Original Research

In-Vivo Evaluation of a Reinforced Ovine Biologic for Plastic and Reconstructive Procedures in a Non-human Primate Model of Soft Tissue Repair

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Abstract

Background. Biologic matrices are used in plastic and reconstructive surgical procedures to aid in the kinetics of soft tissue repair and promote functional tissue formation. The human acellular dermal matrix AlloDerm is widely used; however, it is offered at a relatively high cost, and its dermal composition may not provide an ideal remodeling scaffold. OviTex Plastic and Reconstructive Surgery (PRS) Resorbable and Permanent are reinforced biologic matrices engineered with layers of ovine forestomach matrix embroidered with small amounts of polymer to optimize biophysical performance. This study compared the healing outcomes of these matrices in a non-human primate model of soft tissue repair.

Methods. Animals were implanted with test articles in surgically created full-thickness midline abdominal wall defects and evaluated macroscopically and histologically at 2, 4, 12, and 24 weeks.

Results. Both OviTex PRS Permanent and Resorbable matrices exhibited earlier host cell infiltration, neovascularization, and collagen deposition and also fully remodeled into the host tissue by 12 weeks post implantation. AlloDerm had less host cell infiltration and neovascularization at early time points and never fully integrated into the surrounding host tissue. There was no statistical difference in overall inflammation between AlloDerm and either OviTex PRS product at any time point, despite small amounts of polymer reinforcement in OviTex products.

Conclusions. In a primate soft tissue repair model, OviTex PRS Permanent and Resorbable matrices performed comparably with the leading human acellular dermal matrix. OviTex PRS Permanent and Resorbable are less expensive than alternatives like AlloDerm and may promote faster host cell proliferation and functional remodeling in some soft tissue repair applications.

ePlasty 2022;22:e43 Epub September 2022

Keywords: plastic and reconstruction; matrix repair materials; reinforced biologic; decellularized extracellular matrix; reinforced tissue matrix; wound healing; biologic matrices; acellular dermal matrix

Introduction

Biologic matrices are frequently used in plastic and reconstructive surgeries to promote soft tissue regeneration due to their biocompatibility, limited inflammatory response, and ability to remodel into host tissue while providing physical support. Biologic matrices are composed of decellularized extra cellular matrices (ECM) prepared from dermal, forestomach, small intestinal submucosa, pericardium, and urinary bladder tissues. The ability of the matrix to provide a scaffold for host cell infiltration, neovascularization, and wound healing depends on processing, sterilization, and preservation methods as well as source tissue.[1,2] In addition to physical characteristics, the presence of cell adhesion and signaling proteins in the ECM have been found to promote cell repopulation and matrix remodeling, leading to functional tissue formation.[3] Biologic matrices have also been found to reduce inflammation and increase neovascularization.[3]

Concerns have been raised over whether biologic matrices derived from xenogeneic tissues can elicit a heightened immune

response compared with allogenic matrices. However, the vast majority of the scientific literature has concluded that the tissue processing methods rather than the source of tissue raw material dictates the host immune response.[4] For example, clinical studies have shown that porcine- or bovine-derived acellular dermal matrices (ADMs) do not cause an exaggerated immune response compared with human ADMs, and in some cases these xenogeneic matrices may outperform ADMs.[5,6] Many studies have shown that porcine, bovine, or human ADMs, which are processed with certain chemicals, crosslinked, or inefficiently decellularized, can invoke an elevated immune response.[7-11]

Due to their efficacy in soft tissue repair and regeneration, biologic matrices have become the standard of care for many plastic and reconstructive surgical procedures.[12] The most used biologic for these applications has historically been the human cadaveric ADM AlloDerm (Allergan Aesthetics).[12] As a dermal matrix, AlloDerm has been shown to promote wound healing in burn patients[12] and to result in relatively normal skin architecture and no wound contracture in a murine model of full-thickness skin wounds.[13] However, despite its adoption, studies have shown that AlloDerm may not always promote optimal tissue regeneration, especially when acting as a scaffold for non-dermal host tissue infiltration.[14] There is some preclinical evidence that AlloDerm may cause chronic inflammation resulting in scarring or fibrosis.[14] In a murine model where AlloDerm was implanted subcutaneously, a thick fibrous capsule formed around the implant and persisted up to 12 months post surgery.[14] At 6 months, there was an elevated inflammatory response evidenced by foreign body giant cells that persisted until the 12-month time point.[14] These results indicate that alternative non-dermal, biologic matrices should be considered.[15]

Reinforced biologic matrices combine a decellularized ECM reinforced with a small amount of synthetic polymer and have gained popularity due to their engineered mechanical profiles and the biologic properties encoded in the ECM component. These reinforced biologics, known as reinforced tissue matrices (RTMs), include OviTex Plastic and Reconstructive Surgery (PRS) products (TELA Bio Inc). OviTex PRS matrices are comprised of layers of ovine forestomach matrix (OFM) reinforced with either permanent polypropylene (PP) or resorbable polyglycolic acid (PGA). The OFM is prepared without using harsh chemicals, enzymatic, or crosslinking reagents, leaving a native, intact ECM structure that retains over 150 known ECM proteins.[16,17] These ECM proteins are not only present but are also functional in their ability to promote cell migration and infiltration to the RTM in vitro and in vivo.[17] As ECM proteins are generally conserved among species, most of the ECM proteins present in OFM are identical to those found in human and other mammalian tissues.[16,18] Of note, within the same species ECM proteins are expressed at various levels in various organs and tissues.[19] Therefore the source of ECM used in creating a biologic matrix will have an impact on the type and amount of ECM proteins present in the final device and may influence its functional properties. OFM has been successful in the treatment of acute and chronic wounds as well as more complex soft tissue reconstruction procedures.[20-23] In a non-human primate (NHP) model of abdominal wall repair, OviTex matrices with similar construction but intended for hernia repair elicited minimal inflammatory response, retained implant geometry, and demonstrated high levels of cell infiltration and neovascularization compared with other biologic matrices and synthetic meshes.[11] Clinically, these OviTex matrices have shown low rates of surgical site infections and low recurrence rates when used in hernia repair.[24-27] Whereas OviTex PRS matrices share many of the same design features as the OviTex matrices for hernia repair, the OviTex PRS matrices are engineered with increased mechanical compliance.

Given the performance of OviTex hernia matrices and OFM-based devices across a range of soft tissue reconstruction applications, OviTex PRS may be a suitable alternative to the current standard of care ADM in certain plastic and reconstructive procedures. This study compared the performance of 2 OviTex PRS matrices to AlloDerm in a NHP soft tissue repair model. Implant geometry and architecture over time, wound healing progress, and inflammation were evaluated.

Methods and Materials

General

The animal protocol for this study was reviewed and approved by the Behavioural Sciences Foundation (BSF; Basseterre, Saint Kitts and Nevis) Institutional Animal Care and Use Committee (IACUC). BSF holds a certificate of Good Animal Practice with the Canadian Council on Animal Care (CCAC) and observes Guidelines for the Care and Use of Laboratory Animals (as outlined in NIH Publication #85-23 Rev 1985). OviTex PRS Resorbable (Ovitex PRS Res) and OviTex PRS Permanent (Ovitex PRS Perm; TELA Bio Inc) as well as AlloDerm Regenerative Tissue Matrix Ready To Use (AlloDerm, Allergan Aesthetics) were implanted according to their respective instructions for use. Statistical analysis was conducted using GraphPad Prism 9.4.0 (version 673, GraphPad Software, Inc). All results are expressed as mean and SEM. Data was analyzed on a per-subject basis. A one-way ANOVA was used to determine differences between groups at each time point. Mixed effects analyses with Tukey multiple comparison testing were used to determine differences between test article groups at each time point for groups showing statistical significance as determined by the ANVOA. A one-way ANOVA was used to determine differences within groups over time. Mixed effects analyses with Tukey multiple comparison testing were also used to determine differences within test article groups over time. Significance was defined as $P < .05$.

