response similar to other crosslinked ECM biomaterials, marked by “a dense accumulation of neutrophils and mononuclear cells located primarily at the edge of the implanted device” at 1 week (see **Fig. 3G**) without cell infiltration into the matrix. However, by 16 weeks, the CuffPatch was partially degraded with a “robust inflammatory cell reaction and multinucleated giant cells throughout the matrix” (see **Fig. 3H**). In this case, the host response was more successful in rejecting and deconstructing the foreign body as indicated by strong chronic inflammation, giant cell accumulation in and around the matrix, and degradation.³⁶

Incorporating

For devices that can be incorporated, a fundamentally different set of host-implant interactions occur. (Incorporation is a term often used in the discussion of ECM biomaterials clinically and in the literature, but without clear definition. From the authors' experience, most questions regarding ECM biomaterial incorporation are related to whether the material will allow cells and blood vessels to penetrate the matrix. Therefore, in this article incorporation is defined as the ability of an ECM biomaterial to repopulate with host cells and revascularize with host blood vessels.) Initially, cells can penetrate and populate these matrices, and produce proteins and enzymes to simultaneously break down collagen fibers and reassemble collagen fibers to replace the tissue. The rate of breakdown and assembly have not been accurately quantified for any of these materials. Ultimately the rate can be considered dependent on the multitude of variables between products such as the retained ECM components following processing to remove cells, the sterilization type, and the starting structure of the fibrous network making up the anatomic location of harvest (ie, pericardium, dermis, intestinal submucosa).

