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Abdominal wall reconstruction using biological tissue grafts: present status and future opportunities

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Surgeons often encounter the challenge of treating acquired abdominal wall defects following abdominal surgery. The current standard of practice is to repair most defects using permanent synthetic mesh material. Mesh augments the strength of the weakened abdominal wall fascia and enables the hernia repair to be performed in a tension-free manner. However, there is a risk of acute and/or chronic infection, fistula formation and chronic abdominal wall pain with the use of permanent mesh materials, which can lead to more complex operations. As a means to avoid such problems, surgeons are turning increasingly to the use of xenogenic and allogenic materials for the repair of abdominal wall defects. Their rapid evolution and introduction into the clinical operating room is leading to a new era in abdominal wall reconstruction. There are promising, albeit limited, clinical data with short-term follow-up for only a few of the many biological tissue grafts that are being promoted currently for the repair of abdominal hernias. Additional clinical studies are required to better understand the long-term efficacy and limitations of these materials.

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Overview of the disease

Incisional hernia is one of the most frequent complications following abdominal surgery. Despite advances in medical technology, the repair of abdominal wall defects continues to be imperfect and costly, resulting in serious, chronic healthcare problems. Current practice guidelines and medical evidence support the use of a permanent prosthetic mesh for the repair of incisional hernia as a means to reduce the risk of recurrent hernia. Patients who are not repaired with mesh, either owing to clinical contraindications or by surgeon choice, have a much higher incidence of recurrent incisional hernia compared with patients who are repaired with mesh [1–3].

A variety of different implantable synthetic mesh materials are available commercially for incisional hernia repair. However, no single material has gained universal acceptance or preference. Permanent synthetic materials, such as polypropylene mesh, are strong and easy to handle but are associated with a number of potential complications, including mesh extrusion, chronic pain, bowel adherence, obstruction and fistula formation [4–9]. Such complications can lead to more complex and costly surgeries, as well as the development of a recurrent hernia. Another potential problem with permanent synthetic mesh is its susceptibility to bacterial colonization and chronic infection [10,11]. Bacteria adhere avidly to the polymers of mesh and immediately lay down a biofilm, which protects them from host immunological defenses and antibiotics: thus ensures their long-term survival and leads to chronic infection of the hernia wound [12]. The increased morbidity and costs associated with infected mesh are so dire that surgeons should avoid placing permanent mesh in grossly infected fields and should probably

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avoid placing it in clinical circumstances where the risk of infection is increased. Contraindications to the use of mesh are listed in BOX 1.

The ideal mesh

The ideal mesh should be made from a natural, biodegradable substance and should also be relatively inert, causing little or no foreign body reaction. An ideal mesh should also possess the following characteristics:

- Resistance to bacterial colonization and chronic infection
- Biocompatibility and noncarcinogenicity
- Available readily at acceptable costs
- Ability to withstand physiological stresses over a long period of time
- No additional pain caused after implantation
- Promotion of strong tissue in-growth
- Avoidance of substantial contraction
- No development of adhesions to visceral structures induced

No synthetic implants meet these ideals. Finally, an ideal mesh should provide cells with a supportive framework and the necessary signals for host cells to grow, differentiate and interact, while at the same time it should degrade slowly as the wound gains strength and new fascia is formed. However, if a formed hernia is unable to produce adequate collagen into the supportive mesh framework an ideal mesh should not degrade.

Why biological tissue grafts?

For the purpose of this review, the term biological tissue graft will be used to characterize materials derived from biological sources. The rationale for using a biological tissue graft for abdominal wall reconstruction is to avoid acute and chronic mesh infection and unwanted chronic inflammation that occurs frequently in response to permanent synthetic materials. Alternative approaches for closing difficult hernias or abdominal defects when permanent mesh is contraindicated have included primary closure, absorbable mesh and autogenous tissue transfer [13–16]. Two of the most common autogenous tissue transfer techniques are the tensor fascia lata graft and the bilateral sliding rectus abdominus myofascial flap, also known as the components separation technique [17]. Despite the advantages and utility of autogenous tissue, recurrent hernia and wound complication rates are often unacceptably high, as are problems related to the donor site. Collectively, these contraindications and problems have provided the impetus to employ biological tissue grafts for abdominal wall reconstruction.

Box 1. Situations in which permanent mesh is relatively contraindicated.

- Ascites (risk of spontaneous bacterial peritonitis and nonincorporation)
- Peritoneal contamination
- Any dirty or contaminated wound:
  - Gross spillage from hollow organs
  - Penetrating trauma
  - Chronic open wounds or adjacent contaminated wound
  - Low-volume spillage from small/large bowel
- Previously infected or irradiated wounds
- Removal of infected mesh
- Remote infection

Biological tissue grafts

The art and science of using tissue grafts from animal (xenogenic) and human (allogenic) sources for abdominal wall reconstruction is nascent. Biological tissue grafts are rendered acellular through various methods of preservation and fabrication and are offered as acellular materials that provide biological scaffolding for host cellular repopulation and revascularization. From a pathophysiological viewpoint, there are two different indications for the use of biological tissue grafts in abdominal wall reconstruction. One is for the repair of those abdominal wall defects secondary to trauma, cancer or infection and the other is for the repair of those defects secondary to hernia disease. Despite some encouraging early results, several clinical complications have been reported following the use of these biological materials to reconstruct abdominal wall defects. As is the case with any new medical device or product introduced into clinical practice, experience and time will ultimately define their utility and limitations. At present, there are limited data from prospective trials and case series; they are mostly short-term follow-up of patients treated with biological tissue grafts for abdominal wall reconstruction. Despite the absence of long-term outcome studies, the use of xenogenic and allogenic materials in clinical practice is growing rapidly for want of a better solution to difficult hernia repairs, especially in contaminated or infected surgical fields.

Several biological tissue grafts are available commercially for use in the USA for abdominal wall reconstruction (TABLE 1). These grafts vary in performance characteristics, such as cellular response, strength, biodegradability, susceptibility to infection and tendency to transmit diseases. These materials also have mechanical properties that can change following *in vivo* implantation.

Scaffolding materials

Intestine

Surgisis®

Small intestinal submucosa (SIS) (Surgisis® Cook Biotech, IN, USA) is a commercially available xenogenic tissue grafting material composed essentially of a mammalian extracellular matrix (ECM). It is created from the submucosa of the small intestine of pigs in a manner that removes all cells, but retains the natural 3D composition of the ECM, which acts as a scaffold into which cells can migrate and multiply. This biomaterial

Table 1. Biological tissue graft characteristics and concerns.

Product	Manufacturer	Tissue origin	Price (US$/cm^2)	Concerns	Ref.
Surgisis®	Cook (IN, USA)	Pig small intestine	3.40	Susceptible to bacterial degradation, increased hernia recurrence with closed-space infection	[203]
Permacol™	Tissue Science Laboratories (Hampshire, UK)	Pig dermis	8.33	Crosslinking prevents integration and wound remodeling. Limited published experience in abdominal wall reconstruction	[204]
CollaMend™	Davol Inc. (RI, USA)	Pig dermis	16.00	No published clinical series in abdominal wall reconstruction	[205]
SurgiMend™	TEI Biosciences Inc. (MA, USA)	Cow dermis	22.00	No published clinical series in abdominal wall reconstruction	[206]
Alloderm®	LifeCell (NJ, USA)	Human dermis	26.08	Expensive, small size, variable thickness of grafts. Potential for disease transmission. Thins out over time, stretches. Susceptible to bacterial degradation, increased hernia recurrence with closed-space infection. Time-consuming 'quilting' for large defects	[207]
Allomax™	Davol Inc. (RI, USA)	Human dermis	28.00	No published clinical series in abdominal wall reconstruction. Potential for disease transmission	[205]
Tutopatch®	Tutogen Medical (NJ, USA)	Cow pericardium	ND	Limited published experience in abdominal wall reconstruction	[208]
Veritas®	Synovis Surgical Innovations (MN, USA)	Cow pericardium	8.60	No published clinical series in abdominal wall reconstruction	[209]
Periguard®	Synovis Surgical Innovations (MN, USA)	Cow pericardium	1.90	Cross-linked by a process using gluteraldehyde. No published clinical series in abdominal wall reconstruction	[209]

was first developed in 1987 at Purdue University (IN, USA) and was approved by the US FDA in 1999 for soft tissue repair. This product has been evaluated extensively in a number of reconstructive applications, including vascular and genito-urinary systems, burns, wound healing and repair of abdominal defects (inguinal, paraesophageal, incisional/ventral and diaphragmatic hernia). The propriety form of SIS marketed by Cook Biotech for hernia repair is Surgisis.

