

Blood vessel matrix: a new alternative for abdominal wall reconstruction

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Abstract

Background Biologic matrices offer a new approach to the management of abdominal wall defects when the use of other foreign material is not ideal. A member of our team (GEA) developed a biological decellularized matrix generated from harvested blood vessels of swine blood vessel matrix (BVMx). The aim of our study was to investigate whether this novel collagen-based biological matrix is safe and effective for the repair of abdominal wall hernia defects in a rat model.

Methods Full thickness abdominal wall defects were created in rats and repaired with our BVMx. After implantation as an underlay for 30 and 90 days, animals were sacrificed and the implanted material evaluated for herniation, adhesions, breaking strength, inflammation, and revascularization.

Results No evidence of herniation was noted at 30 ($n = 7$) or 90 ($n = 7$) days after repair. Adhesions, if present, were filmy and easily separated. The mean area of visceral adhe-

sions to the BVMx was $18.9 \pm 11.0\%$ at 30 days and $7.1 \pm 3.1\%$ at 90 days post implantation ($P = 0.33$). The breaking strength of the BVMx–fascial interface was 4.5 ± 0.8 N at 30 days and 4.5 ± 2.4 N at 90 days post implantation ($P = 0.98$). Histologic analysis demonstrated that the BVMx elicited a mild transient inflammatory response and supported fibroblast migration, deposition of newly formed collagen, and neovascularization.

Conclusions These data confirm that this BVMx supports vascular ingrowth and provides adequate strength for the repair of abdominal wall defects. Future studies in a large animal model are required to assess its validity for human application.

Keywords Abdominal wall reconstruction · Biologic matrix · Tissue engineering · Hernia

Introduction

Abdominal wall defects due to trauma, infection, cancer, or incisional hernias are a common clinical problem. Reconstruction of these defects remains a difficult surgical challenge. Although multiple approaches for reconstruction have been advocated the most commonly utilized method involves obtaining a tension-free closure with the use of synthetic mesh material. The implantation of these non-absorbable foreign materials has been shown to restore abdominal wall integrity and reduce hernia recurrence rates [1, 2]. However, these materials have also been shown to induce a strong inflammatory reaction resulting in scar formation, chronic pain, adhesions to the underlying abdominal viscera, and bowel fistula [3–6]. These materials can also contribute to surgical site infection, skin erosion, and seroma formation [4–6]. Because the clinical and economic

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effects of these mesh-related complications are staggering, alternative materials for repair of abdominal wall defects are needed. Consequently, a variety of extracellular matrix-based scaffolds have been introduced to the clinical market for the repair of abdominal wall defects. However, complications such as infection, lack of tissue in-growth, and laxity have been seen in animal and human studies with currently available biologic matrices [7–11].

A member of our team (GEA) developed a biological decellularized matrix generated from harvested blood vessels of swine [12]. A unique chemical and mechanical cleaning sequence was developed that preserves the distinctive three-dimensional structure of collagen and elastin in the blood vessel wall. Previous animal studies using this blood vessel matrix (BVMx) in the vascular and genitourinary system have demonstrated histologic and urodynamic properties superior to those achieved with other currently available biologic matrices [12, 13]. Encouraged by these results we sought to investigate whether this novel collagen-based biological matrix, made from decellularized swine aorta, is safe and effective for the repair of abdominal wall hernia defects. The aim of our study was to evaluate the adhesion formation, tensile strength, and inflammatory and neo-vascular response to the BVMx after implantation in a rat hernia model.

Materials and methods

Preparation of the blood vessel matrix

The decellularizing process has been described previously [14]. Briefly, swine thoracic aorta, dissected down to the iliac vessels, is harvested. A previously tested and validated chemical and mechanical process is then applied to this tissue resulting in a completely decellularized biological matrix composed of collagen and elastin. The harvested aorta is initially washed in running distilled water, until no visible traces of blood are evident, then placed in a solution containing Triton-X detergent and ammonium hydroxide. The solution and the aorta are placed on a shaker for several cycles of 72 h. Thereafter, the detergent is thoroughly washed out. Subsequently, the BVMx is lyophilized and then sterilized using cold gas. The final product is a collagen sheet ranging between 1 and 1.1 mm in thickness.