Soft Tissue Repair Model

Animal screening and handling, surgical procedures, and

Table 1. Histology Scoring Matrices

Score	Overall inflammatory score	Presence of specific inflammatory cell types	Neovascularization	New collagen formation	Implant:tissue ratio	Presence of synthetic or biologic aspects of implant	Presence of osseous metaplasia
0	Absent	Absent	Absent	Absent	No implant present; defect entirely spanned by tissue.	No synthetic or biologic aspects of implant detectable	Absent
1	Minimal-rare	Minimal-rare 1-5/per high power field (hpf; 40x obj)	Minimal capillary proliferation, focal, 1-3 buds	Minimal, narrow band, ~1-2 cell layers thick	Defect predominantly spanned by tissue.	Biologic or synthetic aspects of implant barely detectable	Minimal, focal, nearly imperceptible
2	Mild	Mild, 5-10/hpf	Groups of 4-7 capillaries with supporting fibroblastic structures	Thin, localized band, <~10 cell layers thick	Implant and tissue comparable.	Biologic or synthetic aspects of implant slightly detectable	Mild, focally extensive, inconspicuous
3	Moderate, heavy	Moderate, heavy infiltrate, with preservation of local architecture	Broad band of capillaries with supporting structures	Moderately thick, contiguous band along length of tissue	Defect predominantly spanned by implant.	Biologic or synthetic aspects of implant easily detectable	Moderate, multifocal or locally extensive, readily apparent
4	Marked, packed	Marked, packed, with effacement of regional architecture	Extensive band of capillaries with supporting fibroblastic structures	Extensive, thick zone with effacement of local architecture	Tissue absent; defect entirely spanned by implant.	Overwhelming presence of biologic or synthetic aspects of implant	Severe, regionally extensive, overwhelming with effacement of local architecture

postsurgical procedures were performed as previously described.[11,28,29] The study included 36 male and female adult Vervet monkeys (Cercopithecus aethiops) ranging in weight from 3.5 to 7 kg. The test article groups for AlloDerm, OviTex PRS Res, and OviTex PRS Perm each included 12 randomly assigned animals. Under anesthesia, a longitudinal mid-abdominal skin incision of approximately 7 cm was made to expose an area of the linea alba and muscle wall. A 7 x 3–cm full-thickness defect was created in the midline of the abdominal wall and sections of both rectus muscles, including the fascia and the peritoneum, were removed.

The abdominal wall defect was then repaired with one of the test articles cut to be equal in size to the defect (approximately 7 x 3 cm). The implant was anchored at each of the 4 corners with 2-0 non-absorbable polypropylene sutures in an interrupted pattern and further sutured to the edges of the rectus abdominal muscle and fascia with non-absorbable 2-0 polypropylene suture in a running pattern. The subcutaneous tissue was closed with 2-0 absorbable polydioxane sutures, and the skin was closed with 2-0 non-absorbable nylon sutures. At the time points 2, 4, 12, and 24 weeks post implantation, 3 animals from each group were sacrificed.

The surgical site and the test articles were evaluated by a veterinarian via gross necropsy for signs of abnormalities and to qualitatively note implant geometry as previously described.[11,28] The entire implant and surrounding tissue were removed and photographed. A midline cross-section of each implant was excised and cut in half, and each piece was placed in 10% neutral buffered formalin for histologic analysis.

Histology

The formalin-fixed sections of the implant and surrounding tissue were embedded in paraffin, cut into sections, and stained with either Hematoxylin and Eosin (H+E) or Verhoeff-Van Gieson (VVG) stains (Tejas Pathology Associates). Each of these types of stain was used on 2 slides from each animal, 1 from the left side of the host-implant interface and 1 from the right of side of the host-implant interface (4 total slides per animal). The slides were evaluated by an American College of Veterinary Pathology (ACVP) board-certified veterinary pathologist who was blind to treatment and time point (CBSET Inc). Slides were analyzed using light microscopy to evaluate gross histomorphology including collagenous/fibroproliferative response, proliferation of inflammatory cell types, neovascularization, osseous metaplasia, and implant presence. Slides were scored using established standard toxicological pathology criteria on a scale from 0 to 4 for H+E–stained slides **(Table 1)**. The scale differed for each parameter; however, 0 always represented absence of measured effect and 4 represented the most robust effect **(Table 1)**. Implant-to-tissue ratio, a measure of implant persistence in relation to the surrounding host tissue, was scored based on the relative amount of biologic/collagenous implant material or synthetic implant material present in relation to the new tissue formation inside the defect site. Collagen formation was assessed both semi-qualitatively, including amount and arrangement of collagenous tissue

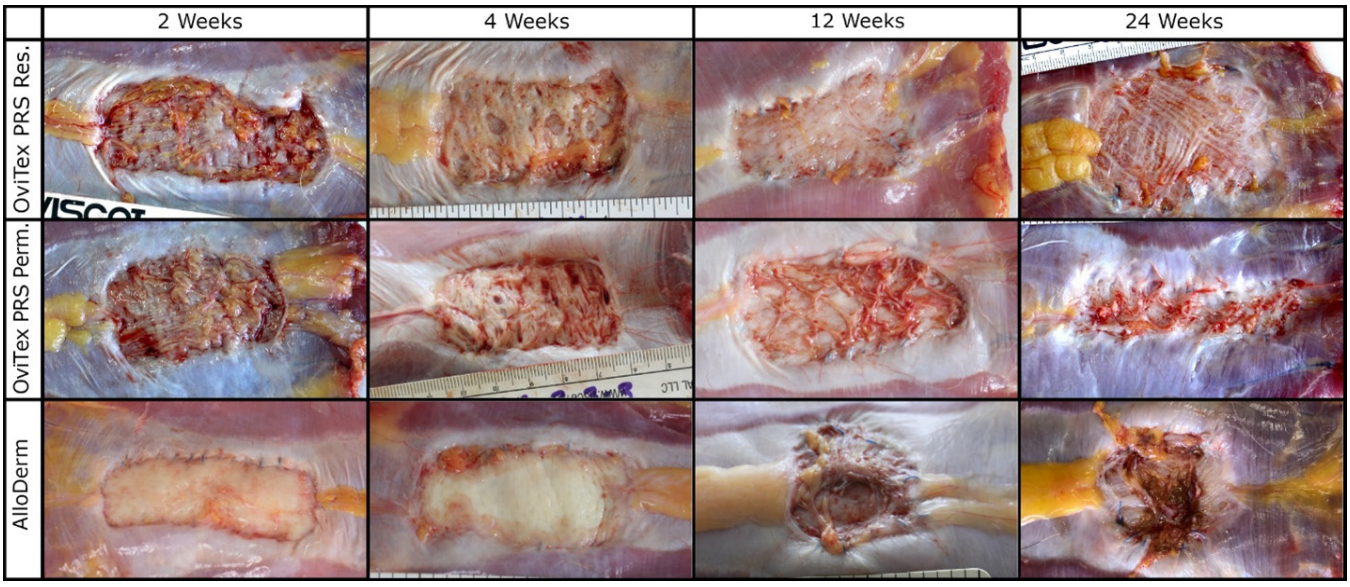

FIGURE 1. Representative photographs of wound site and test articles taken at 2, 4, 12, or 24 weeks post implantation surgery. Photographs are not to scale. Test articles included OviTex PRS Perm and Res, as well as AlloDerm Ready to Use biologic.

within implants (intramatrix) and peripheral to implant areas (peripheral to matrix), as well as after integration of implants. Neovascularization, as determined by extent of blood vessel presence, was determined within implant areas (intramatrix) and peripheral to implant areas (peripheral to matrix) as well as after integration of implants. VVG-stained slides were used to assess the amount and distribution of elastin within implants and within the host tissue defect site. Images were acquired using an Olympus VS120 scanner and analyzed with Olympus cellSens Dimension v1.17 software.