Proprietary process & composition

Surgisis is derived from porcine donors. To prepare Surgisis, pig jejunum is collected and the mucosa, muscularis externa and serosa are removed mechanically leaving only the submucosa layer of the intestine. This layer consists primarily of a collagen-based ECM containing few resident connective tissue cells. During processing, the tissue is defatted and its cells destroyed with paracetic acid, which also disinfects the tissue [18]. It is sterilized terminally with ethylene oxide, yielding a pathogen-free, noncross-linked biomaterial that contains a 3D structure. Surgisis is available as a four- or eight-layer product. The eight-layer product (Surgisis Gold®) is used most commonly for abdominal (ventral) hernia repair, whereas the four-layer material is marketed for paraesophageal and groin hernia repair. Surgisis can be stored at room temperature and has a shelf life of 18 months. It must be rehydrated in sterile saline at room temperature for 10 min prior to use.

The nonwater portion of rehydrated Surgisis is approximately 90% protein [19]. The high protein content consists primarily of collagen (types I, III and V) that forms the scaffolding of the 3D network of the ECM [19]. The remainder of the ECM is comprised mainly of carbohydrates, such as glycoproteins, proteoglycans and glycosaminoglycans (hyaluronic acid, chondroitin sulfate A, dermatan, heparin and heparin sulfate), as well as some lipid [20]. Many glycoproteins and proteoglycans in SIS contain specific sites on their protein portion that facilitate host-derived cell attachment within the ECM and thereby contribute not only to the repopulation of the matrix but also to the cellular processes necessary for tissue remodeling into mature functional tissue [21,22].

Growth factors

The noncollagenous portion of Surgisis (SIS) contains numerous growth factors that may signal the essential aspects of the host tissue repair and remodeling process, such as cell migration and differentiation. These protein molecules include fibroblast growth factor (FGF)-2 and a transforming growth factor (TGF)-β-related protein [23,24]. In addition, vascular endothelial growth factor (VEGF) has been identified as a component of SIS [25]. VEGF is also an important regulatory molecule that induces the migration of endothelial cells. While the presence of trophic growth factors for wound healing is potentially valuable for a biological tissue graft, it is

unknown currently whether or not their concentrations in the material are biologically significant or critical to the function of the material.

Disease transmission

One theoretical concern with the use of any biological material is the risk of disease transmission. Consequently, multiple steps are taken in the processing of the tissue by the manufactures, including the careful selection of source tissue and the treatment of the tissue with peracetic acid during processing to ensure that the risk of transmission of known pathogens is extremely low [26]. To date, there have been no reported cases of *in vivo* disease transmission to humans from Surgisis.

Cellular & immunological response

Histological and immunological evidence indicates that SIS is not rejected by the host but induces a dynamic immune and cellular response after implantation. Investigators have shown that SIS elicits a local and systemic T-helper (Th)2-associated immune response characterized by the production of anti-inflammatory cytokines and noncomplement-fixing antibodies [27]. This response may be an important factor in SIS remodeling by modulating postsurgical inflammation and the host's acceptance of the xenograft. In a follow-up study, this graft-site response was shown not to suppress the antibody- or cell-mediated immune response to other antigens, such as bacterial and viral pathogens [28].

Effective regeneration and repair of abdominal wall defects depends on early re-establishment of cellular infiltration. Researchers have described a self-limited early acute inflammatory response that is largely resolved by day 14; this consists mostly of polymorphonucleocyte (PMN) infiltration at 1 week following implantation of the multilaminated SIS in a rodent model of abdominal wall hernia repair [29,30]. By day 14, the number of mononuclear cells increases and at week 4, fibrocytes and collagen fibers are present, together with a modest influx of mononuclear cells into the matrix [29,31]. Histological examination of the healing response shows that SIS invokes limited inflammation and also leads to a progressive deposition of organized connective tissue in a manner that is consistent with natural wound healing. A total of 90 days after implantation, the mononuclear cell infiltrate diminishes and there appears to be relatively few foreign body giant cells and more well organized collagen, skeletal muscle and adipose tissue [29,30]. The quality and strength of the regenerated tissue that replaces the SIS tissue graft in humans is unknown at present. It is possible that the composition and strength of the regenerated tissue differs among patients with hernia disease and patients who have surgically-induced abdominal wall defects repaired with SIS. When compared with wounds repaired with polypropylene mesh, SIS has significantly less foreign-body reaction and more organization of connective tissue at 90 days postimplantation. The source of cells that contribute to this remodeling process is not understood fully although circulating, marrow-derived cells deposit preferentially in scaffolds of ECM [32].

Severe inflammatory reactions are known to result in adhesions. When used to repair abdominal wall defects, SIS has been shown consistently in several animal models to have less formation of dense adhesions compared with polyproplylene mesh [29,31,33]. In one study, the average surface area of adhesions to SIS (<50%) was less than to polypropylene (>75%) 8 weeks after implantation [33]. The nature of the adhesions in the SIS-treated animals were also soft and dissected easily, whereas the adhesions to the synthetic polypropylene mesh were more dense and tenacious [33].

A recent publication reported that porcine DNA was detected in an implanted SIS-based product used for tendon reconstruction [34]. Processing of biologically derived materials is of great importance because more or less processing can alter the native composition and structure of the ECM. Extensive processing can render natural ECMs inhospitable to the host. Surgisis is processed in such a way as to provide a high level of safety with an intact, noncross-linked ECM that maintains natural composition and structure [JOHNSON C, COOK BIOTECH INC., PERS. COMM.].

Capillary ingrowth

Effective regeneration and repair of abdominal wall defects depends on early wound angiogenesis. Growth factors present in the SIS matrix and host cells that invade SIS elicit early signals for capillary ingrowth. In a rat model, microscopic evaluation on hematoxylin and eosin stains of SIS mesh explanted at 1 week showed a scant amount of newly formed blood vessels [29]. In a similar animal model, moderate vascularization of the SIS mesh was noted at 4 weeks [31]. In this study, neovascularization continued and by 8 weeks vessels were noted at greater than 50% thickness of the implant [31]. Recent studies in rodents demonstrate that lyophilized SIS is revascularized more rapidly through angiogenesis compared with the vacuum pressed SIS following their implantation into the abdominal wall [JOHNSON C, COOK BIOTECH INC., PERS. COMM.].

Biomechanical strength characteristics

Biological tissue grafts must not only be strong enough to withstand the physiological demands placed upon them when implanted but they must also incorporate into the tissue adjacent to the matrix over time. In its dehydrated state, SIS is brittle and sutures will tear through it. However, when rehydrated with saline, it becomes strong and difficult to tear. Several investigators have demonstrated that multilaminate SIS provides the initial mechanical strength appropriate for applications, such as body wall repair [35–37]. In fact, animal studies have shown that eight-layer SIS is significantly stronger than the natural abdominal wall fascia. In studies of strength, force measurements were made of the maximum force required to tear a multilayer SIS device. In these studies, the maximum load to failure for eight-layer SIS was 433.6 ± 79.5 N, for four-layer SIS was 130 ± 29 N and for natural abdominal wall fascia 145.5 ± 72.2 N [30,33]. However, two-layer SIS was found to be weaker (42 ± 9 N) than natural fascia [38].

After implantation Surgisis becomes weaker over time. A 45% decrease in the strength of eight-layer Surgisis has been observed during the first 10 days after implantation in a dog model [37]. However, the bursting strength of the wound remains higher than the natural abdominal wall tissue. Approximately 1 month after implantation the strength of eight-layer SIS returns to baseline. This increase in strength probably reflects a combination of the original implanted material and newly deposited host-derived tissue. In another study, full-thickness abdominal wall defects were created in rats and repaired with SIS. Results of this study showed a nadir of strength in the implanted material to be at the 30-day evaluation point [29].