Experimental model, post-operative care, and evaluation

The study protocol was reviewed and approved by the Institutional Animal Care and Use Committee at the Baylor College of Medicine. Full-thickness abdominal wall defects were created and subsequently repaired with BVMx in 15 male Sprague–Dawley rats (250–300 g; Charles-River

Laboratories, Wilmington, MA, USA). The surgical procedures were performed under aseptic conditions using a modification of a validated rat model previously described by Demir et al. [15]. At the start of the experiment, the animals were anesthetized using isoflurane/N₂/O₂ inhalation. The abdomen was shaved and cleaned with alcohol 70%, after which a 5-cm paramedian skin incision was made and skin flaps were raised. A ventral hernia defect (1.5 × 2.5 cm) was created, centered midline between the xiphoid and pubis, by incising through the full thickness of the abdominal wall, including fascia, muscles and peritoneum. The defect was then repaired by implantation of a 2.0 × 3.0 cm sterile piece of BVMx. The matrix was rehydrated at room temperature for 15 min in sterile, normal (0.9%) saline prior to implantation, then placed in an underlay position (intra-peritoneally) and fixated transmurally with interrupted sutures (polypropylene 5-0; Ethicon, Somerville, NJ, USA) placed 1 cm apart (Fig. 1). No attempt was made to place the omentum beneath the implant. The skin and soft tissues were then closed over the mesh with stainless steel surgical clips, which were removed 1 week postoperatively. All animals were given Ampicillicin (63 mg) after the surgical procedure and then housed in individual cages, fed standard laboratory chow, and allowed tap water ad libitum. Animals were weighed daily and checked for local and systemic complications such as infection, wound dehiscence, signs of extreme pain or discomfort, and impaired mobility.

Harvest of the blood vessel matrix

The rats were sacrificed on postoperative day 30 or 90 by an overdose of Nembutal and the implanted BVMx was

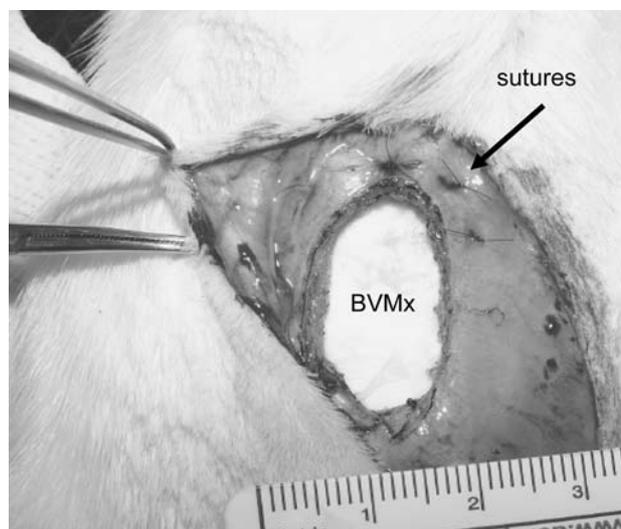


Fig. 1 Representative photograph illustrating the underlay placement of the BVMx implant below the fascial defect. The implant is secured by interrupted permanent sutures. Complete intra-peritoneal placement of the blood vessel matrix (BVMx) was achieved

harvested. At harvest, bilateral subcostal incisions were made and the resulting U-shaped flap was slowly lifted to reveal adhesions, if present. Subsequently, intra-abdominal adhesions to the BVMx were scored, the integrity of the repair assessed, and the repair material examined for the presence of herniation and infection. Infection was defined as pus or infected seroma around the implanted BVMx and wound anytime before or when the animals were euthanized. Cultures were taken only when these signs of overt infection were present.

After dissection of any adhesions, the BVMx implantation sites were excised en bloc with the anterior abdominal wall fascia and peritoneum. Tissue strips (approximately 3.0×1.0 cm), consisting of both the anterior abdominal wall and the mesh, were then cut and the sutures removed. One piece was preserved fresh in 0.9% saline and used immediately for mechanical testing. The other pieces were fixed in 10% formalin and used for histology.

