

Fundamentals of Extracellular Matrix Biomaterial Assimilation: Effect of Suture Type on Attachment Strength and Cell Repopulation

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Background: The clinical results with extracellular matrix biomaterials are confounded by expectations of material response based on years of experience with permanent or degradable synthetic polymers. However, the remodeling or assimilation of extracellular matrix biomaterials is dictated by cell-mediated processes rather than fibrous encapsulation or hydrolytic degradation. Previously, we found that tissue adherence and revascularization were dictated by proximity with de-epithelialized host tissue. We now investigate the effects of polymer and fixation type on attachment strength and rate of cell repopulation in an intra-abdominal implant model.

Methods: An intra-abdominal implant model in rats was used to probe assimilation properties at 4 weeks and 12 weeks with permanent and degradable suture types as well a combination of suture and biologic attachment (mesothelial abrasion). The mechanical strength of the attachment was measured by peel testing and the repopulation by automated cell counting of histologic sections.

Results: The intensity of the biologic response was greater with degradable polymers than permanent polypropylene. Tissue attachment strength ranged from 2 to 15 N but changed in elasticity with time. The magnitude and distribution of cell repopulation was highly variable by suture type but ultimately did not affect the long-term strength of the soft tissue attachment.

Conclusions: The tissue approximating polymer sutures were stretchy and of similar strength regardless of degradation rate or polymer type. The strongest attachment, most rapid repopulation of the deep matrix regions, and most uniform distribution of cells were found with the addition of biologic attachment. (*Plast Reconstr Surg Glob Open* 2020;8:e2635; doi: [10.1097/GOX.0000000000002635](https://doi.org/10.1097/GOX.0000000000002635); Published online 20 March 2020.)

INTRODUCTION

Materials derived from the extracellular matrix (ECM) of humans or animals, ECM biomaterials,^{1,2} have been widely adopted in the United States and Europe for complex abdominal wall,³⁻⁶ breast,⁷⁻⁹ chest wall,^{10,11} and diaphragmatic reconstructions,¹² as well as a myriad of other soft tissue reinforcement applications.¹³ However, the introduction of these ECM biomaterials for soft tissue repair

have posed a particular challenge for surgeons as they are neither walled off with fibrous encapsulation like permanent synthetic polymers nor degraded at a consistent rate via hydrolysis like degradable synthetics.^{1,14,15} Instead, the post-implantation behavior of these materials is an active, cell-mediated process dependent on the wound-healing environment.¹⁴ The response can vary by the type and quantity of cells recruited as well as the external stimuli exerted on those cells from growth factors, the biochemistry of the matrix integrin interactions, and/or from mechanical loading. As a cell-based process, it can also be affected by the patient's wound-healing ability if compromised (eg, diabetes, immunosuppressive treatment, etc.), the location of material implantation, the availability of a local vascular supply, or the surgical techniques employed. Understanding the assimilation process with ECM biomaterials and the variables that affect it will ideally lead to

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adapted surgical techniques and patient selections that take advantage of these characteristics. Inversely, poor clinical outcomes with ECM biomaterials are possible when used in sub-optimal patient conditions or surgical techniques.^{16,17} For example, poor clinical outcomes have been attributed to the ECM biomaterial not “remodeling” or “integrating” but may instead be related to expectations of degradation (ie, resorb by hydrolysis) rather than the ECM biomaterial assimilation process and the environmental cues that actually dictate the response.^{18–20}

Previously, we developed an intraperitoneal implant model for investigating the parameters altering the assimilation process with ECM biomaterials including tissue approximation, injury, and distance from a vascular bed.²¹ The model compared permanent polypropylene mesh to a commercially available ECM biomaterial derived from neonatal bovine dermis. While synthetic mesh was generally encapsulated and adherent to all contacting tissues regardless of model variables, the adherence and revascularization for the ECM biomaterial was heavily influenced by local tissue approximation with injured or de-epithelialized host tissue. The results suggested that surgical techniques may be modified or refined when using ECM biomaterials to achieve desired outcomes such as tissue ingrowth, revascularization, and mechanical adherence to host tissue.

An additional modifiable surgical variable is the choice of suture material employed for securing ECM biomaterials. Suture biochemistry evokes a locally variable inflammatory response. The host response to the permanent or degradable polymers may potentially lead to significant changes in revascularization, cell repopulation, and/or strength of the mechanical attachment to host tissue that could alter clinical outcomes. Therefore, the goal of this study was to investigate the effects of polymer and fixation type on the strength of attachment and rate of cell repopulation of the matrix in an intra-abdominal implant (IAI) model. We hypothesized that increasing suture-related inflammation would increase the quantity of cells repopulating the matrix, the revascularization of the implant, and the strength of the tissue attachment.