Another strength characteristic of mesh material that can be used to predict the success or failure of the repair after implantation includes the suture-holding capacity. This characteristic can be compared with a known synthetic material to give a sense to its strength. Obermiller and colleagues demonstrated that the suture-holding capacity, defined as the force required to tear the suture from the material or cause material failure at the suture site, was found to be significantly lower for Surgisis compared with polypropylene (287.9 ± 34.3 vs 370 ± 56.2 N, respectively) [35]. These authors noted that the material failure of SIS occurred as suture tears through the repair material (mesh–suture interface) initiated at the suture insertion sites rather than at the suture–fascia interface, which has previously been described in other animal models [35]. Despite this shortcoming, animal studies have reported a low recurrent hernia rate when surgically created abdominal wall defects were repaired with multilaminate SIS [30,37,38].

Degradation

Many biological tissue grafts are absorbed by the body over time (i.e., they are biodegradable) and so serve only as a temporary scaffold for cells to grow into. Studies demonstrate that Surgisis is biodegradable and absorbed completely. Indeed, a cardinal feature of ECMs whose collagens are not cross-linked is for them to become absorbed almost completely following implantation. Surgisis tissue implants are repopulated gradually by host cells and replaced by differentiated host tissues. One potential drawback with absorbable biological tissue grafts, such as SIS, is their speed of degradation. From animal studies, it has been shown that Surgisis grafts are histologically absent 28 and 56 days following implantation in dog bladder [39] and murine subcutaneous pockets [32], respectively. However, when used to repair abdominal wall defects in dogs approximately 25% of the SIS was histologically absent by 1 month, 75% by 2 months and 100% by 4 months [33].

The clinical utility of such a degradable material depends on a balance between the rate of degradation and the rate of remodeling. If a mesh degrades prior to adequate cellular infiltration, differentiation, collagen deposition and neovascularization, the overall quality and strength of the newly formed tissue will be insufficient for abdominal wall repair. Recently, clinical reports have described an accelerated degradation of implanted Surgisis when used to reconstruct abdominal wall defects in infected fields that result in closed-space infections [40,41]. The accelerated rate of degradation in the presence of closed-space infection exceeded the subsequent remodeling process of the native tissue and probably resulted in early recurrent hernia formation.

Susceptibility to infection

Surgisis was marketed originally for use in contaminated and infected wounds. Early observations demonstrated the presence of antimicrobial peptides within pig intestine [42]. However, subsequent *in vitro* and *in vivo* studies have shown that Surgisis does not have intrinsic antimicrobial properties [43,44]. In a rodent model, bacterial adherence and proliferation were evaluated on the surface of implanted Surgisis and compared with AlloDerm® and five other permanent mesh prosthetics [45]. After 5 days and a standardized inoculation of the implanted materials with *Staphylococcus aureus*, similar levels of adherent bacteria were found on the surface of Surgisis as on several permanent and one biological (AlloDerm) implant. Since this was an acute experiment, the long-term consequence of this bacterial colonization is not known. Surgisis probably relies on leukocyte infiltration and vascular ingrowth before it acquires any antimicrobial defense to bacteria. Should Surgisis become colonized with a large inoculum of bacteria that secrete collagenases and proteases prior to becoming vascularized or infiltrated with leukocytes, it will likely degrade rapidly. Hence, the ability of Surgisis tissue implants to become incorporated sucessfully into a contaminated or infected wound is probably dependent on the characteristics of the wound and the speed of angiogenesis. Experimental studies have shown effective SIS graft remodeling in the presence of a challenging inoculum of *S. aureus* [45]. Moreover, the infectivity of these inoculated wounds implanted with SIS was significantly less compared with permanent synthetic material at 28 days [45].

Clinical experience with small intestine submucosa

Following extensive *in vitro* and *in vivo* testing, Surgisis was cleared by the FDA for treating partial-thickness wounds. A total of seven peer-reviewed publications have reported on the effectiveness of Surgisis in abdominal wall reconstruction [40,41,46–50], of which three include the same patient cohort reported by Franklin over time with an increasing number of patients and longer follow-up.

These publications demonstrate that Surgisis can be used safely in the reconstruction of abdominal wall defects, but with certain precautions. Franklin reported his early series with four-ply Surgisis placed laparoscopically in 25 patients. In this study, 14 repairs were performed in clean-contaminated cases and 11 in dirty cases. There was one postoperative complication of a wound infection secondary to an enterocutaneous fistula. There were no recurrent hernias noted with a median follow-up of 15 months (range 1–20 months) [46]. Franklin and colleagues reported their clinical results in a larger cohort of 81 patients undergoing a total of 90 laparoscopic hernia repairs

with follow-up extending to 5 years with an overall recurrence rate of 3.7% [48]. Uno and colleagues from Duke University, NC, USA, reported their experience with eight-ply Surgisis in 17 patients with abdominal wall hernias in potentially contaminated or grossly infected fields [41]. They reported a 50% incidence of postoperative complications following repair with Surgisis in the infected setting. It is important to note that all patients in this study had their dirty wounds closed completely. This resulted in a closed-space infection in six patients, all of whom were reoperated upon. Recurrent hernia developed in all six patients. With a mean follow-up of 15.7 months there was no observed recurrent hernia in any patient who did not develop postoperative infection. In one patient, the Surgisis degraded rapidly with loss of the bioprosthesis within 7 days. A total of 10% of patients experienced seromas [41].

Initially, Surgisis implants accumulate fluid between the laminated layers of the product and cause seromas to form [29]. This may be related to the absence of pores and therefore a limited capacity for water to flow through the material. Indeed, the measured porosity values of hydrated Surgisis were noted to be lower from the mucosal side compared with the serosal side [51].

The experience of the University of Illinois at Chicago with SIS is the largest reported series to date using SIS to reconstruct abdominal wall defects [40]. In this series, 53 consecutive patients undergoing ventral abdominal hernia repair with Surgisis mesh from 2002 to 2004 were reviewed retrospectively. The mesh was placed as a generous underlay with at least 5-cm underlay beyond the fascia edges in all patients, either by a laparoscopic or open intraperitoneal approach [40]. Many of the patients were critically ill, had dirty wounds and emergent laparotomy. Unlike other studies, the results were analyzed from an intension-to-treat point of view and there were no exclusions. Postoperative outcomes were stratified and analyzed according to wound class. Two patients experienced postoperative peritonitis and had partially digested Surgisis mesh removed at repeat laparotomy for intra-abdominal sepsis. Four patients underwent repeat operations for retrorectus closed-space infection anterior to the mesh. There was rapid liquefaction of a mesh placed as an onlay onto the granulated abdominal wall of a patient with an enterocutaneous fistula [40]. The authors noted that the use of Surgisis in dirty wounds in critically ill patients was associated with high complications, need for repeat operation and recurrent hernia (39%) compared with patients with clean and clean-contaminated wounds (9%).

Nfonsam and colleagues from The Cleveland Clinic (OH, USA) reported their use of Surgisis in 33 patients [49]. Recurrent hernia occurred in four out of eight (50%) patients with dirty wounds repaired in an open fashion but in no patients with clean or clean-contaminated wounds at a mean follow-up of 16 months. A consistent finding reported by the surgeons from Duke, The Cleveland Clinic and The University of Illinois is the increased recurrent hernia incidence of 35–50% in patients with dirty wounds compared with a recurrent hernia rate of less than 10% in clean and clean-contaminated cases. These recurrent hernias were the consequence of closed-space infection adjacent to the mesh in almost every circumstance. For this reason, Helton and colleagues recommend caution when using Surgisis mesh in critically ill patients with a grossly infected wound. They recommend leaving the fascia partially open above the mesh and subcutaneous tissues widely open along with the use of a negative pressure dressing in order to eliminate any chance of closed-space infection as a means of avoiding early mesh liquefaction prior to its incorporation.

Skin

Permacol™

Permacol™ was developed by an independent, research-based tissue engineering company called Tissue Science Laboratories plc (Hampshire, UK), which was founded in 1995. Permacol surgical implant was approved for use in Europe in 1998 and in 2000, the product was launched successfully in the USA under the brand name Pelvicol™ Acellular Collagen Matrix after an FDA clearance was granted. Permacol surgical implants have been employed across all surgical disciplines, including urological, gynecological, plastic and general surgery. In general surgery, it is indicated specifically for the repair of abdominal wall defects and complex or recurrent hernias.