Adhesions

The presence of adhesions to the BVMx was quantified by extent (percentage), severity, and density and the organs connected by the adhesions. In brief, the percentage of intra-abdominal adhesions to the biologic matrix was measured by placing a transparent grid, divided into 25 equal squares, over the BVMx. The numbers of squares with adhesions were counted. The total of these squares over the total number of squares provided a percentage of adhesions to the BVMx. The severity of adhesion formation was recorded, for each rat, using a validated scale ranging from 0 = no significant adhesions to 4 = thick and broad adhesions involving the abdominal wall [16]. Two independent observers assessed adhesion coverage, and severity of the BVMx surface. In cases of inter-observer variance, the mean was scored. Adhesions were separated and the abdominal wall, including the BVMx, was removed.

Material properties and integration strength

The material properties of the BVMx were obtained using an Instron Model 3340 (Northwood, MA, USA) testing device equipped with a 500 N load cell. System control and data analysis were accomplished with Instron Series IX/S software. Samples cut in both the longitudinal and circumferential orientations from the blood vessel were tested in tension by applying a uniaxial strain rate of 25 mm/min. Sample dimensions were measured using digital calipers. For each test, force/displacement information was collected and from these data a stress–strain curve was generated to obtain the ultimate tensile stress (UTS) and elastic modulus for each sample. Modulus is defined as the slope of the lin-

ear region of the stress–strain curve and UTS is the maximum stress obtained before failure.

To evaluate the strength of the integration between the implanted material and surrounding tissue, samples were excised from similar locations in each animal at 30 and 90 days post-implantation. These strips were cut parallel to the transverse axis of the prosthesis and included the prosthesis, the tissue/prosthesis interface, and normal abdominal tissue. The sutures securing the prosthesis were cut and therefore did not contribute to the integrity of the interface during testing. Samples were tested in the Instron machine as described above. The maximum load required to induce a complete break in the sample and the mode of failure were recorded. After this initial failure, the BVMx was excised from any remaining fascia and re-tested to determine the UTS of the implanted matrix.

Histology

Histological examination of the implanted BVMx and its surrounding tissue was performed after fixation in 10% formalin. Paraffin-embedded tissue blocks created from the en bloc resections of the BVMx with the anterior abdominal wall fascia were stained with hematoxylin and eosin. The slides were coded and analyzed by an independent pathologist investigator (WJ). Microscopic evaluation was performed to quantify the presence of inflammatory cells and vasculogenesis within the implanted material as described by Badylak et al. [17].

Statistical analysis

Values represent mean \pm standard error of mean (SEM). An unpaired Student's *t*-test was performed when the differences between the 30 and 90-day time points for adhesion formation, tensile strength, and the morphologic response to the BVMx were compared. A *P* value less than 0.05 was considered significant. Statistical analysis was performed using Prism statistical software (GraphPad Prism 3.0, San Diego, CA, USA).

Results

Clinical evaluation

In this series there were no intra-operative complications and all animals survived the operation. Post-operatively, the animals in this study appeared well groomed, alert, and very active without signs of distress throughout the time the implant was in place. One animal was noted to have a small postoperative clear fluid collection over the implanted material diagnosed at sacrifice at day 30. One animal from

the 90-day group was sacrificed on the second post operative day secondary to wound dehiscence with exposed graft material probably due to a surgical technical error during closing. This animal was excluded from the study. The weights of the animals increased progressively after implantation of the BVMx with a weight gain of 4.4 ± 7.2 g noted after 30 days and 81.8 ± 46.4 g after 90 days. There was no clinical indication of implant failure evidenced by bulging of the surgery site diagnosed during the post-operative period. Furthermore, there was no evidence of bowel perforation, obstruction, or fistula formation in any animal during this study. The post-mortem evaluation of the BVMx at 30 ($n = 7$) and 90 ($n = 7$) days postoperatively confirmed no evidence of herniation around or through the implant site and the sutures were still present. We also observed that the mesh remained flat except for minimal folding of the material edges, in most cases without a perceptible macroscopic appearance of shrinkage (Fig. 2).