Results

Gross Morphology and Implant Geometry

In the 24-week group, 1 animal was lost from each of the OviTex PRS Perm and OviTex PRS Res groups due to trauma not associated with study conduct. To compensate for this loss, 2 samples (n) from the left side of the host-implant interface and from the right side of the host-implant interface were analyzed histologically for the remaining 2 animals from these groups. Representative images of the test articles and defect sites are provided in **Figure 1**. At the earliest 2-week time point, both OviTex PRS Perm and OviTex PRS Res showed marked capillary formation and vascular budding across the entire surface of the matrices **(Figure 1)**. In comparison, AlloDerm showed only light blushing of the matrix at 2 weeks indicative of early capillary formation, and at 4 weeks there remained a clear zone of acellular tissue through the middle of the AlloDerm implants, with a ~5-mm border of vascularized graft **(Figure 1)**. At the later time points (12 and 24 weeks) in these representative images, there appeared to be radial expansion of OviTex PRS Res and elongation of OviTex PRS Perm **(Figure 1)**. The AlloDerm implants, however, appeared to retain their original implant geometry **(Figure 1)**.

Histological Assessment

Presence of the implants over time was assessed in histologic sections taken from animals sacrificed at 2, 4, 12, and 24 weeks post implantation. At early time points, no difference in implant-to-tissue ratio was apparent among the various matrix types. By 12 weeks and 24 weeks, however, OviTex PRS Perm and OviTex PRS Res biologic components were both fully remodeled into the surrounding host tissue, though the polypropylene in the OviTex PRS Perm group persisted as expected, whereas the AlloDerm implants could still be distinguished from host tissue **(Figure 2a and Figure 3)**. The persistence of the polypropylene in the OviTex PRS Perm group resulted in a statistically higher implant-to-tissue ratio than both the OviTex PRS Res and Alloderm at the 24-week time point. The presence of the AlloDerm biologic component was statistically higher compared with the presence of OviTex PRS Res at 2 weeks and to the presence of OviTex PRS Perm at 4 weeks **(Figure 2c and Figure 3)**. The AlloDerm biologic persisted at 12 and 24 weeks and was statistically higher than both OviTex PRS Perm and Res biologic components, which were no longer apparent at 12 and 24 weeks **(Figure 2c and Figure 3)**. The synthetic component of OviTex PRS Perm remained present at all time points as expected and was significantly higher than that of AlloDerm and OviTex PRS Res, except at 2 weeks when the synthetic components of OviTex PRS Perm and Res were equally present **(Figure 2b and Figure 3)**. OviTex PRS Res retained a synthetic component at 4 weeks; however, after this time point the synthetic component completely resorbed **(Figure 2b)**.

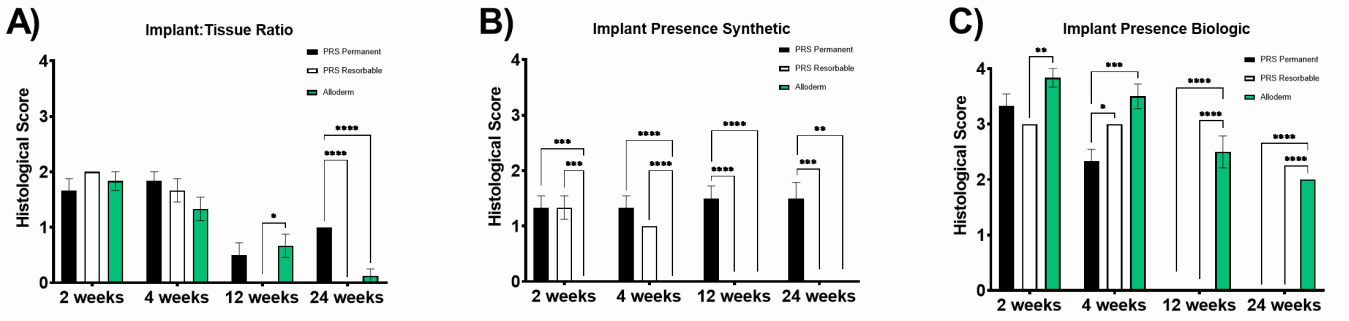

FIGURE 2. Implant-tissue ratio and presence of implant biologic and synthetic components. N = number of animals, n = number of representative slides per animal. 2 weeks: OviTex PRS Perm N = 3, n = 2; OviTex PRS Res N = 3, n = 2; AlloDerm N = 3, n = 2; 4 weeks: OviTex PRS Perm N = 3, n = 2; OviTex PRS Res N = 3, n = 2; AlloDerm N = 3, n = 2; 12 weeks: OviTex PRS Perm N = 3, n = 2; OviTex PRS Res N = 3, n = 2; AlloDerm N = 3, n = 2; 24 weeks: OviTex PRS Perm N = 2, n = 4; OviTex PRS Res N = 2, n = 4; AlloDerm N = 3, n = 2. Statistical differences were determined by an ANOVA followed by a mixed effects analysis with Tukey multiple comparisons testing to determine where the statistical differences were between groups. *, **, ***, and **** PRS vs AlloDerm P < .05, .01, .001, and .0001, respectively.

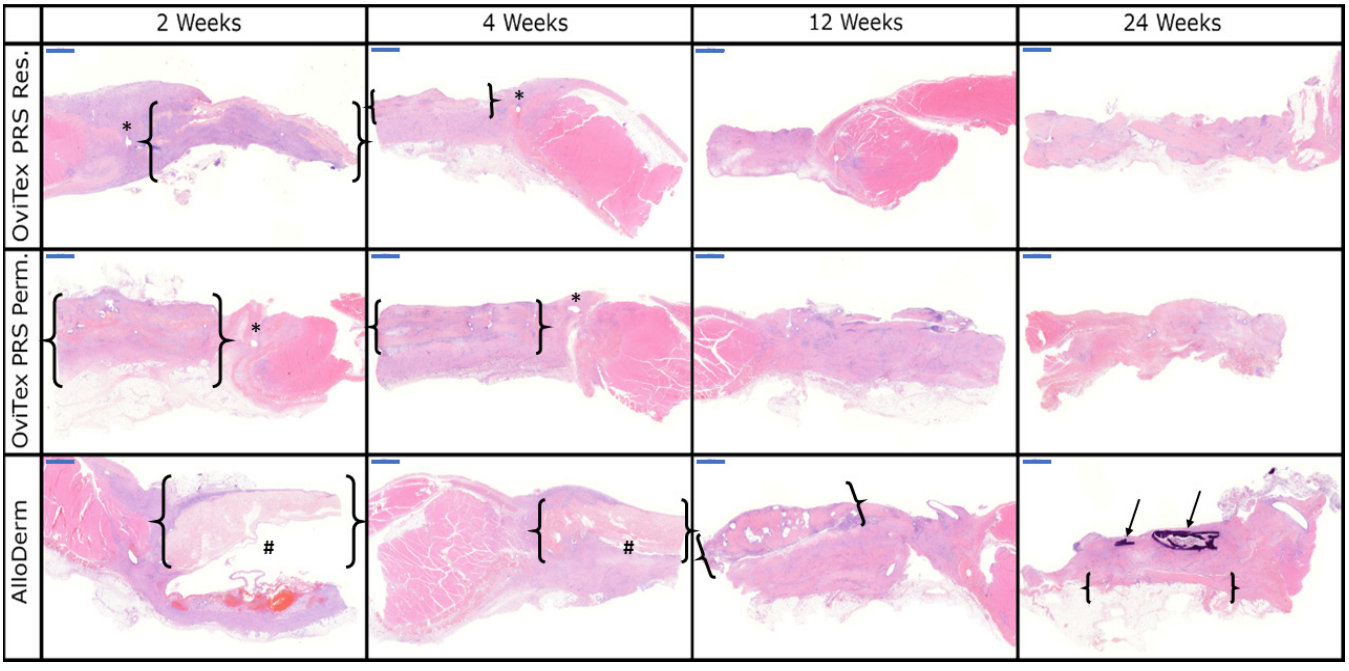

FIGURE 3. Low magnification view of representative H+E-stained histology sections from NHPs 2, 4, 12, and 24 weeks post implantation of OviTex PRS Res, OviTex PRS Perm, or AlloDerm in abdominal wounds. Blue scale bars represent 1000 µm. Brackets: implanted material, *: location of the implant to ab wall anchoring suture, #: location of pocket, arrows: osseous metaplasia.