Proprietary process & composition

Permacol is derived from porcine donors. It is a cross-linked product and uses nonreconstituted (intact) porcine dermal collagen, which is very similar in structure to human tissue [52]. During processing, all noncollagenous material and cells, including nuclear materials capable of producing an adverse response from the body, are removed from the porcine tissue. The remaining collagen and elastin, which retains its original 3D structural architecture, are then stabilized with diisocyanate, which cross-links the collagen fibrils [53,54]. The finished biological tissue graft is sterilized by gamma irradiation. It is not freeze-dried and it requires no rehydration prior to use; the product is ready to use out of the package.

Growth factors

There are no published data on whether or not growth factors exist in Permacol.

Disease transmission

Unlike bovine-derived materials, transmissible spongiform encephalopathy (TSE) is not a possibility with Permacol, as there are no known prion-related diseases in pigs. To date, there have been no reported cases of cross-infection between species (pigs to humans) and, while not impossible, this is considered improbable.

Cellular & immunological response

In vitro tests required by the FDA have confirmed a lack of immunogenic response [55]. In an animal model, implanted cross-linked acellular porcine dermal collagen tissue grafts elicit an initial cellular infiltration dominated by neutrophils and macrophages. Although this infiltration peaks at 7–14 days, it is milder

and does not persist as compared with the inflammatory reaction elicited from implanted synthetic material (i.e., prolene) [56]. In fact, the inflammatory reaction stimulated by these xenogenic implants declined rapidly, reaching negligible levels by day 90 post implantation [56]. In another rodent study, adhesions and tissue reaction were also decreased in response to porcine-derived collagen implants, as compared with polypropylene mesh [57].

Capillary ingrowth

The manufacturer claims that Permacol provides a permanent support for the ingrowth of new tissue and its associated blood supply. Neovascularization of the graft material has been reported to occur as early as 7 days following implantation in animals [54,56]. However, no data regarding the extent or timing of graft revascularization in patients have been published.

Biomechanical strength characteristics

For optimal hernia repair, biological tissue grafts must be engineered to withstand the maximum intra-abdominal forces acting on the abdominal wall during activities of daily living. The manufacturer of Permacol claims that the patented cross-linking technology, which is introduced into their porcine dermal collagen tissue graft, strengthens the material. Tests performed by the company report that Permacol has an initial mean tensile strength of 21,000 ± 6000 kPa [58], which is substantially stronger than the mean intra-abdominal pressure measured during standing (2.7 kPa) and coughing (14.3 kPa) [59]. An animal study comparing the tensile strength of cross-linked acellular porcine dermal collagen implants with synthetic mesh (i.e., polypropylene) showed that the porcine dermal collagen was initially weaker than at 15 days postimplantation [56]. However, a time-dependent increase in tensile strength was observed in this study, reaching comparable strength with polypropylene at 90 days postimplantation. With this increased strength, it keeps its flexibility owing to its retained elastic properties.

Degradation

In 1975, Oliver and colleagues demonstrated that cross-linking porcine tissues protected the biomaterial from biodegradation, prolonging their permanence following implantation [60]. Tissue Sciences Laboratories employs a cross-linking method in their preservation/processing of Permacol. Company-supported research has carried out rodent ventral abdominal hernia models; from these studies, the company demonstrated the persistence of the implanted Permacol mesh at 9 months [61]. However, there are no published peer-reviewed, experimental or clinical reports to substantiate the manufacturer's claim that Permacol is not degraded over time, especially within contaminated or infected fields.

Susceptibility to infection

Collagen is resistant to all enzymes except collagenase. This enzyme is responsible for the breakdown and resorption of implanted collagen materials. Several bacteria have been shown to possess collagenolytic activity [62,63]. Experimental studies have demonstrated that collagen cross-linked with glutaraldehyde imparted a high degree of stability to the collagen against the activity of the degrading enzyme, collagenase [64,65]. Owing to its cross-linking, Permacol should be resistant to bacterial degradation and therefore safe and effective to use in contaminated or infected hernia repairs. Recent publications have reported on the use of Permacol in contaminated surgical fields with some short-term success. However, the long-term stability and behavior of Permacol in dirty or contaminated fields is not yet established.

Clinical experience with Permacol

A comprehensive literature search identified only five papers reporting on the use of Permacol to close abdominal wall defects [66–70]. Liyanage and colleagues described a patient in whom Permacol was used to repair a large incisional hernia in a clean-contaminated surgical field. Besides the development of a seroma and wound dehiscence, the patient did well without hernia recurrence at 12 months of follow-up [66]. Another case report, also in a clean-contaminated surgical field with a 12-month follow-up, found minimal short-term complications and no hernia recurrence with the use of Permacol in the reconstruction of a large abdominal wall defect [69]. In 2004, Verey and colleagues reported on their experience with the use of Permacol for abdominal wall closure in a series of ten patients [67]. In this study, two out of ten abdominal wall defects were repaired in infected surgical fields. With follow-up times of 2–11 months, no recurrent hernias were reported, but two patients developed minor wound infections and one patient required implant removal secondary to adhesions [67]. In 2005, Permacol was used successfully to close the abdominal wall to avoid compartment syndrome following kidney transplantation in three pediatric patients with no evidence of recurrent hernia at 18 months postoperatively [68]. Cobb and colleagues recently described their experience with the use of Permacol for repair of ventral hernias in 60 patients and compared these outcomes with historical controls using synthetic mesh (polytetrafluoroethylene [PTFE]/polypropylene [PP]; Composix, CR Bard Inc., NJ, USA). In the Permacol group, wound contamination was present in only 7% of the patients. With a mean follow-up of 14 months, postoperative complications included four (6.6%) recurrent hernias, two (3.3%) wound infections and two (3.3%) seromas [70]. By comparison, with a mean follow-up of 31 months, postoperative complications in the synthetic group included one (1.2%) recurrent hernia, two (2.4%) wound infections and one (1.2%) seroma. Six additional complications were also reported in this group [70].

The manufacturers of Permacol are actively seeking volunteer participation in clinical series and case reports to increase awareness and familiarity of their product and to accumulate clinical experience on this new biomaterial [BOND, TISSUE SCIENCE LABORATORIES, PERS. COMM.].

CollaMend™

CollaMend™ (Davol Inc., RI, USA) is a xenogenic tissue graft. In March 2006, it received FDA clearance for reinforcement of soft tissue defects where weakness exists, such as the repair of hernias. However, all claims about the product's performance

characteristics for repair of abdominal wall defects are derived from the manufacturer. There are no peer-reviewed publications regarding the use of CollaMend in abdominal hernia repair.

Proprietary process & composition

CollaMend is derived from porcine donors. It is a lyophilized, cross-linked product that uses porcine dermal collagen. During processing, all noncollagenous cellular components are removed, and all viruses are completely inactivated. The final product is completely acellular and elicits only a minimal inflammatory response [KEEGAN J, DAVOL INC., PERS. COMM.]. The thickness of this biological tissue graft is 1.0 ± 0.2 mm and comes in sizes up to 20 × 25 cm. It can be stored at room temperature and must be rehydrated in sterile saline for 3 min prior to use.

Growth factors

No data are available.

Disease transmission

See Permacol section.

Cellular & immunological response

No data are available.

Capillary ingrowth

No data are available.

Biomechanical strength characteristics

Tests performed by the company report that CollaMend has an initial average tensile strength of 186 N. Additional tests demonstrate an average suture pull-out force and burst strength of 33.4 and 422.8 N, respectively.

Degradation

Company-supported research has carried out rodent ventral abdominal hernia models up to 13 weeks. From these studies the company reported that, at explant, the CollaMend graft was approximately 80% intact [KEEGAN J, DAVOL INC., PERS. COMM.]. However, there are no published peer-reviewed experimental or clinical reports to substantiate this claim. The company believes that implanted CollaMend will degrade completely after approximately 1 year.

Susceptibility to infection

No data are available.

Clinical experience with CollaMend™

Data supporting the clinical use of this material are lacking. At the time of this review, the company claims to have several cases awaiting results that are 3 months postimplantation for repair of incisional hernias.

SurgiMend™

SurgiMend™ (TEI Biosciences Inc., MA, USA) is a xenogenic tissue graft. In 2002, it received FDA clearance for soft tissue repair. However, all claims about the product's performance characteristics for repair of abdominal wall defects are derived from the manufacturer. There are no publications regarding the use of SurgiMend in abdominal hernia repair.