Adhesion formation

At the time of harvest, the implanted BVMx was noted to be remarkably free from adhesions (Fig. 2). Most adhesions, if present, were to the edges of the matrix and involved the omentum. Small and large bowel adhesions were never observed. Although there was a trend towards a reduced number of adhesions at 90 days, the mean area of visceral adhesions to the BVMx was not significantly different between 30 and 90 days post implantation ($18.9 \pm 11.0\%$ at 30 days and $7.1 \pm 3.1\%$ at 90 days, $P = 0.33$). There were no adhesions in two of the rats at 30 days and no adhesions in three at 90 days. When adhesions were present the rats at both time points tended to have filmy, thin adhesions that were easily detachable from the BVMx. The mean severity

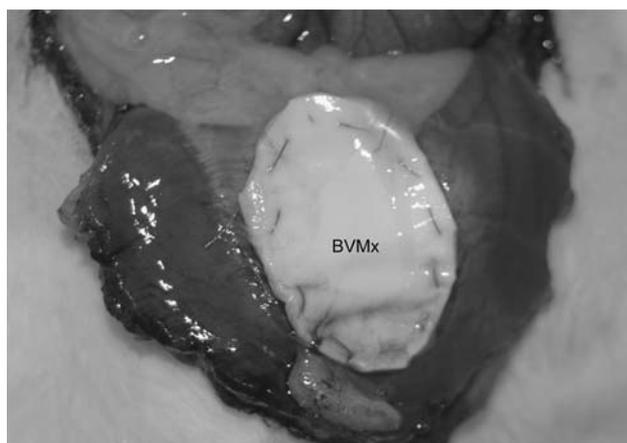


Fig. 2 Harvest photograph of a representative repair site at 30 days post-implantation. The repair site was not involved in adhesion to bowel or omentum. BVMx blood vessel matrix

score was 0.7 ± 0.2 at 30 days and 0.6 ± 0.2 at 90 days post-implantation ($P = 0.61$).

Material properties and integration strength

Prior to implantation rehydrated BVMx specimens, similar to fresh swine aorta, exhibited anisotropic properties, demonstrating significantly less elasticity in the longitudinal direction than in the circumferential direction (longitudinal = 15.9 ± 2.0 MPa, circumferential = 8.2 ± 1.3 MPa, $P = 9.23 \times 10^{-5}$, Fig. 3). Furthermore, the UTS of the BVMx before implantation was also significantly higher in the longitudinal direction (longitudinal = 6.5 ± 1.3 MPa, circumferential = 2.8 ± 0.8 MPa, $P = 5.85 \times 10^{-4}$, Fig. 3). After implantation, tensile testing of the explanted BVMx revealed a decrease in UTS compared to its initial state (30 days = 0.6 ± 0.2 MPa, 90 days = 0.5 ± 0.3 MPa). As shown in Fig. 4, at 90 days after implantation, the breaking strength of the BVMx–fascial interface was 4.5 ± 5.9 N, which is similar to that measured 30 days post-implant (4.5 ± 1.9 N), indicating that the BVMx implants were incorporating well into the host tissue.

Histology

Histologic examination of each explanted BVMx showed that there was excellent fibrous in-growth into the material. Additionally, the histology of explanted specimens showed a new, well-established mesothelial layer on the visceral surface of the mesh.

Histologic examination also confirmed cellular repopulation and vascular growth into the implanted BVMx at 30 and 90 days. The average scores for polymorphonuclear leukocytes (PMN), mononuclear cells, connective tissue

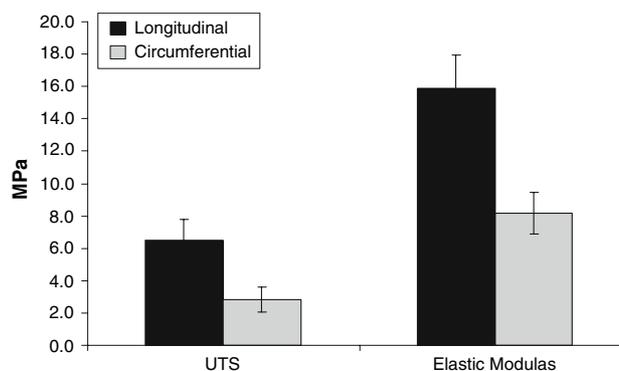


Fig. 3 Material properties of BVMx before implantation. The BVMx exhibits anisotropic properties with a higher strength and stiffness in the longitudinal direction ($n = 4$ longitudinal and 5 circumferential). The difference in elastic modulus is statistically significant with $P < 0.05$. The ultimate tensile strength (UTS) is also higher in the longitudinal direction compared to the circumferential direction ($P < 0.05$)