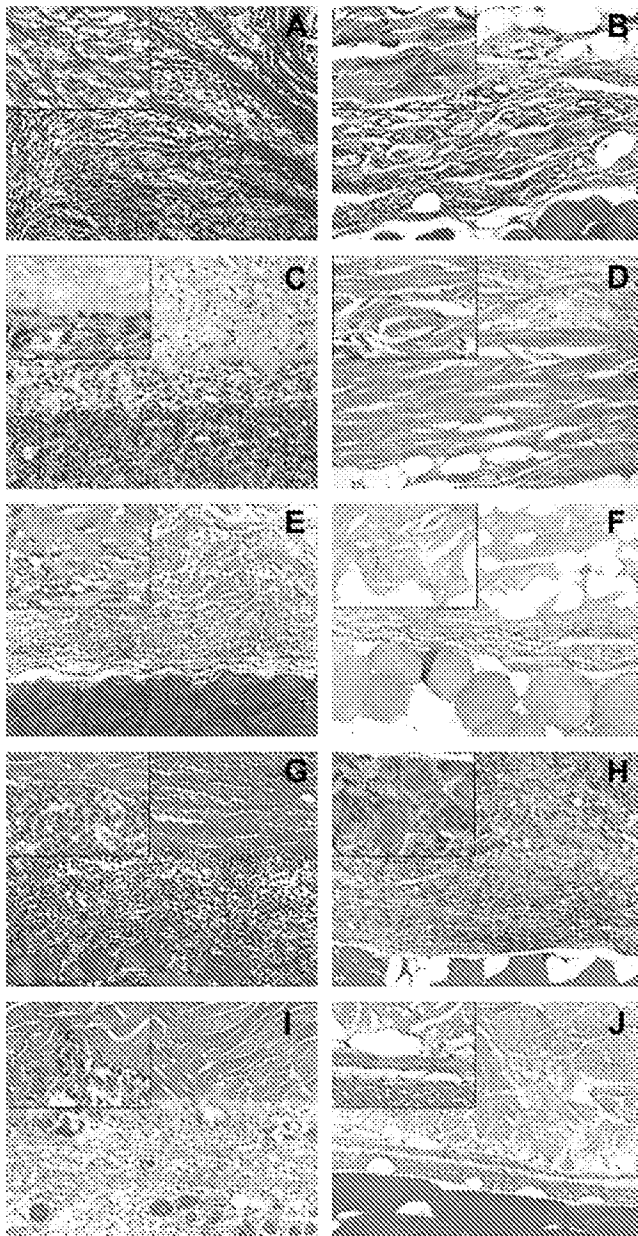


Fig. 3. Histology of ECM biomaterials implanted on a 1-cm² partial thickness muscle defect in rats at 1 week (*left*) and 16 weeks (*right*). Restore (porcine SIS) was infiltrated with a large quantity of inflammatory cells degrading and separating the layers of the device (A) and no evidence of the device was seen at 16 weeks (B). Dense populations of mononuclear inflammatory cells were seen at the edges of Alloderm (human dermis) (C) and the implant was partially degraded by 16 weeks (D). The SurgiMend (fetal bovine dermis) was repopulated with host cells with minimal inflammatory response (E) and "remained virtually unchanged from the time of implantation" at 16 weeks (F). A dense accumulation of neutrophils and mononuclear cells was found at the edge of the CuffPatch (crosslinked SIS) early (G) with chronic inflammation and foreign body giant cells present later (H). Early accumulation of neutrophils, mononuclear cells, and foreign body giant cells at the periphery of Permacol (crosslinked porcine dermis) was present early (I) and there was almost no evidence of scaffold degradation at 16 weeks (J). (From Valentin JE, Badylak JS, et al. Extracellular matrix bioscaffolds for orthopaedic applications. A comparative histologic study. *J Bone Joint Surg Am* 2006;88(12):2673–86; with permission.)

Resorption

At the other end of the device-host biological response spectrum, ECM biomaterials are available that can be rapidly resorbed by the host. Derived from multilaminated layers of thin intestinal submucosa (non-crosslinked SIS technology), Restore and Surgisis retain certain noncollagenous components of the ECM that have been demonstrated to alter cellular interactions. For example, these materials have been reported to retain FGF-2 and GAGs, but not VEGF.^{9,10} In studies, these materials were rapidly infiltrated by inflammatory cells after as little as 7 days (see **Fig. 3A**). Cells separate the layers of the laminated collagen material, leading to rapid resorption of the material and replacement with disorganized scar tissue (see **Fig. 3B**). Similarly, SIS materials have been described as rapidly degraded in a canine model,³⁷ rapidly resorbed in an ovine tendon augmentation study,³⁸ and delaminate by intense infiltration with polymorphonuclear, mononuclear, and foreign body giant cells in primate body wall repair.⁷ The typical expected result following implantation of these devices is rapid degradation and resorption, resulting in scar tissue formation.⁷ Whether this strong response is purely inflammatory or can be more readily associated with immunologic rejection common to cellular xenografts is still being debated. Stronger than expected clinical signs of inflammation have been witnessed clinically in humans^{39,40} with multiple hypothetical explanations related to the processing of SIS materials and constituents retained in the matrix. Some reports found SIS materials containing remnant cell nuclei and other cellular debris that could be immunogenic.⁴⁰ Others have investigated the presence of the immunogenic epitope alpha-Gal retained in SIS materials.⁷ The alpha-Gal epitope is found abundantly expressed on glycoconjugates of nonprimate mammals⁴¹ and associated with xenograft rejection considering an estimated 1% of circulating human immunoglobulin (IgG) is anti-Gal.^{41,42} The presence of anti-Gal antibodies in histological slides of preimplant SIS⁷ and anti-Gal antibodies in patients with SIS implants have been reported.⁴³ Regardless of the immunogenic potential of SIS biomaterials, processing that retains noncollagenous proteins, growth factors, and GAGs^{9,10} may promote the strong inflammatory profile, particularly if these retained constituents have been damaged during processing.

Integration with progressive degradation

Another example of a different expected biological response with a non-crosslinked ECM biomaterial is that of GraftJacket. Graftjacket (Alloderm), sold as an allograft and derived from human dermis, is minimally processed and reported to retain noncollagenous components of the ECM, including elastin and proteoglycans.^{7,8} Alloderm is incorporated, including repopulation with host cells and vasculature.⁸ The early inflammatory response at 7 days is marked by dense layers of mononuclear cells at the periphery of the device (see **Fig. 3C**). These cells, likely a combination of neutrophils and macrophages among others, surround the device and penetrate the outer layers of the implant (see **Fig. 3C**). This low-grade inflammation persists in parts of the matrix, typically in the outer regions, and the implant is slowly degraded.⁴⁴ In a subcutaneous implant study in rats, a human acellular dermis implant is evaluated at 1, 4, 8, and 12 weeks after implantation (**Fig. 4**).⁴⁴ These researchers describe a marked decrease in volume, including a decrease greater than 60% in implant dimension, whereby "host cell infiltration and neovascularization occurred only around the implant."⁴⁴ The material is slowly degraded from the periphery toward the center of the implant and partially replaced with fibrous connective tissue. Animal and human studies report a similar phenomenon as thinning to translucence in rat studies⁴⁵ and clinical failure in human studies.^{46,47}