Proprietary process & composition

SurgiMend is derived from fetal bovine donors. It is a noncross-linked product. Briefly, cow hides (skin) are collected and put through a process in which the hair and epithelium are removed. Subsequently, the cellular components of fetal bovine dermis are removed but type III (20–30%) native, non-denatured collagen is left (vs 2–3% content in humans). This collagen-rich scaffold is then treated chemically to remove carbohydrate and lipids, which eliminates most epitopes and makes them immunogenic. There is no chemical cross linking. It is freeze dried, lyophilized, terminally sterilized (not irradiated) via exposure to ethylene oxide gas and packaged. The final biomaterial is acellular and can be stored at room temperature with a shelf life of 2 years. It must be dehydrated for approximately 60 s prior to use.

Growth factors

No data are available.

Disease transmission

Bovine fetal tissues and skin are essentially free of transmissible infectious agents owing to the placental barrier; in addition, prion diseases are not known to have ever been transmitted through the skin. The manufacturing process includes a chemical viral inactivation step validated to ensure inactivation of enveloped and nonenveloped RNA and DNA viruses [71]. No single report of transmission of disease has ever been described.

Cellular & immunological response

This acellular dermal matrix implant provides a collagen scaffold for new tissue development. The company investigated the use of SurgiMend using a rodent hernia model. In this study, animals were sacrificed at 3 weeks and 9 months after implantation of the biomaterial. Explants at 3 weeks showed no evidence of inflammation or foreign body reaction [72]. At 9 months, the implants were replaced by functional host tissue and no adhesions were noted [72].

Capillary ingrowth

The manufacturer claims that this natural scaffold allows for rapid vascular ingrowth and remodeling, seen on histological examination of explants, as early as 3 weeks postimplantation [72].

Biomechanical strength characteristics

The mean intra-abdominal pressure in humans is highest during jumping (22.8 kPa) and during a Valsalva maneuver (26.6 kPa) [59,73]. Interestingly, lifting a 10 pound weight only generates a mean intra-abdominal pressure of 3.4 kPa. The average tensile strength of SurgiMend is 20,000 kPa [71]. Moreover, for comparison with other biological tissue grafts, the

average suture pull out force is 35.5 N [71]. A transformation between the pressure units of N and kPa is difficult and therefore one should not compare these values directly. The authors found that this product does not stretch much and only in one direction, but handles nicely. It is also pliable, similar to regular skin, and supple and conformable, making it easy to suture into place.

Degradation

No data are available from human clinical implantation.

Susceptibility to infection

No data are available.

Clinical experience with SurgiMend™

Data supporting the clinical use of this material are lacking. A single case report, offered by the manufacturers, described a patient in which SurgiMend was used to repair an incarcerated incisional hernia. Besides the development of a wound infection the patient did well without hernia recurrence at 6 months of follow-up [74].

AlloDerm®

AlloDerm (LifeCell Corporation, NJ, USA) is a commercially available allogenic tissue graft. It is created from cadaveric skin in a manner that removes all cells but preserves the tissue without damaging the essential biochemical and structural components necessary for normal tissue regeneration. It was approved by the FDA for use in burns, full-thickness wounds and soft tissue reconstruction in 2001. Since this biological tissue graft has not been changed significantly in structure from the starting material, it has been classified by the FDA as 'minimally processed human tissue'.

Proprietary process & composition

AlloDerm is derived from human donors. It is a noncross-linked product. The proprietary process starts with the procurement of skin from consenting deceased donors and/or their families at the time of death by independent tissue and organ banks across the nation. The collected skin is placed in antibiotic solution and then transported to LifeCell Corporation. Within 12 days of procurement and verifying that the donated skin is eligible for transplantation (see Disease transmission section), it is processed. Processing begins with high ionic-strength solutions to uncouple the bonds between the different layers of the skin (epidermis and dermis). All cells of the dermis are then removed using sodium deoxycholate. This step eliminates the potential for tissue and graft rejection. When processing is complete, all donor DNA and major histocompatibility antigens are destroyed and all that remains is a 3D array of proteins with a structurally intact vascular basement membrane, intact collagen fibers and bundles of type I, III, IV and VII and intact elastin filaments for biomechanical integrity, laminin and glycosaminoglycans [75]. The resulting dermal ECM is then freeze dried in a manner that prevents damaging hexagonal ice crystals from forming within the tissue graft. The product is then refrigerated in its freeze-dried form and can be stored for up to 2 years [76]. Prior to use, AlloDerm must be rehydrated in isotonic saline at room temperature for 20–30 min.

Growth factors

No data are available.

Disease transmission

The risk of transmission of known pathogens from this product is extremely low. The first step to ensure this safety is the careful selection of donors. Under FDA regulations, LifeCell Corporation is required to make a donor-eligibility determination on all collected tissues. This eligibility is based upon donor screening of medical records and/or history (obtained by donor relatives) to confirm the absence of risk factors for, and clinical evidence of, communicable diseases, such as HIV, hepatitis B and C viruses, syphilis and human transmissible spongiform encephalopathy. The donor's blood is also tested for the presence of these communicable diseases. LifeCell Corporation relies upon tissue recovery organizations to assume primary responsibility for donor screening and testing, to assess the suitability and safety of donated tissue. Therefore, the quality assurance measures set by the manufacturer begin with honesty of the procurement organizations and donor relatives. As an additional safeguard, microbiology for bacteria and fungi are performed on each tissue after it has been processed. Any pathogen growth is regarded as contamination and results in failure to obtain quality assurance release. In addition, histology testing is completed on each lot of final product to verify cell removal. An independent evaluation of the manufacturer's processing demonstrated that HIV-1 and the surrogate for hepatitis C virus are reduced (>99.9%) to nondetectable levels [77]. Other viruses, such as hepatitis A and human parvovirus (PPV), were also found to be reduced by more than 99% [77].

Despite these measures, LifeCell Corporation had a recall of AlloDerm in September 2005, owing to fears that one of the tissue recovery organizations was not performing mandated donor screening processes [201]. Currently, there have been no case reports of anyone contracting any disease from an AlloDerm graft. However, infectious disease owing to the transmission of pathogens cannot be ruled out completely. Therefore, it is recommended that the proposed use of this allogenic material should be discussed with patients prior to implantation and that they are adequately informed of the potential risks in order to provide appropriate consent.

Cellular & immunological response

Clinical and experimental studies have shown that AlloDerm does not induce a severe foreign body reaction, which is often seen with synthetic implants. Graft biopsies taken 8 months after implantation in humans have revealed evidence of cellular repopulation and the absence of a chronic inflammatory response [78]. Histological examination of tissue explants taken 28 days after implantation in animals demonstrate that the layers

of AlloDerm are populated with fibroblasts and an inflammatory infiltrate consistent with postoperative changes [79]. One consistent finding reported in animal studies is that visceral adhesions are virtually absent on explanted AlloDerm grafts up to 9 months [79,80].

Capillary ingrowth

Histological analysis and fluorescein dye testing of implanted AlloDerm grafts demonstrated neovascularization of the biological tissue graft 28 days after implantation in a rabbit model [79]. Similar findings were reported by other investigators at 3 and 9 months using a swine animal model [80]. In humans, histological analyses of AlloDerm, biopsied 8 months after implantation, showed evidence of abundant capillaries throughout the biological tissue graft [78].

Biomechanical strength characteristics

Several animal models have investigated the tensile strength of AlloDerm when used for abdominal wall hernia repair. For these experiments, the breaking strength was determined using a tensiometer. AlloDerm has an initial tensile strength of 144 ± 44 N [81]. At 1 month postimplantation in an animal model of ventral hernia, the mean breaking strength of the AlloDerm–fascial interface was similar to that of Gore-Tex graft material (288.6 ± 97.1 vs 337.0 ± 141.2 N/mm^2, respectively), but lower than primary fascial closure (521.2 ± 233 N/mm^2) [74]. However, a longer follow-up study using a similar experimental design in swine, revealed no statistical difference in the mean breaking strength between the AlloDerm–fascia interface (106.5 ± 40.1 N) and primary fascial repair (108.1 ± 20.9 N) at 9 months [80]. Compared with implanted synthetic material (Gore-Tex), the mean breaking strength at 9 months between the AlloDerm–fascia interface (106.5 ± 40.1 N) was higher than that of the Gore-Tex–fascia interface. Evaluation at 9 months also revealed that the AlloDerm patch was stronger than native fascia [80].