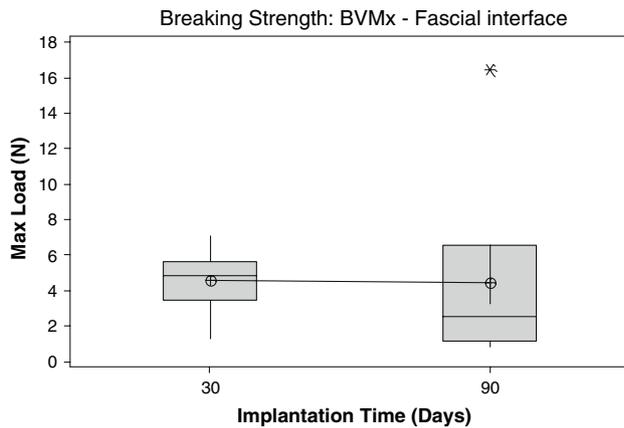


Fig. 4 Mean adhesion breaking strength of the BVMx–fascial interface after implantation. At the 90-day time point, there is one outlying data point as indicated by the *asterisk*

organization, and vascularity are shown in Table 1. At 30 days post implantation, the BVMx appear to elicit a mild inflammatory response. The cellular infiltration included a mixture of PMNs, mononuclear cells, and fibroblasts. At 90 days post implantation, the number of mononuclear cells was significantly lower than at 30 days ($P = 0.008$). In contrast, connective tissue deposition was prominent at both time points, but the amount of organization of this neo-connective tissue was significantly greater at 90 days than at

Table 1 Average scores of microscopic examination

	30 days	90 days	<i>P</i> value
Polymorphonuclear cells	1.8 ± 0.2	1.4 ± 0.2	0.24
Mononuclear cells	2.8 ± 0.2	1.8 ± 0.2	0.008
Tissue organization	0.8 ± 0.2	2.2 ± 0.2	0.001
Vascularity	2.6 ± 0.3	2.6 ± 0.3	0.55

30 days ($P = 0.001$). In addition, at 90 days the collagen fibers were denser, thicker, and oriented in the same direction compared to that at 30 days post-implantation (Fig. 5). Active neo-vascularization was confirmed at both time points. At 30 days, small blood vessels and fibroblasts infiltrations were noted towards the inside layer of the matrix (Fig. 6). At 90 days, the blood vessels were larger than at 30 days, and the fibroblasts disappeared but the fibrocytes were still seen in some areas of the implanted biomaterial.

Discussion

The technique most commonly utilized to achieve a tension-free closure of abdominal wall defects makes use of synthetic mesh material. However, the currently available synthetic materials are suboptimal contributing to many

Fig. 5 Histologic examination of the BVMx graft material 30 days after implantation. **a** H&E staining ($\times 400$ magnification) and **b** Trichrome staining ($\times 400$ magnification) demonstrating numerous capillaries (*arrows*) growing in new collagen fiber tissue (H&E, **a**). There is some infiltration of the matrix with inflammatory cells and fibroblasts. Collagen fibers are noted in an irregular distribution (Trichrome, **b**)

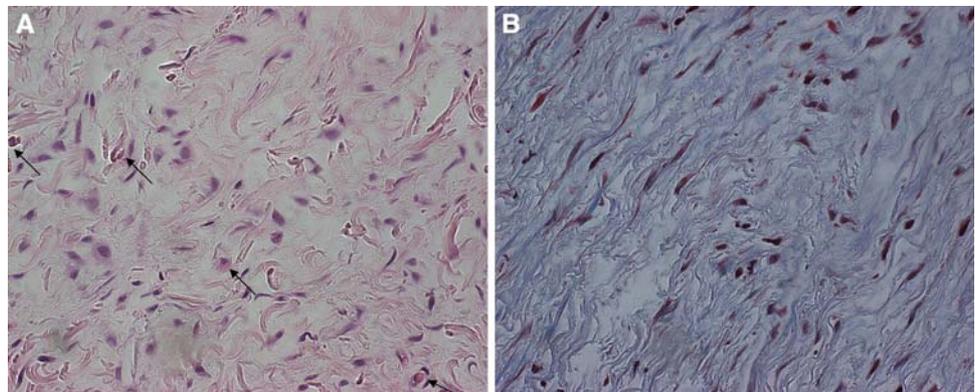
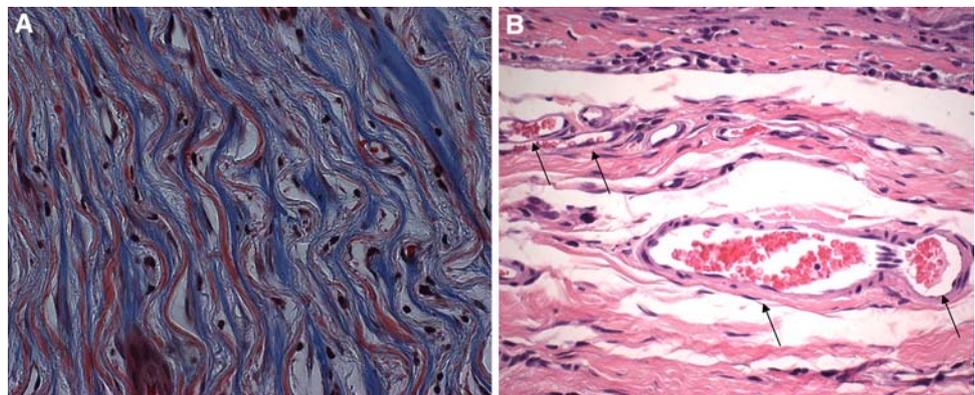