Histology was also used to assess new collagen formation in and around the implant and to determine the influence of matrix type on wound healing and the quality of remodeled tissue. As these assessments evaluate intramatrix and peripheral-to-matrix tissue response, they are dependent on the presence of the implant and correlate with the implant-to-tissue ratio. As the implants remodel, these evaluation areas decrease in size and the overall measure of fibrosis/collagen organization more accurately portrays the quality of the new and surrounding host tissue. Initially, both OviTex PRS Perm and Res had slightly more intramatrix new host collagen deposition than AlloDerm, but only OviTex PRS Perm had statistically higher host collagen infiltration compared with AlloDerm **(Figure 4a)**. The overall fibrosis collagen organization for OviTex PRS Perm was significantly higher than that for OviTex PRS Res and Alloderm at 2 weeks **(Figure 4c)**. This became significant for both OviTex PRS Perm and Res products at 4 weeks post implantation, at which point OviTex PRS Perm and Res had significantly increased intramatrix new host collagen deposition compared with AlloDerm **(Figure 4a)**. At this time, OviTex PRS Perm and Res

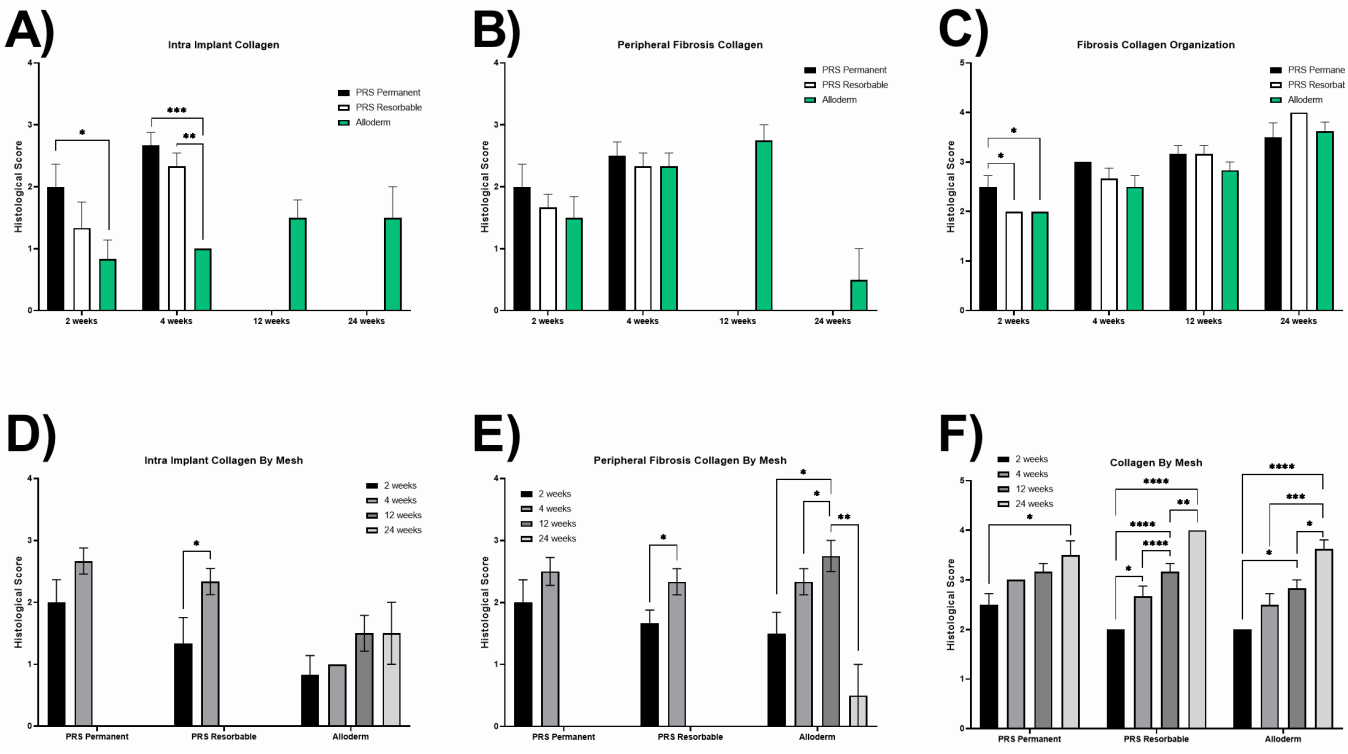

FIGURE 4. Histological scores of new collagen formation from tissue sections of NHPs 2, 4, 12, and 24 weeks post implantation of OviTex PRS Res, OviTex PRS Perm, or AlloDerm. New collagen formation was measured within the visible matrix (intramatrix) and around the matrix implant (peripheral to matrix). Once the matrix had fully integrated into the surrounding host tissue and no distinct matrix could be identified any longer, the peripheral-to-matrix category could no longer be measured. Statistical differences between groups at each time point were determined by an ANOVA followed by a mixed effects analysis with Tukey multiple comparisons testing to determine where the statistical differences were between groups. *, **, ***, and **** PRS vs AlloDerm P < .05, .01, .001, and .0001, respectively. Statistical differences within groups over time were determined by an ANOVA followed by a mixed effects analysis with Tukey multiple comparisons testing to determine where the statistical differences were between groups. *, **, ***, and **** PRS vs AlloDerm P < .05, .01, .001, and .0001, respectively.

displayed localized bands of host collagen about 10 cell layers thick, whereas AlloDerm only displayed minimal, narrow bands of new host collagen **(Figure 4c)**. OviTex PRS Perm and Res were both fully integrated into the surrounding host tissue at 12 weeks, and new host collagen continued to form until the final 24-week time point, at which time both OviTex PRS Perm and Res had significantly more host collagen deposition than at 2 weeks **(Figure 4f)**. OviTex PRS Res also experienced an increase at every other time point, including 2 to 4 weeks, 2 to 12 weeks, 4 to 12 weeks, and 12 to 24 weeks **(Figure 4c)**. The AlloDerm implants saw significant increases in host collagen deposition from 2 to 12 weeks, 2 to 24 weeks, 4 to 24 weeks, and 12 to 24 weeks **(Figure 4c)**. However, the AlloDerm implants were still able to be distinguished from the peripheral host tissue at 12 and 24 weeks **(Figure 4b)**.

Neovascularization of the implant sites was also assessed histologically. At 2 weeks after matrix implantation, the OviTex PRS Perm and Res products had a significantly increased concentration of capillaries and supporting fibroblastic structures in the peripheral area surrounding the implant compared with the AlloDerm implants **(Figure 5b)**. Intramatrix neovascularization of OviTex PRS Perm and Res was also increased at 2 weeks compared with Alloderm, but not to a significant extent **(Figure 5a)**. By 4 weeks, however, both OviTex PRS Perm and Res had statistically increased intramatrix neovascularization compared with AlloDerm intramatrix neovascularization **(Figure 5a)**. Neovascularization across the entire implant site was comparable among all implant groups at all time points **(Figure 5c)**. There was a significant increase in intramatrix vascularity for both OviTex PRS Perm and Res from 2 to 4 weeks and for AlloDerm from 2 to 12 weeks **(Figure 5d)**. There was a statistically significant decrease in vascularity for AlloDerm from 2 to 24 weeks.