METHODS

IAI Model and Study Design

The IAI model is described previously.²¹ In brief, 2cm by 2cm squares of neonatal bovine dermis (SurgiMend

3.0, Integra LifeSciences, Boston, Mass.) were implanted intra-abdominally, lateral to a midline incision in an IACUC approved protocol. One implant was secured by 2 sutures on each side, with 3 animals per condition and per time point (4 weeks and 12 weeks). One implant was tested for mechanical strength of the attachment and the other reserved for histology. Each suture was mechanically tested separately, resulting in 6 replicates for mechanical strength and 3 replicates for histological results. Six different conditions were tested as described in Table 1 and Figure 1.

Surgical Procedure

A total of 36 adult, male, Sprague-Dawley (~275g) rats (Charles River Laboratories, Wilmington, Mass.) were anesthetized by isoflurane, the abdomen shaved, and prepped with povidone iodine. A 4-cm incision was made through the skin and linea alba to enter the peritoneum. Bilaterally, implants were placed and sutured to the abdominal wall lateral to the midline. Transfacial sutures with knots in the subcutaneous space, and a partial thickness bite of the implant were employed to prevent suture exposure and adhesions on the visceral surface (Fig. 1). In the biologic/de-epithelialization (BIO) condition of suture plus biologic attachment, a scalpel was used to abrade the peritoneum in a 2 × 2 cm² square corresponding to area of implant contact, before implant placement. The muscle and skin were closed in layers with interrupted polypropylene suture and skin staples, respectively. Animals were housed in individual cages, monitored daily, and fed ad libitum. Skin staples were removed after 7 days.

Explantation and Tissue Harvest

Animals were euthanized at the indicated time points. Implants were visualized and photographed. Presence or absence of the suture material and characteristics of the tissue attachment were observed. The mobility of the implant was categorized as highly elastic if the implant could be pulled away from the abdominal wall >1 cm with forceps, moderately elastic if <1 cm from the abdominal wall, or stable if immobile.

The implant randomly selected for mechanical testing was bisected with scissors. An Allis clamp was placed firmly onto the implant and attached to a hand-held force transducer. The transducer was pulled uniformly away until tensile failure and the maximum load recorded.

Table 1. Suture Types and Degradation

| Trade Name | Base Material | Time to 50% Loss of Strength (days) | Time to Total Absorption (days) |
|-------------------------|--|-------------------------------------|---------------------------------|
| Vicryl Rapide (Ethicon) | 90% glycolide and 10% L-lactide (lower molecular weight than Vicryl)* | 5 | 42 |
| Vicryl (Ethicon) | 90% glycolide and 10% L-lactide† | 21 | 56–70 |
| Maxon (Covidien) | Polyglyconate, a copolymer of glycolic acid and trimethylene carbonate | 28 | 182 |
| PDS II (Ethicon) | poly (<i>p</i> -dioxanone) | 42 | 182–238 |
| Prolene (Ethicon) | Polypropylene | Permanent | Non-absorbable |

*With a coating of 90% Caprolactone and 10% glycolide followed by a mixture composed of equal parts of copolymer of glycolide and lactide (polyglactin 370) and calcium stearate.

†With a coating of copolymer of glycolide and lactide (polyglactin 370) and calcium stearate.