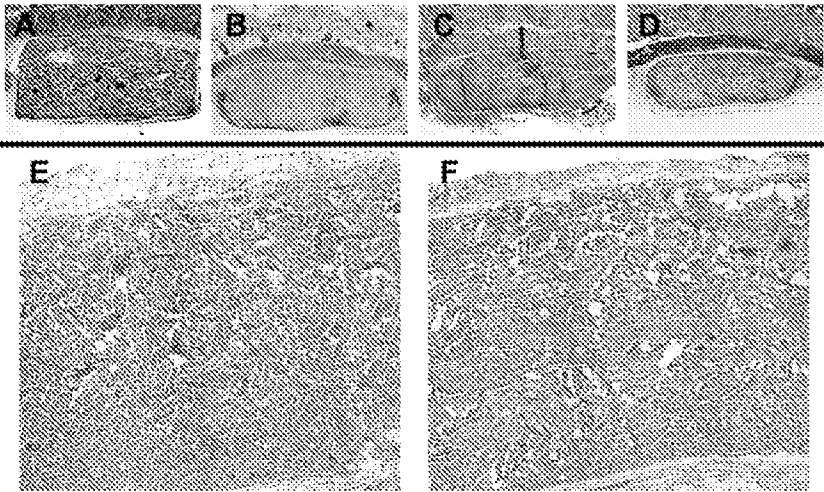


Fig. 4. Histology images of subcutaneous histological sections (*top*) of Alloderm stained with Masson trichrome and subcutaneously implanted in rats demonstrate slow steady degradation of the implant from the periphery toward the center with time progression between (A) 1, (B) 4, (C) 8, and (D) 12 weeks. Sections of SurgiMend (*bottom*) stained with hematoxylin and eosin (H&E) and implanted subcutaneously in rats show the ECM biomaterial populated by host cells at 4 weeks (E) and persisting without apparent alteration in the cell density or larger collagen fiber architecture for 15 months (F) in this non-load-bearing application. (*Images A–D* courtesy of Hwang K, Hwang JH, et al. Experimental study of autologous cartilage, acellular cadaveric dermis, lyophilized bovine pericardium, and irradiated bovine tendon: applicability to nasal tip plasty. *J Craniofac Surg* 2007;18(3):551–8; with permission.)

Adoption and adaptation

Encapsulation and degradation are not the only results in the use of ECM biomaterials. Non-crosslinked ECM biomaterials derived from fetal bovine dermis (for example SurgiMend or TissueMend) demonstrate adoption by host fibroblasts, and can persist as a new, generative tissue (gTissue), being adapted as necessary to meet the demands of the mechanical loading environment. At the time of implantation, the highly porous material readily traps blood, acting as a sponge to trap cells, growth factors, and cytokines, to seed the matrix. The biomaterial is rapidly repopulated with host cells and supporting vasculature. Acute histology indicates a muted inflammatory response in comparison with other ECM biomaterials (see **Fig. 3E, F**), including sparse quantities of neutrophils, and macrophages. By 4 weeks, in a rat intramuscular implant, the material is populated with fibroblasts, and a few remaining inflammatory cells (**Fig. 5A**). In contrast to other ECM biomaterials, the interface between muscle and implant is essentially seamless and the collagen fiber architecture of the material appears essentially unchanged (see **Fig. 5A**). By 12 weeks, the intramuscular implant persists with no perceptible alteration to the collagen fiber structure and no chronic inflammatory response (see **Fig. 5B**). The material is still populated with host fibroblasts, and a few remaining apoptotic immune cells, including granulocytes and macrophages, can be found, typical of resolving wound healing. Fetal ECM biomaterials in subcutaneous non-load-bearing applications have been tested in rats after 15 months with the gTissue remaining as a living connective tissue, adopted by the host, populated with fibroblasts, without inflammation, change in cell quantity, or major alteration in the larger collagen fiber architecture (see **Fig. 4F**).