One limitation with this product is that several sheets of AlloDerm are usually required to repair abdominal wall defects in humans. Concern has been raised that the suture lines used to quilt several grafts together represent a potential weak area due to the lack of tissue ingrowth. However, the bursting strength of the AlloDerm–AlloDerm interface (149.1 ± 76.7 N) after suture removal at 9 months has been reported to be stronger than that of the AlloDerm–fascia interface in animals (106.5 ± 40.1 N) [80].

The biomechanical strength of AlloDerm is important with respect to the prevention of recurrent hernia. However, animal model data are inadequate with regards to demonstrating the prevention of hernia recurrences, since no animal hernia models currently show similar wound alterations as detected in human hernia disease. Despite these limitations, Menon and colleagues demonstrated no hernia recurrence at 1 month when abdominal wall defects in rabbits were repaired with AlloDerm [79]. However, after 9 months, Silverman and colleagues reported a 9% incidence of hernia formation after AlloDerm repair in a similar swine model [80]. In this study, hernias appeared to result from a failure at the junction of the implant and the native fascia [80]. Clinical studies with at least 12 months of follow-up have reported an incidence of recurrent hernias of approximately 5% when used in clean surgical fields [78,82].

Degradation

In a swine model, full-thickness abdominal wall defects were created and repaired with AlloDerm. At 9 months, animals were sacrificed. Verhoeff's stain demonstrated the presence of elastin, indicating the persistence of the AlloDerm matrix [80]. However, histological analyses of AlloDerm biopsied from a patient 2 years after implantation showed no evidence of elastin, indicating the complete degradation of the biological tissue graft [83].

Susceptibility to infection

In a live animal model, bacterial adherence and proliferation were evaluated on the surface of implanted AlloDerm. At 5 days after a direct inoculation of the implanted biomaterial with bacteria, a significant amount of adherent bacteria were shown on the surface of AlloDerm. The amount of bacteria present on the AlloDerm was significantly higher compared with peritoneum and Gore Dual Mesh Plus but not compared with Surgisis or other permanent prosthetic meshes [44]. However, in a series of 17 patients treated at the Michael E DeBakey VAMC in Houston (TX, USA), AlloDerm has demonstrated considerable tolerance to local septic complications in contaminated environments. In this preliminary study, many of the patients were critically ill and had contaminated wounds at the time of repair. Although 24% of these patients developed graft infections, 100% resolved with local wound care and 0% required removal [84]. AlloDerm, like all collagen based biomaterials, is very vulnerable to attack by enzymes, such as collagenase, produced by invading bacteria, which leads to accelerated rates of degradation. A theoretical concern is that infection weakens the mesh by decreasing its tensile strength.

Clinical experience with AlloDerm

There are ten patient series published on the use of AlloDerm for abdominal wall reconstruction but no randomized clinical trials. Two of these reports are duplicate publications of the same patient cohort [85,86]. The bulk of these published clinical reports have a very short-term follow-up, are small case series, use a variety of operative techniques for the implantation of AlloDerm and, overall, represent a heterogeneous cohort of patients. For all of these reasons, it is difficult to comment upon the long-term efficacy of AlloDerm for repair of abdominal wall defects.

Two studies have reported on the use of AlloDerm in trauma patients as a means to close the abdomen and avoid compartment syndrome [87,88]. In both studies, patients with open abdomens were returned to the operating room in a delayed fashion when the surgeon felt the time was optimal to gain

primary delayed closure. Overall complications were low and recurrent hernias were reported in only one patient, although follow-up was short.

In 2004, Buinewicz and colleagues published a retrospective review of their clinical experience with AlloDerm for abdominal wall reconstruction in 44 patients [82]. AlloDerm was used for indications, such as transverse rectus abdominis mastopexy (TRAM) flap donor site closure, incisional/ventral hernia repair and as a replacement for infected synthetic mesh. A total of 18% of these repairs were performed in the setting of gross infection. A variety of techniques were used for tissue graft implantation, including overlay (n = 29) and interposition (n = 15). The latter technique was performed using two layers of AlloDerm. With a mean follow-up of 20 months, there were two seromas, three postoperative wound infections, two wound dehiscence and two recurrences. All patients were treated conservatively and no tissue grafts required explantation. One unique aspect of this study was the use of a multilayer (sandwich) closure technique where two sheets of AlloDerm were placed: one deep, as an underlay, and one superficial, as an onlay [82]. More recently, Kolker and colleagues described the use of a double-layer implantation of AlloDerm after a musciofascial release of the external oblique for the repair of infected, or potentially infected, incisional hernias [89]. In this study the skin was closed over the defects. There were three complications, including two seromas and one superficial wound infection. No recurrent hernias were observed with a mean follow-up of 6 months (range: 2–16 months).

Holton and colleagues reported 21 patients undergoing abdominal wall hernia repair in which there was suspicion, or clear evidence, of infection at the abdominal wall defect site [76]. AlloDerm was placed as an onlay, underlay or interposition tissue graft in these patients. There were ten wound infections, five seromas, one acute dehiscence and five documented recurrent hernias with a mean follow-up of 184 days. Two out of ten patients with wound infection developed recurrent hernia and two of the implanted grafts had to be explanted secondary to infection.

In 2005, several case reports and small case series were published on the use of AlloDerm matrix in grossly contaminated wounds. Hirsch reported a single case in which human acellular dermal tissue matrix was used to repair a large abdominal wall defect in the setting of significant bacterial contamination (i.e., colostomy closure and enterotomy). In this study, the tissue graft was placed using an inlay technique and secured with permanent sutures. The patient developed a wound infection and an enterocutaneous fistula. The fistula ultimately healed with conservative management. At 9-months follow-up, the patient had no evidence of hernia by computed tomography (CT) scan and physical examination [90]. However, with less than 12-months follow-up each, the results of two other series in which AlloDerm was used to repair abdominal wall defects in contaminated fields showed a hernia recurrence rate of 50–60% [91,92].

Butler and colleagues reported their experience with AlloDerm to reconstruct abdominal wall defects in 12 cancer patients with contaminated or potentially contaminated fields [85]. The patients reported in this paper were reported previously in a publication in the same journal 1 year earlier by Silverman [86]. AlloDerm was used as an inlay graft and complications occurred in six out of 12 patients, including seroma (two), partial flap necrosis (one), enterocutaneous fistula (one), partial wound dehiscence (one) and cerebrospinal fluid leak (one). Median follow-up was 6.4 months for the group [85].

The clinical performance of AlloDerm has also been compared with that of two synthetic mesh materials. In a retrospective review on 149 patients with abdominal wall defects from a variety of origins, including incisional hernias and TRAM donor site repair, 110 underwent repair with AlloDerm and 39 with synthetic mesh (PTFE or woven polyethylene). The mean follow-up of this study was 12.6 months for the AlloDerm group and 15.4 months for the synthetic mesh group. The incidence of complications in patients repaired with synthetic mesh was higher than the incidence of complication in patients repaired with AlloDerm: seroma (12 vs 28%), dehiscence (6 vs 18%), infection (7 vs 10%) and recurrence (4.5 vs 13%) [78].

Unlike artificial permanent synthetic meshes, which contract over time, AlloDerm thins out and stretches over time. In one study, 20% of AlloDerm patches increased in size by 14% [79]. The clinical significance of this with respect to wound strength and risk of recurrent hernia is thus far unknown or at least unreported.

AlloMax™

In 2006, Tutogen Medical, Inc. began to manufacture an acellular human dermal graft for hernia repair and the reconstruction of the abdominal wall in the USA. The product will be marketed through Davol Inc., a subsidiary of CR Bard Inc., under a new trade name, AlloMax™.

Proprietary process & composition

Allomax is derived from human donors. It is a noncross-linked product. The company sources donor tissues from multiple independent, FDA-inspected, recovery organizations in Europe and the USA. The donated skin, obtained postmortem, is tested serologically and stored refrigerated in hyperosmolar solution until released for processing using the Tutoplast® Process (see Tutopatch®).

Disease transmission

Recovery agencies conduct extensive medical and social history evaluations of the donor and relatives for evidence of relevant communicable diseases, such as HIV and hepatitis B and C viruses. Donors whose medical histories reveal any form of these communicable diseases are rejected. Also excluded are those donors with a history of cancer, disease of unknown origin, such as Alzheimers disease, or a disease caused by a fungus or yeast infection. Serological testing is also performed on tissues and body fluids for transmissible diseases, such as hepatitis B and C

virus, HIV 1 and 2, human T-lymphotrophic virus 1 and 2, and syphilis. Microbiology for pathogenic bacteria and fungi are also performed following processing. To date, no single documented case of disease transmission from implantation of tissue processed using the Tutoplast processing technique has been reported.