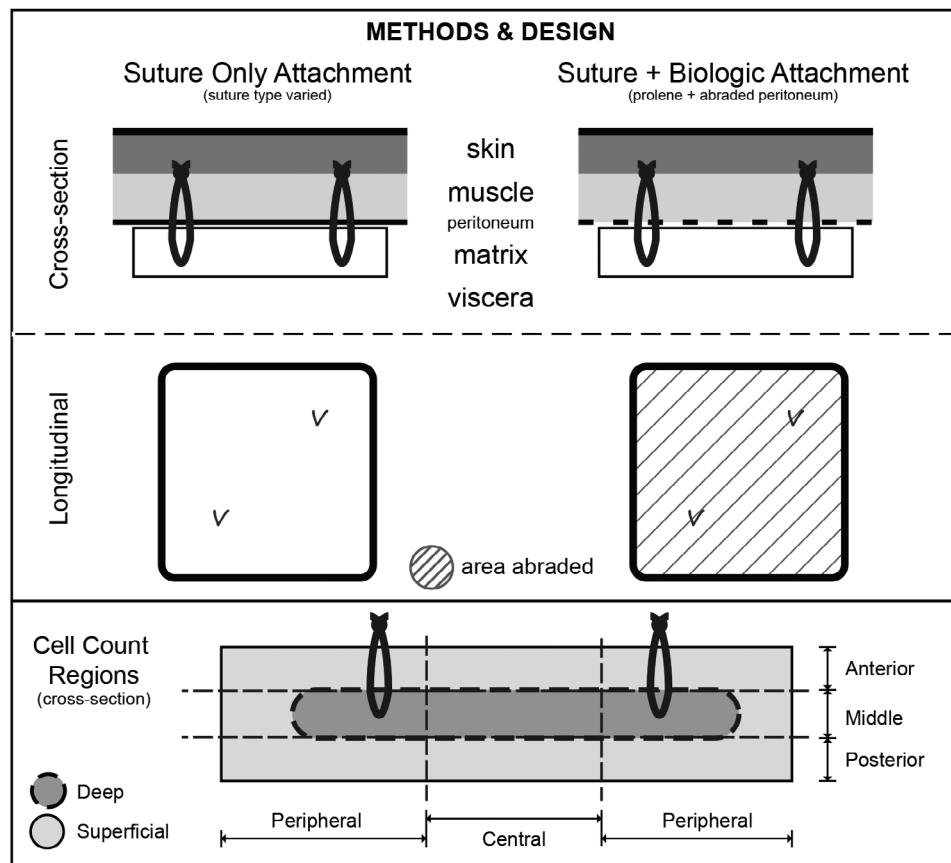


Fig. 1. Methods and experimental design: The ECM biomaterial was placed intra-abdominally shown in cross section (top) with placement of transfascial sutures (black rings) with partial bites of the implant against either the intact peritoneum (left) or against the abraded muscle (right). The area abraded and suture location are shown in longitudinal section (middle). Regions and their labels used for quantifying the regional distribution of cell repopulation by histology are depicted in relation to the location of the sutures (bottom)

The contralateral implant was excised in bulk, placed into 10% buffered formalin, and fixed for histological preparation. After 1 week of fixation, specimens were bisected diagonally, capturing a cross section through the entire implant and both suture/attachment sites. Specimens were dehydrated, paraffin embedded, sectioned 5- μ m thick, and stained with Hematoxylin and Eosin or Masson's Trichrome by a contract laboratory (Mass Histology Services, Worcester, Mass.).

Cell Counting

Stained microscope slides were digitized with a Nanozoomer whole slide imaging slide scanner (Hamamatsu, Japan). From the whole slide images, $\times 10$ images (2736 px \times 1472 px, 2.5 mm \times 1.33 mm) were captured regionally in 15 locations, mapping the entire implant cross section to avoid selection bias. Cell nuclei were counted from the H&E images using an automated open-source software (CellProfiler).²² Color images were split into R, G, and B channels, gray scaled, inverted, thresholded, and objects counted. Retained outlines were confirmed to correlate with cell nuclei by visual inspection. Based on the image size and

object counts, results were reported in cells per square millimeter.

Statistics

Results were analyzed by one-way analysis of variance (ANOVA) with $\alpha = 0.05$ assuming equal variance. A Holm-Sidak post-hoc analysis was used for multiple comparisons. Data in figures and tables are reported as means with SD.

RESULTS

Gross Observations

At the time of explantation, the gross morphology of the biologic response and tissue attachment varied by condition. Distinct tissue and discrete blood vessels were emanating from the areas of injury immediately adjacent to the suture in all conditions (Fig. 2). The intensity of this response appeared greater with degradable polymer sutures and was most intense with Vicryl and Vicryl Rapide. At 4 weeks, only the Vicryl Rapide was fully degraded (Table 2). In this condition, thin tissue attachments remained where the suture material had been present,