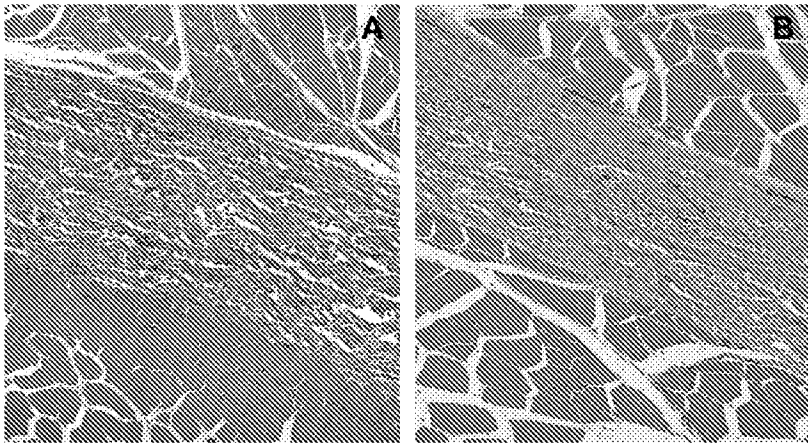


Fig. 5. H&E-stained sections of SurgiMend after (A) 4 weeks and (B) 12 weeks intramuscular implantation in rats. At both time points, the material had incorporated at the implant site, with no evidence of inflammation or fibrous encapsulation. The material was repopulated with host cells, particularly fibroblasts. The edge of the material on all sides was in direct contact with muscle without the classic signs of a foreign body response (ie, no accumulation of inflammatory cells at the implant periphery, no foreign giant cells, no fibrous encapsulation).

However, similar to native connective tissue, gTissue can be adapted by the host if the appropriate cell signalling exists. Although the precise set of signaling conditions modulating the fetal ECM biomaterial is undefined, some parameters have been identified. Clear differences are seen in external skin wounds compared with internal surgical placement (see section on Applications). Furthermore, the mechanical loading environment appears to be a controlling factor in fetal ECM biomaterial adaptation. For example, replacement of tendon in a small animal model resulted in the rapid adaptation of the collagen fiber architecture of the material from its characteristic crosshatch pattern to the more aligned and oriented fibrillar structure of native tendon in as little as 4 weeks after repair (**Fig. 6**).

APPLICATIONS

The use of ECM biomaterials is rapidly expanding as the general utility of these materials has gained acceptance. Understanding the clinical advantages and limitations of these materials is crucial to their overall effectiveness in aiding patient outcomes. Currently, only limited clinical data have been published describing the use of any individual material listed in **Table 1**, and none have been reported in direct comparison. Clinicians' goals and patient specific intended outcomes should be matched to the appropriate expected responses described above. Therefore, in the following discussion, cases familiar to the authors, and from the clinical experience of one author (A.L.), are highlighted in which the adoption and adaptation response, gTissue functionality, and lack of inflammation were desirable characteristics.

Tendon and Ligament Repair

ECM biomaterials have been used in tendon repair procedures for more than a decade with clinical success. These materials are used to augment primary repair of tendons, to reinforce weakness, and to promote healing in a tissue that represents a significant