Fig. 6 Histologic examination of the BVMx graft material 90 days after implantation. **a** Trichrome staining ($\times 400$ magnification) demonstrating more fibrocytes and well organized collagen fibers, and **b** H&E staining demonstrating larger blood vessels throughout the matrix ($\times 400$ magnification)



unacceptable complications. Most of these complications are related to chronic inflammatory responses incited by the mesh and result in adhesions, enterocutaneous fistulae formation, scar formation, high infection rates, and chronic pain [3–6]. Consequently, many investigators have shown interest in the utilization of extracellular matrix scaffolds for abdominal wall reconstruction because of their potential capacity to resist infection and induce a milder inflammatory response, angiogenesis, and host cell migration. However, these presently available biological materials have significant limitations. Complications associated with these costly materials, such as rapid breakdown and loss of the graft material, especially in infected fields, and undesirable host foreign body reaction have been reported in animal and human studies when used to repair abdominal wall defects [7–11, 18]. As a consequence the search for the optimal source of reconstruction material for clinical use continues.

The main sources of currently available extracellular matrices are skin (dermis), fascial structures (pericardium), and small intestine submucosa. A member of our team (GEA) previously developed a biological decellularized matrix generated from harvested blood vessels of swine. A unique chemical and mechanical cleaning sequence was developed which preserves the distinctive, natural three-dimensional structure of collagen and elastin in the blood vessel wall. This tissue engineered blood vessel has been used successfully as a xenogenic tissue graft in various urological and vascular applications. In bladder augmentations, the BVMx demonstrated urodynamic and histologic properties superior to those resulting from augmentation with other biologic matrices in a rat model [13]. Microscopically, the BVMx was covered with multi-layers of uro-epithelial cells and with smooth muscle cells and fibroblasts that had migrated onto the matrix. In vascular graft studies, BVMx seeded with autologous endothelial cells showed no long-term intimal hyperplasia, shrinkage, or fibrosis when used to replace the carotid artery in a sheep model [12, 14]. In our study, we have shown that BVMx also serves as a viable option in the repair of abdominal wall tissue defects.

One ongoing concern with all mesh materials used to repair abdominal wall defects, especially when the prosthesis comes into contact with internal organs, is tissue remodeling without adhesion formation. Possible long-term consequences of increased adhesion formation include subsequent intestinal obstruction and perforation. In a comparison study of different synthetic prosthetic materials in an animal model, polypropylene mesh was noted to cause adhesions that covered over 70% of the implanted material [19]. By comparison, animal studies evaluating adhesion to various biologic matrices, have found a significant reduction in the number and severity of these harmful adhesions

[20–22]. This is consistent with our study. We found a reduced number of adhesions between 30 and 90 days post implantation with less than 10% adhesions between the BVMx and surrounding tissues at 90 days after implantation. Furthermore the adhesions, if present, did not involve any internal organs and could be easily detached from the BVMx.