The impact of matrix type on host tissue infiltration and proliferation was also determined. Tissue sections stained with Verhoeff Van Gieson (VVG) showed host fibrovascular proliferation between implant layers composed of collagen and elastin **(Figure 6)**. At 2 weeks after abdominal soft tissue defects were closed with either OviTex PRS Perm or Res, abundant host fibrovascular tissue infiltration could be seen as represented by asterisks in **Figure 6**. In contrast, at this time point, AlloDerm was only associated with mild infiltration of host spindle cells **(Figure 6)**. Areas lacking interstitial filling were more apparent in AlloDerm

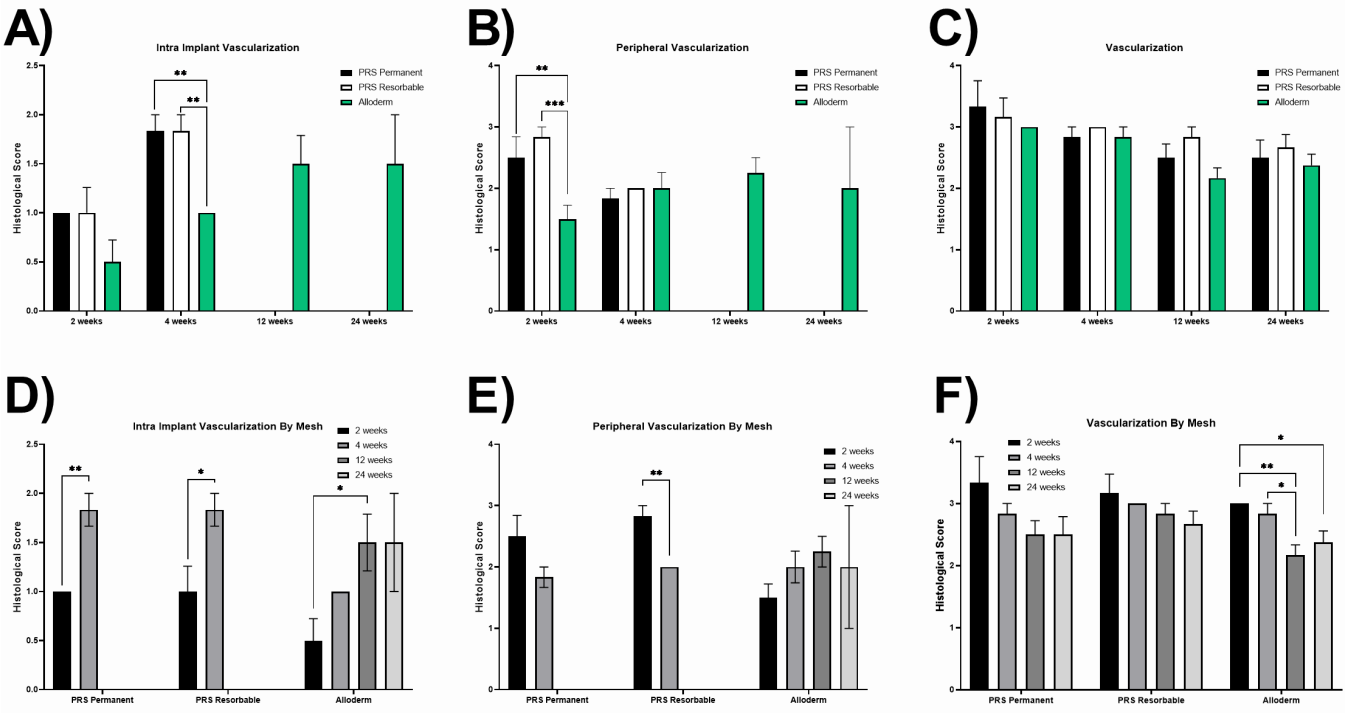

FIGURE 5. Histological scores of the extent of neovascularization from tissue sections of NHPs 2, 4, 12, and 24 weeks post implantation of OviTex PRS Res, OviTex PRS Perm, or AlloDerm. Neovascularization was measured within the visible matrix (intramatrix) and around the matrix implant (peripheral to matrix). Once the matrix had fully integrated into the surrounding host tissue and no distinct matrix could be identified any longer, the peripheral-to-matrix category could no longer be measured. Statistical differences between groups at each time point were determined by an ANOVA followed by a mixed effects analysis with Tukey multiple comparisons testing to determine where the statistical differences were between groups. *, **, ***, and **** PRS vs AlloDerm P < .05, .01, .001, and .0001, respectively. Statistical differences within groups over time were determined by an ANOVA followed by a mixed effects analysis with Tukey multiple comparisons testing to determine where the statistical differences were between groups. *, **, ***, and **** PRS vs AlloDerm P < .05, .01, .001, and .0001, respectively.

implants at 2 weeks post implantation as represented by "#" in **Figure 6**. At 2 weeks in all 3 test articles, implant collagen fibers were readily observed as denoted by the black arrows in **Figure 6**. In addition, at 2 weeks all 3 test articles displayed elastin fibers as denoted by black arrows **(Figure 6)**. Compared with both OviTex PRS Perm and Res, AlloDerm implants appeared to have a higher, more moderate concentration of elastin fibers initially at 2 weeks. Both OviTex PRS Res and OviTex PRS Perm contained minimal to mild elastin fibers at 2 weeks; however, OviTex PRS Res appeared to have slightly more elastin content **(Figure 6)**. At 4 weeks post implantation, host fibrovascular tissue continued to proliferate on and within the OviTex PRS Perm and OviTex PRS Res test articles **(Figure 6)**. At 4 weeks post implantation, the AlloDerm implants still only had mild infiltration of host fibrovascular tissue with some interstitial regions between the AlloDerm implant collagen remaining unfilled **(Figure 6)**. At 4 weeks post implantation, AlloDerm implants appeared to have moderate concentrations of elastin, whereas OviTex PRS Perm had minimal to mild elastin content and OviTex PRS Res had mild elastin content **(Figure 6)**. At 12 weeks post implantation, all OviTex PRS Perm and OviTex PRS Res implants were fully infiltrated by host fibrovascular tissue and remaining ECM could not be detected, whereas all 3 AlloDerm implants were still present **(Figure 6)**. At this time, OviTex PRS Res had minimal to mild elastin concentration, whereas OviTex PRS Perm and AlloDerm implants had mild elastin presence. At 24 weeks post implantation, AlloDerm implants were still not fully integrated into surrounding host tissue **(Figure 6)**. At this final time point, elastin fibers were sparse in Ovitex PRS Perm. OviTex PRS Res appeared to have locally higher concentrations of elastin fibers compared with OviTex PRS Perm due to consolidation of implant architecture during remodeling causing the elastin fibers to cluster **(Figure 6)**. Alloderm implants retained similar levels of elastin as at the 12-week time point but with prominent clustering **(Figure 6)**.