Growth factors

No data are available.

Cellular & immunological response

No data are available.

Capillary ingrowth

No data are available.

Biomechanical strength

No data are available.

Degradation

No data are available.

Susceptibility to infection

No data are available.

Clinical experience with AlloMax

There are no publications on the clinical use of this biological tissue graft.

Pericardium

Tutopatch®

Tutogen Medical, Inc., (NJ, USA) utilizes its Tutoplast process of tissue preservation and viral inactivation to manufacture sterile biomaterial made from human and animal tissue. Tutopatch is created from bovine pericardium and has received FDA clearance for indications of general and plastic surgery. However, there are limited data on this biological tissue graft for use in abdominal hernia repair.

Proprietary process & composition

Tutopatch is derived from bovine donors. It is a noncross-linked biological tissue graft material harvested from cattle that are 18–23 months old. It is prepared using the Tutoplast process, which, in contrast to other processes that employ freeze drying, deep freezing or cryopreservation, utilizes a technique in which tissues are soaked and washed in a series of aqueous solutions and organic solvents. This process removes water and substances that could cause rejection or allergic reaction and any disease transmission elements. Briefly, processing begins with the removal of the fat from the tissue. Destruction and washing out of cells is then carried out using osmotic contrast bathing. This step removes bacteria, exposes any intracellular viruses and removes the antigenicity. Treatment with hydrogen peroxide follows, which denatures the soluble proteins and inactivates viruses. The tissue then undergoes a strong alkaline treatment with NaOH to inactivate prions and destroy any DNA and RNA present [93]. The final product then undergoes terminal sterilization with gamma irradiation that eliminates any ancillary microbial contamination. The implants have a 5-year shelf life, can be stored at room temperature for extended periods of time and require rehydration prior to use.

Disease transmission

Measures aimed at minimizing the risk of disease transmission to humans from this biological product start with the careful selection of the source tissue. The bovine material used for this product is obtained from 'closed herds' predominantly in the USA, a source of cattle deemed free of bovine spongiform encephalopathy and inspected/cleared by the US Department of Agriculture. In terms of transmissible spongiform encephalopathy infectivity, the WHO has deemed bovine pericardium as a tissue with no detectable infectivity [202]. Moreover, studies have shown that the company's proprietary Tutoplast process not only removes the tissue antigenicity but also inactivates conventional and unconventional viruses and prions responsible for transmissible spongiform encephalopathy [94]. To date, no single documented case of disease transmission from implantation of Tutopatch has been reported.

Growth factors

No data are available.

Biomechanical strength characteristics

Tutopatch has demonstrated a strength of 42 N/cm, which is significantly higher than the abdominal wall tension in humans (16 N/cm) [95,96]. Information exists regarding tensile strength of noncross-linked bovine pericardium (Tutopatch) compared with synthetic materials. With 7.3 N of tensile strength, James and colleagues established that bovine pericardium was the stronger after implantation of 52 weeks compared with polypropylene [97]. More recently, the tensile strength of Tutopatch was compared with PTFE (Gore-Tex) in a rat model. Experimental abdominal wall defects were created in rats and repaired with Tutopatch or Gore-Tex. Tensile strength of the Tutopatch assessed at 2 weeks postimplant was equal to that of the synthetic material (1400 vs 1352 g) [98].

Capillary ingrowth

No data are available.

Degradation

No data are available.

Susceptibility to infection

No data are available.

Clinical experience with Tutopatch

Recently, a clinical study was published on the use of Tutopatch for repair of large abdominal wall defects that could not be closed, primarily in infants with gastroschesis. In this series of 24 patients, postoperative complications included wound infection (one), seroma (one) and abdominal mesh revision (one) [99].

Veritas®

Veritas® Collagen Matrix is a biological material derived from bovine pericardium being marketed by Synovis Surgical Innovations, a division of Synovis Life Technologies, Inc., (MN, USA) for soft tissue repair. This product was FDA approved in 2003. Bovine pericardium is known for its excellent handling characteristics. The product is not being marketed fully yet but is currently undergoing a limited field evaluation.

Proprietary process & composition

Veritas is derived from bovine donors. It is a noncross-linked product. To prepare Veritas, bovine pericardium is procured from cows younger than 30 months of age in FDA approved slaughter houses in the Midwestern USA. The pericardial tissue is put through a variety of processing steps, including sodium hydroxide, propylene oxide and ethanol treatments. No rehydration or rinse is required; the product has a 3-year shelf life and is ready to use out of the package.

Growth factors

No data are available.

Disease transmission

Rigorous sourcing and manufacturing procedures ensure high levels of safety. Animals whose pericardium is harvested for processing are selected by official veterinary surgeons. Moreover, bovine pericardium has one of the lowest risks of disease transmission. No single case of disease transmission has ever been confirmed and is considered improbable.

Cellular & immunological response

Initial abdominal wall implant studies were conducted in canines. Histological analysis of explanted biomaterial has shown that the material is remodeled into host tissue and populated with cells to the same extent the host tissue was cellularized at 28 days postimplantation [100]. Hematoxylin-eosin staining of implants at 3 months postimplantation in a porcine model shows host fibroblast infiltration and proliferation [101]. All of these studies were performed by the manufacturer and no data are available from peer-reviewed publications. Veritas' purity as an acellular material is confirmed by DNA testing. Evidence from DNA extraction suggests that Veritas contains three- to six-times less cellular content than competitive materials tested [102].

Biomechanical strength characteristics

The company claims that the material has exceptional strength and suture retention [96]. In a manufacturer-supported comparison, Veritas, although thinner (0.25–0.75 mm, average 0.45 mm), was found to be equal in tensile strength but provided significantly higher suture retention strength when compared with tested cadaveric fascia lata products [103]. However, there are no data from peer-reviewed publications regarding its strength over time as it undergoes remodeling into native fascia. These studies are in progress.

Capillary ingrowth

The manufacturer claims that, at 28 days, explanted biomaterial shows new blood vessel growth in an animal model [100].

Degradation

No data are available.

Susceptibility to infection

No data are available.

Clinical experience with Veritas

There are no publications reporting on the use of Veritas Collagen Matrix for abdominal wall reconstruction. However, it has been used by several surgeons to repair abdominal wall defects or pelvic floor reconstruction without any adverse affects or evidence of recurrence at 2 years of follow-up [HATCH K, PERS. COMM.].

Periguard®

This product was developed originally by Synovis for staple line reinforcement but has been produced recently in larger sizes (12 × 25 cm) and is also FDA approved for abdominal wall reconstruction or hernia repair. This material is identical to Veritas (bovine pericardium), except that it is cross-linked by a process using gluteraldehyde. There are no published clinical outcomes with the use of Periguard for ventral incisional hernia, though early clinical experience with the material for laparoscopic ventral hernia repair has thus far been encouraging [LOJO J, UNIVERSITY OF PUERTO RICO, PERS. COMM.].

Proprietary process & composition

Following similar procurement from source cows, the material is subjected to apex processing. This process involves collagen cross-linking using glutaraldehyde. When taken out of the package, the material requires a 2-min rinse in saline to remove residual glutaraldehyde. The material has a smooth and a rough side. Per the manufacturer's instructions, the rough side should be placed in direct opposition with the abdominal wall while the smooth side should be placed in contact with the viscera [ORAY BN, SYNOVIS, PERS. COMM.].

Growth factors

No data are available.

Disease transmission

See Veritas.

Cellular & immunological response

No data are available.

Biomechanical strength characteristics

Periguard has equal strength compared with other biomaterials (i.e., Surgisis) and synthetic mesh (Marlex). However, the suture-holding capacity of this material is significantly lower than both the Surgisis and Marlex mesh [29].

Capillary ingrowth

No data are available.

Degradation

Since the material is cross-linked, it should have markedly reduced or little degradation over time when compared with Veritas. However, there are no data available on wound remodeling or degradation.

Susceptibility to infection

No data are available.

Clinical experience with Periguard

There are no publications currently on the use of this material for abdominal hernia repair. However, it has been used for both laparoscopic and open hernia repair in the setting of infection and observed to function well without evidence of recurrence with up to 4 years of follow-up [LOJO J, UNIVERSITY OF PUERTO RICO, PERS. COMM.].