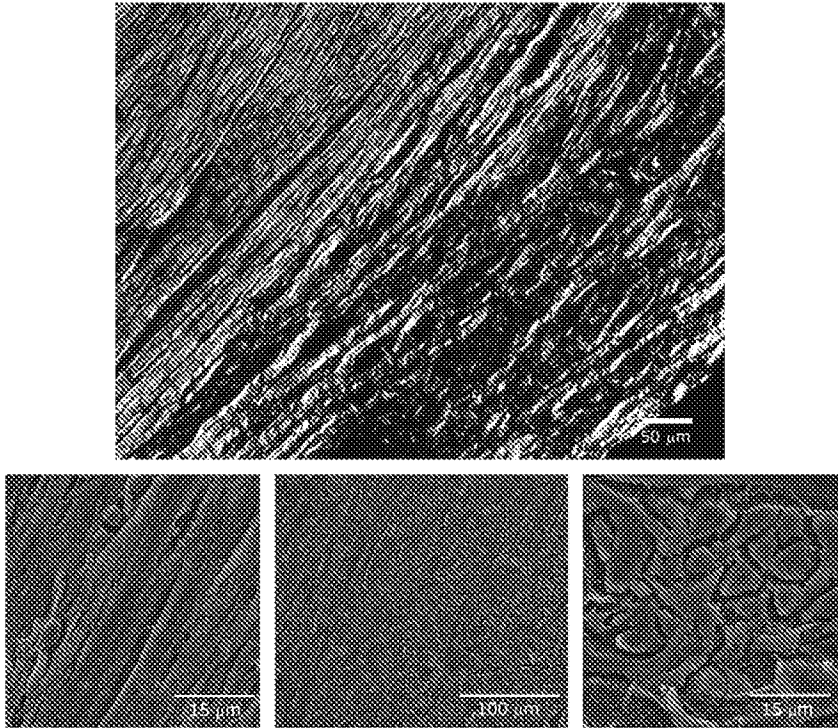


Fig. 6. Polarized light microscopy image (*top*) of SurgiMend undergoing structural adaptation in response to loading in a rat tendon repair application. The crosshatch pattern of the dermis-derived material can be seen on the right at 4 weeks post implantation in a tendon defect. SurgiMend on the left has been adapted to the loading environment and now has a collagen fiber architecture indicative of tendon. High magnification SEM images highlight the seamless transition region (*bottom middle*) and the collagen fiber orientation and alignment of the SurgiMend (*bottom right*) and the SurgiMend adapted into tendon (*bottom left*).

clinical challenge. Tendons tend to have a limited vascular supply, and large tears, like those common in the rotator cuff, do not heal spontaneously, necessitating surgical intervention with high recurrence rates. In podiatric applications, these materials are commonly used as a wrap during Achilles tendon repair, tendon-lengthening procedures, and other foot and ankle tendon reattachment procedures.^{48–50} For example, SurgiMend has been successfully used to reinforce the repair of a complete rupture of the tibialis anterior tendon in a diabetic patient with results after 6 months demonstrating a return to full strength (grade increased from 2 to 4 out of 5 on the Medical Research Council scale of manual muscle strength) and restoration of heel-walking ability.⁵¹ Other case studies have reported use of SurgiMend in the repair of an injured posterior tibiotalar ligament, in which the material was sutured under high tension (**Fig. 7B**). In these procedures, when primary attachment cannot be achieved and suture wire with bone anchors is required to reattach the torn ligament, SurgiMend has been used to promote biologic regeneration of tendon tissue around a supporting suture in what would otherwise be a large tissue gap.

Novel uses of these materials are redefining classic tendon repair by taking advantage of the unique attributes of certain ECM biomaterials. In one particular case study,

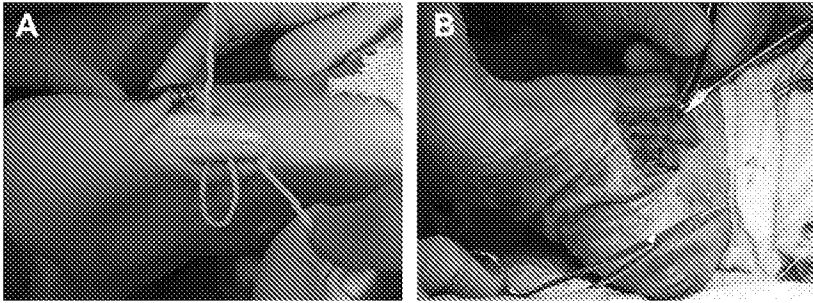


Fig. 7. (A) Reapproximation of an Achilles tendon after debridement of the central portion, weaving SurgiMend string. The patient reported less pain and a more rapid return to mobility. (B) SurgiMend sutured under high tension in the repair of an injured posterior tibiotalar ligament.

a thin string of SurgiMend, approximately 2 mm wide by 1.5 mm thick by 25 cm long, was used in the surgical repair of an Achilles tendon in a patient suffering from chronic Achilles tendonosis. After longitudinal debridement of the deteriorated, inflamed, central portion of the Achilles tendon, the tissue was reapproximated using the SurgiMend string rather than standard, nonresorbable suture (see Fig. 7A). Under these conditions, a material that can be adopted and adapted to the patient without inciting an inflammatory response is ideally suited, considering it is being applied in a disease state associated with excessive chronic inflammation. The results for this particular patient included a return to full weight-bearing activities in half the expected time and an almost immediate reduction in pain.