Overall inflammatory scores, which considered the entire inflammation response and inflammatory cell subtypes, were not statistically different among the OviTex PRS Perm, Res, and AlloDerm implants at any time point and ranged from minimal to mild **(Figure 7a and Figure 8)**. Initial infiltration was composed primarily of neutrophils, lymphocytes, macrophages, and giant cells for all groups **(Figure 7 b, f, d,**

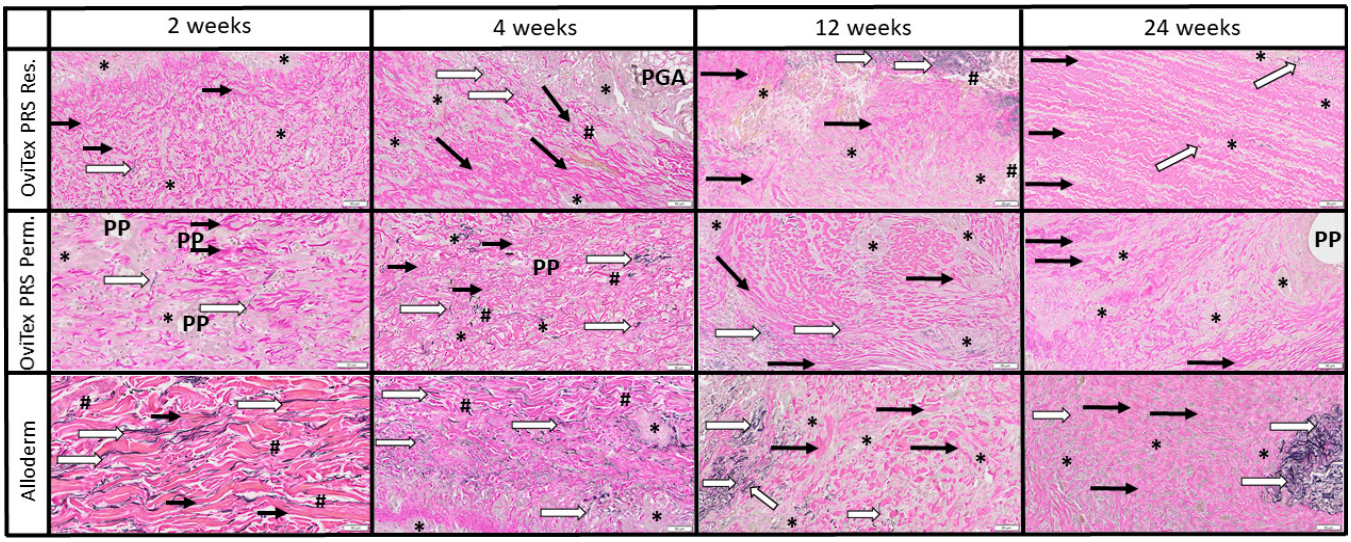

FIGURE 6. High magnification view of VVG-stained representative histology sections from NHPs 2, 4, 12, and 24 weeks post implantation of OviTex PRS Res, OviTex PRS Perm, or AlloDerm in abdominal defects. Elastin fiber nuclei: black; collagen: red; muscle and other tissues: yellow. Black arrows: collagen, *host fibrovascular tissue, #areas of sparse host tissue, white arrow: elastin fibers.

and e). Whereas average initial lymphocyte, macrophage, and giant cell infiltration was minimal, average neutrophil infiltration was mild across all groups **(Figure 7 b, f, d, and e and Figure 8)**. At 2 weeks, OviTex PRS Perm displayed a significantly increased neutrophil response compared with AlloDerm; however, this did not persist at any later time points **(Figure 7b and Figure 8)**. AlloDerm had a statistically higher level of neutrophil infiltration at the 4-week time point compared with both OviTex PRS Perm and Res devices **(Figure 7b and Figure 8)**. At 4 weeks, AlloDerm also had a significantly higher giant cell population compared with OviTex PRS Perm and Res **(Figure 7e)**. At 24 weeks, the OviTex PRS Perm group displayed a minimal eosinophil response that was statistically higher than the other 2 groups despite no eosinophil proliferation in PRS Perm at earlier time points **(Figure 7c)**. The eosinophil response was largely localized to the permanent suture in the PRS Perm implant.

The presence of osseous metaplasia was also assessed via histology. At early time points (2 and 4 weeks), osseous metaplasia was not present on any of the OviTex PRS Perm, Res, or AlloDerm matrices **(Figure 9)**. At 12 weeks after implantation, one of the animals implanted with AlloDerm displayed locally extensive osseous metaplasia, but none of the animals implanted with OviTex PRS Perm or Res displayed this phenomenon **(Figure 9)**. At 24 weeks post implantation, all the animals implanted with AlloDerm displayed minimal to locally extensive osseous metaplasia **(Figure 9)**. At 24 weeks post implantation, 1 animal implanted with OviTex PRS Res displayed locally extensive osseous metaplasia **(Figure 9)**. At 24 weeks, none of the animals implanted with OviTex PRS Perm showed any sign of osseous metaplasia formation **(Figure 9)**.

Discussion

Biologic matrices are used in plastic and reconstructive surgeries to provide physical reinforcement, to accelerate wound healing kinetics, and to promote the formation of healthy functional tissue; however, not all biologic matrices stimulate these responses to the same extent. AlloDerm biologic tissue matrix derived from human cadaver dermis has become the industry standard in the plastic and reconstructive surgical space.[12] A newer class of biologic matrices known as reinforced tissue matrices (RTMs) may offer a cost-effective, non-dermal alternative with similar performance characteristics to traditional ADMs. Two such RTMs are OviTex PRS Perm and OviTex PRS Res. These matrices are both engineered from layers of OFM embroidered together with either polypropylene (PP) or polyglycolic acid (PGA) filaments using patterns designed to withstand biomechanical forces. These matrices are especially promising given the performance of other OviTex matrices and OFM-based devices across a range of soft tissue applications. This study compared OviTex PRS Perm and OviTex PRS Res with AlloDerm biologic matrix in regard to their retention of original geometry, new collagen deposition and neovascularization, and inflammatory response in a non-human primate model of soft tissue repair. This particular animal model was used because Old World primates have greater than 98% genetic similarity to humans and therefore display similar immune and wound-healing responses.[30]

Implant geometry was qualitatively assessed to determine whether the integrity of any of the biologic matrices in this study was altered by the biomechanical forces of the abdominal wall. The NHP soft tissue repair model of a full-thickness midline abdominal wall defect is an especially challenging

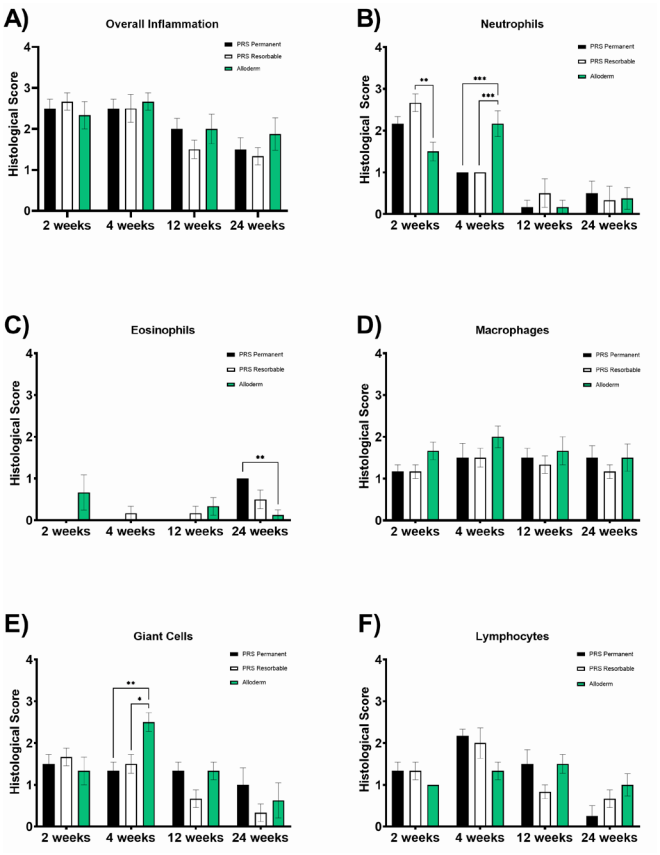

FIGURE 7. General inflammation and immune cell proliferation in abdominal wounds closed with PRS Perm, PRS Res, or AlloDerm. Sections of implants at 2, 4, 12, or 24 weeks post surgery were taken for histology, stained with H+E, and analyzed for the presence of general inflammation or specific immune cell types. N: number of animals, n: number of representative slides per animal. 2 weeks: OviTex PRS Perm N = 3, n = 2; OviTex PRS Res N = 3, n = 2; AlloDerm N = 3, n = 2; 4 weeks: OviTex PRS Perm N = 3, n = 2; OviTex PRS Res N = 3, n = 2; AlloDerm N = 3, n = 2; 12 weeks: OviTex PRS Perm N = 3, n = 2; OviTex PRS Res N = 3, n = 2; AlloDerm N = 3, n = 2; 24 weeks: OviTex PRS Perm N = 2, n = 4; OviTex PRS Res N = 2, n = 4; AlloDerm N = 3, n = 4. Statistical differences were determined by an ANOVA followed by a mixed effects analysis with Tukey multiple comparisons testing to determine where the statistical differences were between groups. *, **, ***, and **** PRS vs AlloDerm P < .05, .01, .001, and .0001, respectively.

model to assess matrix performance.[31,32] In this model, implants experience exaggerated biomechanical forces during the repair process. Though this model is not totally representative of the forces that matrices experience in plastic and reconstructive procedures, it represents a worst-case scenario for the matrices studied. Whereas there appeared to be some expansion of both OviTex PRS Perm and Res matrices over time **(Figure 1)**, all matrices were able to withstand the biomechanical forces to which they were subjected, demonstrating the strength of the newly remodeled tissue.