Summary & conclusion

Throughout history, multiple approaches have been used to reconstruct abdominal wall defects. Currently, these defects are repaired most commonly using a wide variety of non-absorbable synthetic mesh materials. This material bridges the defects and allows for a tension-free repair, which significantly reduces the recurrence rate by nearly 30% compared with primary suture repair. However, the use of permanent prosthetic materials is limited by their nonviability, lack of specialized function, incomplete or irregular cellular infiltration, severe immunological reaction or rejection and increased risk of infection. These features have led to several devastating and costly clinical problems, such as fibrosis, restriction of abdominal wall mobility, chronic pain, bowel obstruction, enteric fistula and adhesion formation. Therefore, the search for a better material for abdominal wall reconstruction continues to be a major challenge.

A wide variety of new implantable biological tissue grafts have been developed and introduced into the clinical market for the repair of tissue defects and loss as a result of hernia disease, as well as trauma, cancer or infection. While there is insufficient clinical experience currently to make a determination on their long-term efficacy, the sudden and rapid emergence of these grafts have provided surgeons with an important new tool in their surgical armentarium for treating abdominal wall defects. More clinical work is necessary to determine which patients would benefit the most from repair using a biological tissue graft. To date, the best clinical outcomes reported with biological tissue grafts for abdominal wall reconstruction occur in patients in the absence of gross infection. A high recurrent hernia incidence in the setting of contaminated or infected wounds underscores the necessity of performing additional clinical research and product development with biological tissue grafts in order to better understand their utility and limitations.

Expert commentary

Advances in tissue engineering sciences have led to the rapid development of numerous biological tissue grafts for various human ailments. As of May 2006, there are eight FDA approved biological tissue grafts being marketed for abdominal wall repair in the USA. Published experimental data and clinical evidence exist for four of these products (Alloderm, Surgisis, Permacol and Tutopatch), though there are no available public data for four of the materials. While clinical experience with Alloderm, Surgisis and Permacol is increasing rapidly, the long-term efficacy of these tissue grafts is still unknown. A 5-year follow-up exists only for Surgisis and the single report suggests that the product functions well as a mesh prosthetic for the long-term repair of abdominal wall hernia in clean and clean-contaminated fields. While the companies developing and marketing biological tissue grafts make various claims for the superiority of their product over others, there are, at present, no clinical trial data comparing one biological tissue graft with another and no data demonstrating superiority of one product over another. Moreover, any comparison between biological tissue grafts and synthetic materials has to consider the distinct properties of all the various synthetic structures, not just one.

In principle, there are two different indications for biological tissue grafts, one is for the repair of an acute abdominal wall defect created by trauma, cancer or infection and the other is for the repair of a chronic, progressive abdominal wall defect (i.e., hernia disease) resulting from defective collagen metabolism. Whereas acute wound defects can be repaired with a biological tissue graft as a scaffold to induce *in situ* normal tissue regeneration, such an approach may lead to an inadequate and weak scar in hernia patients. Indeed, the use of biological tissue grafts for treating hernia disease waits for the successful proof of concept as to whether totally absorbable tissue grafts will result in long-term, strong wounds in hernia patients who have a presumed defect in collagen metabolism. Currently, there are a number of questions and concerns that remain unanswered about the use of these materials (TABLE 1). Longer-term studies in larger number of patients are necessary to better understand the utility and limitation of these biological tissue grafts for abdominal wall reconstruction.

Five-year view

The ideal biological tissue graft may take one of a number of possible forms in the near future. The most economical and proficient graft would be one that is derived from a plentiful source, thus making it affordable. In addition, the ideal graft material should have an adequate shelf life so that it can be taken off the shelf and used immediately, be 100% biocompatible and resistant to infection. Degradation and replacement of the graft material by host tissue should ultimately occur in a manner that maintains or increases the strength of the abdominal wall repair. It may also be hypothesized than an ideal composition of a biological tissue graft may be able to restore normal wound healing in hernia formers and thereby strengthen the resulting scar. No bioscaffold has yet to be shown to possess all of these ideal characteristics.

There is increasing evidence that biological tissue grafts will become more customized or individually tailored for specific needs. Animals can have their own tissues (such as myofibroblasts or stem cells) harvested and seeded onto ECMs prior to being transplanted back into their body. This approach primes or preconditions the biological tissue graft with the intended recipient animal's own progenitor cells. Such an approach could add to the overall effectiveness of a biological tissue graft, making it more resistant to bacterial colonization and accelerating the deposition of collagen, which may increase the strength profile more rapidly [104]. It is probably only a matter of time before such a process is used in patients undergoing abdominal wall reconstruction. In fact, a similar approach has recently been used for the development of an orthotopic neobladder. A section of a patient's own bladder was harvested, nurtured *in vitro* and supplemented with growth factors to allow it to mature and grow prior to retransplanting it back into the patient's body [105]. However, experimental studies have shown that cells grow differently when seeded on various collagen matrices [106]. Since all biological tissue grafts are processed in different manners it is impossible to achieve standard physiochemical results and so considerable variations in the amount and type of components present within these collagen grafts is to be expected. As a result, different types of matrices may drive cell differentiation along different pathways.

Alternatively, a genetic approach to this problem may be utilized. Many patients with ventral incisional hernias have a genetic predisposition to hernia owing to deficiencies in wound healing and collagen metabolism. The penetrance of such a hernia phenotype is probably the result of several genes and environmental factors [107]. When such biological determinants are identified in the future by genomics and proteomics, it is likely that the polygenetic trait defects could be repaired by *in vitro* transfection of normal genes into fibroblasts; they would then be seeded onto an ECM tissue graft, which is then implanted into a patient. The resulting wound healing process would follow normal or more exuberant healing, resulting in the creation of a stronger and more durable wound. The most likely candidate genes for such genetic studies should include fibrillar type I and III collagens and matrix metalloproteinases [107]. Hernia disease may also be treated by future pharmacotherapy of the wound itself or by appropriate design modifications of the scaffold materials that will enable more optimal tissue regeneration. Another area of research that is likely to improve the performance of biological tissue grafts will focus on ways to reduce colonization and digestion of the graft by bacteria. This may be accomplished through antibacterial surface treatments, nonfouling surfaces and antibiotic-controlled release strategies. Also, general advances in controlled drug release will permit the development of devices with both device and drug functionality.

Glycosaminoglycans such as heparin and chondroitin, have been added successfully to collagen matrices to improve angiogenesis [108]. Strategies to accelerate neovascularization of transplanted biological tissue grafts after implantation will facilitate their engraftment through the early delivery of oxygen, nutrients, host immune cells and antibiotics. The preseeding of stem cells or progenitor cells into tissue grafts could also offer an advantage with respect to the need for rapid revascularization as these cells are resistant to low oxygen conditions. All of these approaches to create a 'designer ECM' are within reach in the near future. Perhaps such an approach will be called 'smart biological tissue grafts'.

Key issues

- Within the past 10 years, hernia surgery has shifted from primary suture closure to mesh repair.
- The use of permanent mesh has reduced the recurrence rates of incisional hernia following repair from 40% to less than 10% when placed as a generous underlay.
- An ideal mesh product for all clinical situations has not yet been developed.
- Surgeons should individualize treatment for patients with incisional hernia, balancing their risk of recurrence against their risk of developing mesh-related complications.
- The use of permanent prosthetic materials for repair of an incisional hernia in clean, elective cases is recommended until there are clinical data with at least a median 5 years of follow-up demonstrating that hernia recurrence rates with biological tissue grafts are equivalent to permanent prosthetic materials.
- Advances in tissue sciences and bioengineering are evolving rapidly such that there will almost certainly be allograft and xenograft materials in the future that are better suited for incisional hernia repair than what exists at present.
- Acellular tissue matrices must be completely resorbable in order to avoid a chronic foreign body response.
- Only short-term clinical studies have been published on four of the biological tissue grafts available for ventral abdominal hernia repair; additional prospective clinical studies with longer follow-up are needed to learn more about the advantages, limitations and complications of biological tissue grafts.
- One potential near-term improvement in existing acellular graft materials may be achieved by preseeding the grafts with a patient's own stem cells. These cells can be harvested, cultured and then seeded into acellular matrix, allowing them time to differentiate and incorporate into the material prior to its implantation into the patient.

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