Plastic and Reconstructive Procedures of the Foot and Ankle

Surgeons are creatively expanding the repertoire of procedures that use these devices, particularly for plastic and reconstructive procedures. Our experience with SurgiMend alone has seen the product successfully used in plantar fat pad augmentation and resurfacing of the metatarsophalangeal (MTP) joint in lower limb procedures. In clinical use by the author (A.L.), SurgiMend has been demonstrated to support adipose tissue growth in the stabilization of the calcaneal fat pad. In patients with advance degenerative joint disease or hallux rigidus of the first MTP, SurgiMend has been wrapped around the bone and remaining cartilage following debridement of exostoses and damaged cartilage similar to the methodology employed by Berlet and colleagues.⁵² This procedure has helped restore joint motion, reduce pain, and delay or eliminate the need for more complicated and nonreversible procedures like arthrodesis or joint replacement with a prosthesis.

Skin and Wound Healing

In podiatric medicine, one of the most common applications for ECM biomaterials is in dermal regeneration and the healing of difficult open wounds, although the mechanism of healing and repair is not equivalent to that of surgical implantation. Closing complex full-thickness wounds of the foot and ankle is challenging because of the varying causes and underlying conditions leading to pressure ulcers, most notably diabetes. Ulcers may persist for months to years, and practicing podiatrists may try repeated applications and multiple products before finding the right means of achieving wound closure. ECM biomaterials have been demonstrated to improve

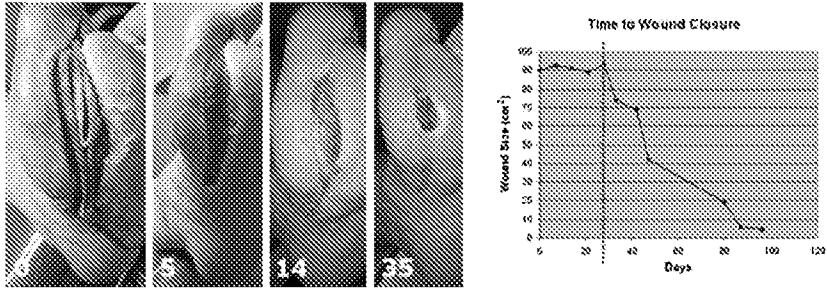


Fig. 8. The use of PriMatrix strips following infection of an ulceration below the first metatarsal head. After extensive debridement and essentially no progress toward closure by 4 weeks, PriMatrix strips were placed (time 28, dotted line on graph). Following the initial application, a second application was added 5 days later as the wound rapidly progressed toward eventual complete closure. (Courtesy of Landsman and colleagues, American College of Foot and Ankle Surgeons, Long Beach, CA, USA, February 2008.)

outcomes in the treatment of diabetic ulcers in prospective^{53–55} and retrospective⁵⁶ clinical studies. For example, in a patient presenting with a long ulceration following infection below the metatarsal head on the left foot, 4 weeks of treatment with negative pressure wound therapy demonstrated essentially no progress toward closure, but immediately progressed toward closure following the application of PriMatrix, an ECM biomaterial similar to SurgiMend but indicated for skin wounds (Fig. 8). These materials are successful in promoting a vascular granulation tissue⁵⁷ even in particularly difficult wounds in high-risk diabetic patients with additional complicating factors such as peripheral artery disease, peripheral neuropathy, rheumatoid arthritis, and end-stage renal disease on dialysis.⁵⁸ Furthermore, these materials can be successful in building tissue in deep tunneling wounds and over exposed bone.

In the treatment of full thickness wounds, multiple applications of the ECM biomaterial may be required before full closure; on follow-up evaluation of the wound, the material can no longer be distinguished from the new granulation tissue. In contrast to the noted response to SurgiMend during surgical implantation, the mechanism of healing does not appear to follow the sequence of events whereby the material is repopulated with cells and persists. Difficulty in reproducing these complex wound-healing environments in nonclinical studies has left this area of investigation largely unstudied. However, the ability of non-crosslinked ECM biomaterials to be altered by the host, and to do so without inciting inflammation, are probable factors distinguishing this mechanism of healing.

SUMMARY

The many options and expanding utility of ECM biomaterials have encouraged clinicians to improve their knowledge of the use and application of these biomaterials. There are diverse biological responses when using different ECM biomaterials in different clinical situations. Although the degradation or encapsulation that can result from using some ECM biomaterials may be acceptable, tissue building may also be necessary, facilitated by appropriate selection and understanding of implant conditions. An understanding of the distinguishing characteristics of ECM biomaterials for intended outcomes can improve patient results and create new possibilities for the healing and repair of challenging foot and ankle conditions.

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