New collagen deposition and neovascularization are critical to the success of soft tissue repair. The NHP model used in this study provides a challenging measure of new tissue formation as it requires matrix infiltration to occur primarily from the margins of the defect, unlike a model in which cells could repopulate the test articles from a multitude of surrounding tissues. A previous study in this NHP model has shown that the rates of matrix repopulation, neovascularization, and ultimately integration and remodeling are dictated by the structure and biological properties of the matrix used in the repair.[11] It has previously been shown that certain porcine and fetal bovine ADMs are slow to be infiltrated by host cells, presumably due the relative density and reduced porosity of these dermal-derived matrices.[11] In contrast, the OFM base of OviTex matrices is an open porous ECM structure, allowing ready access of host cells into the pores and channels of the implant.[33,34] As OviTex matrices are composed of multiple sheets of OFM, fenestrations are engineered to allow for lateral migration of host cells between the OFM sheets. OviTex matrices were more quickly and diffusely remodeled by host cells in this previous NHP model compared with other matrices, likely for these reasons.[11] In the current study, differences in the kinetics of host cell repopulation were apparent in the histological assessment of OviTex PRS Perm, Res, and AlloDerm devices **(Figure 8)**. New host collagen intramatrix deposition was greater in both OviTex PRS Perm and Res devices relative to AlloDerm at 2 and 4 weeks **(Figure 4a)**, indicating early host fibroblast infiltration and collagen deposition. Histologically, OviTex PRS matrices were fully integrated into the host tissue by 12 weeks **(Figure 4c)**, whereas even at 24 weeks, AlloDerm implants remained partially integrated and displayed unorganized collagen deposition **(Figure 6)**. In contrast, at 24 weeks OviTex PRS Perm and Res devices were fully remodeled to functional tissue, as characterized by organized basket-weave mature collagen bundles **(Figure 6)**. The formation of the mature collagen bundles on both OviTex PRS Perm and Res may be in part due to the fact that OFM scaffolds have been shown to retain their native collagen d-spacing and align themselves in the direction of biomechanical strain.[33] OviTex PRS Res appeared to have more mature collagen bundles in comparison with OviTex PRS Perm, which may be due to the difference in polymer reinforcement. As the PGA polymer resorbed in OviTex PRS Res, these matrices were likely more affected by biomechanical strain. As the polypropylene in OviTex PRS Perm is permanent, these matrices were likely subjected to less biomechanical strain and therefore appear to have slightly less alignment and maturation of the new collagen. The formation of mature collagen in the direction of strain can be correlated with the strength of the new host tissue.[33] In contrast, the disorganization of the collagen deposited on the AlloDerm implants reflects that the collagen bundles did not align themselves in the direction of biomechanical strain and therefore did not mature in the same manner.

Host cell infiltration and collagen intramatrix deposition presumably affected the concentration of elastin fibers within the implant sections. AlloDerm implants appeared to contain

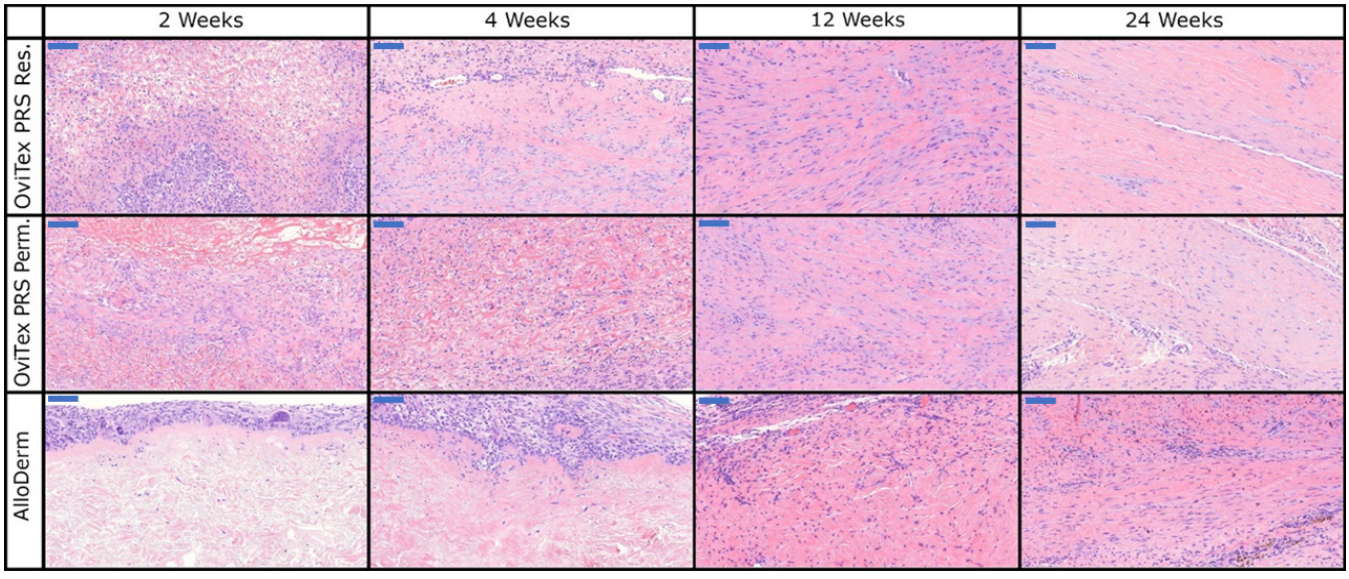

FIGURE 8. High-magnification view of infiltration of implants by immune cells. Representative images of H+E-stained histology sections from NHPs at 2, 4, 12, or 24 weeks post implantation of OviTex PRS Res, OviTex PRS Perm, or AlloDerm in abdominal wounds. Blue scale bars represent 50 µm.