Another concern of any mesh material is its ability to maintain the integrity of the abdominal wall after it is implanted. Therefore, the material used to reconstruct the abdominal wall must be strong enough to withstand the physiologic forces placed upon it after implantation without losing its integrity by ballooning or shrinkage. It must also be able to incorporate over time into the tissue adjacent to the mesh material. One commercially available biologic matrix showed significant delamination one month after implantation and a 21% rupture rate through the material when it was used for hernia repair in animals [9, 23]. Similarly, another biologic matrix showed a nearly 15% hernia recurrence rate at 90 days when used to repair hernia defects in rats [24]. Taken together, these results suggest incomplete incorporation and inadequate tensile strength of these biologic matrices. In our study, we demonstrated that abdominal wall defects repaired with BVMx result in no herniation up to 3 months after repair. This may reflect the fact that our BVMx is designed to withstand high pressures such as that seen in the arterial vascular system. Indeed, in the re-hydrated state, the BVMx is quite strong and difficult to tear with an initial mean tensile strength of $2,800 \pm 800$ kPa. This strength exceeds the highest physiologic intra-abdominal pressures that can be generated in patients (standing 2.7 kPa; coughing 14.3 kPa) [25]. Importantly, over time we have also shown that our BVMx is engineered to maintain sufficient strength to provide the mechanical support necessary for an intact hernia repair. Despite a decrease in the strength of the BVMx during the first 30 days after implantation, the ultimate tensile strength of the BVMx still exceeded that of the native fascia and the normal physiologic stresses of the abdominal wall in humans [25, 26]. This change in strength after implantation is similar to other commercially available biologic matrices [9, 27] and most likely indicates a balance between the rate of simultaneous remodeling and biodegradation of the original implanted material as host-derived fibroblasts create organized collagen along the matrix scaffold.

The intensity of the inflammatory response to an implanted material is critical toward acceptance or rejection of the material. The cellular response to the BVMx after implantation for abdominal wall reconstruction appears favorable at 30 and 90 days post implantation. First of all, histological examination of the BVMx demonstrates that it only invokes a transient mild inflammatory response. These results are consistent with those of Menom et al. [28] who

demonstrated an inflammation infiltrate consistent with postoperative changes one month after the implantation of acellular human dermal collagen matrix in animals. In contrast, Petter-Puchner et al. [10] found a concerning degree of inflammation in a porcine-derived biologic matrix derived from small intestinal submucosa when it was implanted in a rodent model of abdominal wall hernia repair. These authors described an acute inflammatory response that consists mostly of polymorphonucleocyte infiltration and subsequent loss of the graft material following implantation. Second, native fibroblasts appear to infiltrate our BVMx, and deposited new collagen. This early remodeling process, which involves re-establishment of cell infiltrate and progressive deposition of organized connective tissue in a manner that is consistent with natural wound healing is essential for effective regeneration and repair of abdominal wall defects. Finally, our results demonstrate that our BVMx becomes viable through revascularization after implantation. This step is essential in natural wound healing. Moreover, vascularized tissue is better able to deliver oxygen and nutrients to the repair site, allowing for native cell migration and repopulation of the BVMx. While this revascularization process has been shown with other biologic matrices [28, 29], Macleod et al. [30] showed that Permacol (Tissue Life Science Lab, Andover, MA, USA) made from porcine dermis, had no vascularity at 30 days after implantation in a rat model.

Despite the fact that this is a xenograft model, the main limitation of this study is the issue of size and the appropriateness of the animal model. In the same way as many other researchers, we started with a small animal model as a proof of concept, to assess basic properties of the BVMx for hernia repair. The stress and strain and intra-abdominal pressures in a large animal model would resemble more adequately the human intra-abdominal mechanical forces. Furthermore, properties of cell migration and repopulation across 2–3 cm may be completely altered when tested in a model requiring migration of cells and repopulation over 15–20 cm. Therefore, we are planning additional studies to assess the viability of the BVMx for hernia repair in large animal models that more closely resemble human sizes and the forces placed on the material.

Conclusion

In conclusion, our results show that the BVMx can be used safely in the repair of abdominal wall defects with minimal foreign body reaction and adequate strength. It is only through the discovery of new materials and the characterization of the mechanisms governing integration of these materials, allowing fascial and vascular in-growth, that researchers may identify the ideal material. Despite the

fact that a longer term study in a larger animal model is warranted, we think that this novel matrix incorporates many of the qualities required to become the preferred material for abdominal wall reconstruction.

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