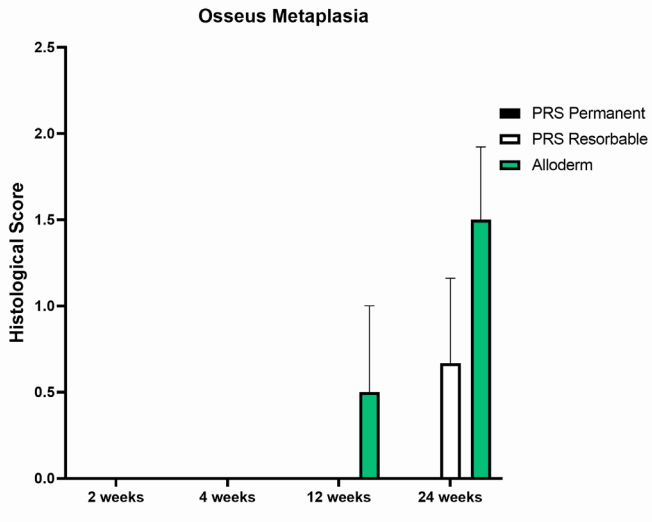

FIGURE 9. Histological scores of osseous metaplasia from tissue sections of NHPs 2, 4, 12, and 24 weeks post implantation of OviTex PRS Res, OviTex PRS Perm, or AlloDerm. Statistical differences between groups at each time point were determined by an ANOVA followed by a mixed effects analysis with Tukey multiple comparisons testing to determine where the statistical differences were between groups. *, **, ***, and **** PRS vs AlloDerm P < .05, .01, .001, and .0001, respectively.

about twice the amount of elastin initially in comparison with both OviTex PRS Perm and OviTex PRS Res **(Figure 6)**. Whereas OviTex PRS Perm and Res both fully remodeled by 24 weeks, AlloDerm implants remained visible and more implant elastin could be observed **(Figure 6)**. There appeared to be a difference in final elastin concentration at 24 weeks between the OviTex PRS Perm and Res products; however, this is likely due to the resorbable versus permanent nature of their polymer components. By 24 weeks, OviTex PRS Res was fully remodeled, and the PGA component was not discernible 12 weeks or 24 weeks post implantation.[35] The full remodeling of the OviTex PRS Res device into functional tissue caused the remaining implant elastin fibers to become locally concentrated as seen in **Figure 4**. In contrast, the elastin fibers were still more diffuse and appeared minimal in OviTex PRS Perm, potentially due to the presence of permanent polymer interrupting or delaying the consolidation of elastin into clusters **(Figure 6)**. Ideally matrices used in soft tissue repair have similar biological make up to the host tissue they are replacing. The native abdominal wall tissue normally has a high collagen-elastin ratio with more collagen needed for support, as a high ratio of elastin content has been correlated with reduced strength.[35] These results show that OviTex PRS Perm and Res were able to support functional abdominal wall remodeling with low levels of elastin. In contrast, the continued presence of elastin fibers on AlloDerm implants after 24 weeks could indicate inefficient remodeling to functional tissue, perhaps due to a different ECM protein composition of its dermal base.

As part of the healing process, neovascularization is a critical component of new tissue growth facilitating the delivery of oxygen and nutrients to host cell infiltrates and the removal of waste products. At the earliest 2-week time point, neovascularization in the tissues adjacent to the implant was statistically greater in the OviTex PRS samples compared with AlloDerm **(Figure 5b)**. This may be due to paracrine signaling from the OFM base material as it contains factors known to play a role in angiogenesis and vasculogenesis.[16] In addition, the sheep forestomach is highly vascular, and OFM has been shown to lead to rapid blood vessel formation in soft tissue

repair.[34,36] In the current study at 4 weeks, there were statistically significant differences in neovascularization within the implants between OviTex PRS samples and AlloDerm **(Figure 5b)**. As previously stated, AlloDerm never fully integrated into the surrounding host tissue within the 24-week wound-healing time frame, and neovascularization of the matrix site at 24 weeks was statistically decreased compared with 2 weeks post implantation **(Figure 5f)**.

Inflammatory infiltrates were anticipated with the placement of the abdominal wall implants, trending from an acute neutrophilic response to a chronic histiocytic response. All matrix types initially induced the expected inflammatory response, which decreased by 24 weeks after implantation **(Figure 7a)**. Despite both OviTex PRS products containing small amounts of polymer compared with AlloDerm, which does not contain any synthetic components, there was no difference in overall inflammatory response at any time point **(Figure 7a)**. Both OviTex PRS Perm and OviTex PRS Res initially had a significantly higher neutrophil response when compared with AlloDerm at 2 weeks. By 4 weeks the neutrophil response to the OviTex PRS matrices subsided, becoming statistically lower than that of the neutrophil response to AlloDerm **(Figure 7b)**. Neutrophils are a first responder to inflammatory stimuli and play a role in the phagocytosis of the implanted materials, initiating the necessary inflammatory process for wound healing[37]. The earlier infiltration of neutrophils in the OviTex PRS matrices may have contributed to the earlier remodeling as compared with Alloderm. At 24 weeks OviTex PRS Perm had a localized increased eosinophilic response compared with OviTex PRS Res and AlloDerm **(Figure 7c)**. Despite there being a statistical difference between the eosinophilic response of OviTex PRS Perm in comparison with AlloDerm and OviTex PRS Res, eosinophil concentration was minimal to rare and localized around the permanent polymer, indicating a minimal inflammatory response to the polypropylene fiber **(Figure 7c)**. Though there is speculation that osseous metaplasia formation is due to chronic inflammation,[38] at 12 and 24 weeks none of the animals that developed osseous metaplasia displayed an elevated inflammatory response **(Figure 9)**. It is therefore uncertain whether inflammatory response had an impact on osseous metaplasia formation; however, this phenomenon could be due to early inflammatory mechanisms yet unknown. Other theories propagate that areas of traumatic damage may be more prone to osseous metaplasia or that liberation of osteoblasts from surrounding bone sources may be causal.[38,39] A previous NHP study[11] found osseous metaplasia formation in 4 animals implanted with synthetic mesh and 2 animals implanted with another dermal matrix. In this current study 4 animals implanted with AlloDerm dermal matrix were found to have osseous metaplasia formation. Between the former and the current NHP study, osseous metaplasia formation was only observed in 1 animal out of the 42 total implanted with OviTex matrices.[11] Further preclinical studies aimed at elucidating the causal factors in osseous metaplasia formation on implanted matrices are needed to understand this phenomenon.[40] This is important as it appears possible that certain matrix types may be more prone to calcification at the wound site than others.

Limitations

The matrices compared in this study are meant for a wide variety of plastic and reconstructive procedures in which they may perform differently. In this study, a soft tissue repair model was used to evaluate the matrices. Therefore, these results must be interpreted with caution when considering other plastic and reconstructive procedures. In addition, the small sample size was impacted by the loss of 1 OviTex PRS Res 24-week animal and 1 OviTex PRS Perm 24-week animal. Multiple tissue sections were analyzed from the remaining 2 animals in these groups in an attempt to restore some statistical power; however, this method does not fully compensate for the reduced group size from 3 animals to 2. Finally, this is a preclinical model and may not accurately predict true clinical outcomes.

Conclusions

The NHP soft tissue repair model of a full-thickness midline abdominal wall defect provides a challenging environment for the comparison of matrices designed to aid in soft tissue repair and regeneration in plastic and reconstructive procedures. Both OviTex PRS and AlloDerm matrices withstood the biomechanical forces during the repair process, and all test matrices gave rise to functional tissue. Whereas overall inflammation between OviTex PRS and Alloderm were similar, there were key differences. These differences included the earlier presence of more neutrophils, a first responder in the inflammatory process needed for wound healing, in the OviTex PRS Res group in levels that were not reached in Alloderm until the 4-week time point. There was also a difference in eosinophils present in OviTex PRS Perm at 24 weeks; however, this was minimal. Despite the early neutrophil and late eosinophil differences identified between groups, the overall inflammatory response that accounts for all cell subtypes was not different between groups at any time point. OviTex PRS devices also had more pronounced early neovascularization and new collagen deposition. Ultimately at 24 weeks only the OviTex PRS devices had been fully remodeled to tissue with mature organized collagen.

In this preclinical study OviTex exhibited earlier host cell proliferation and earlier functional remodeling and neovascularization at the repair site as compared with Alloderm. To further understand the differences in efficacy and safety of these devices, additional preclinical studies with larger sample sizes are being considered.

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Acknowledgements: The authors would like to acknowledge the Pathology Department of CBSET Inc and particularly Dr John Keating for his histology analysis. They would also like to acknowledge Alexander Koblish for his assistance in manuscript preparation.

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Funding: Funding for this study was provided by TELA Bio, Inc.

Disclosures: NO and JK are both employees of TELA Bio, Inc. BCHM is an employee and a shareholder of Aroa Biosurgery Limited. The authors have no other relevant financial or nonfinancial interests to disclose.