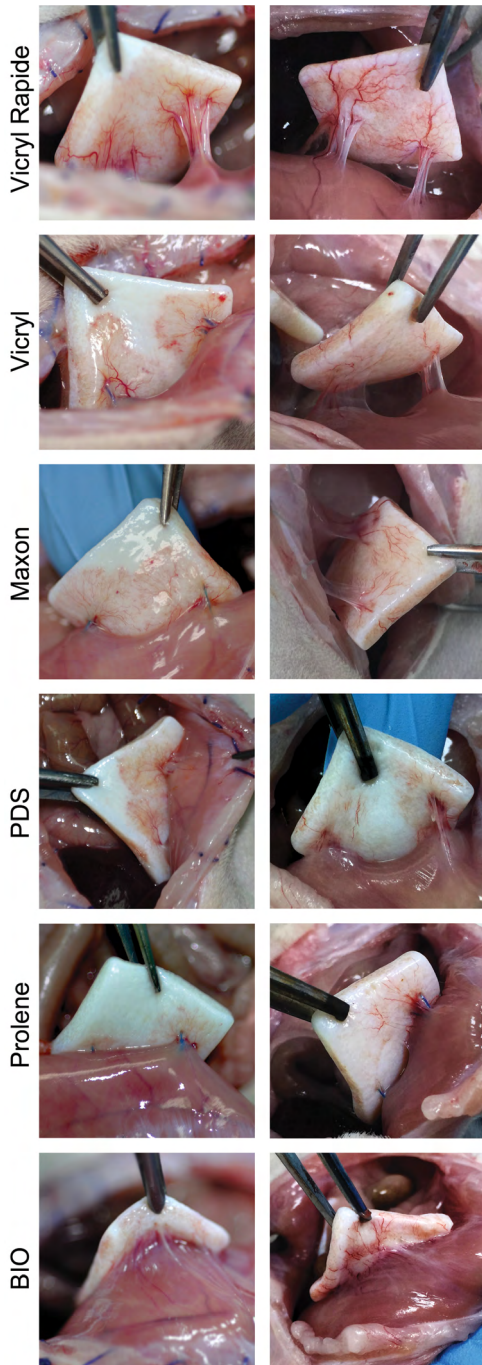


Fig. 2. Gross imaging: representative photographs of the attachments between the implanted ECM biomaterial and the abdominal wall are shown at 4 weeks (left) and 12 weeks (right) for each of the 6 conditions.

which were highly elastic and compliant. In the other conditions, sutures were still visually present and the attachment was stable. At 12 weeks, the presence of the suture could not be grossly observed with any of the degradable polymers (Fig. 2). Tissue attachments remained where the suture materials had been present, and ranged from highly elastic and compliant (Vicryl Rapide and Vicryl) to moderately elastic and compliant (Maxon and PDS)

to stable (Prolene and BIO) (Table 2). At both 4 and 12 weeks, the area of the attachment was limited to the area immediately adjacent to the suture, with the exception of the biologic attachment condition where the area of firm, stable attachment extended to between ~50% and 100% of the muscle contacting surface area (Fig. 2).

Attachment Mechanical Properties

The strength of the tissue attachment between muscle and implant was measured by mechanical testing. At the 4 week time point, the strength of each individual attachment ranged from an average low of $2.13\text{N} \pm 0.93$ for the Vicryl Rapide condition to a high of $15.23\text{N} \pm 2.82$ for the BIO condition (Table 2). The strength at 12 weeks was roughly similar, ranging from an average low of $2.89\text{N} \pm 1.48$ for the Maxon condition to a high of $12.88\text{N} \pm 5.93$ for the BIO condition (Table 2). The mechanism of tensile failure at 4 weeks for Vicryl Rapide, Vicryl, and Maxon involved the tissue attachment with or without remaining polymer breaking. With other conditions (PDS and Prolene) the suture pulled through the muscle and stayed intact. With the biologic attachment (BIO) the suture knot was cut on the anterior side of the abdominal wall before testing, therefore measuring the strength of only the tissue attachment to the abdominal wall and failing at this junction. At 12 weeks, the failure mechanism was the tissue junction for all conditions, including Prolene and BIO where the suture knot was cut on the anterior surface of the abdominal wall before testing. The strength decreased between 4 and 12 weeks for degradable polymer sutures (Fig. 3). At both 4 and 12 weeks, the strength of the biologic attachment was significantly greater than conditions with degradable sutures, and at 12 weeks was significantly greater than all other conditions ($P < 0.05$) (Fig. 3).

Histological Appearance of Attachments

The tissue attachments spanning muscle to implant were observed histologically and representative images stained with Masson's Trichrome are shown in Figure 4. No evidence of suture or degradable polymer was observed in the Vicryl Rapide condition at 4 or 12 weeks and the attachment was connective tissue consisting of loose, disorganized collagen fibers and blood vessels. For the remaining conditions, chronic inflammation and fibrosis associated with the foreign body response to the sutures was observed at the earlier, 4 week time point (Fig. 4). At 12 weeks, the tissue attachments consisted primarily of small blood vessels and collagen fibers of fibrous encapsulation (Fig. 4). In the BIO condition, implant and muscle were in tight approximation without the observable fibrous encapsulation that is seen around the polypropylene suture within the implant (Fig. 4). Under higher magnification of the muscle-to-implant junction, the collagen around the muscle fibers intertwine with the implant and a transition from host collagen and implanted collagen is difficult to discern (Fig. 5).

Cell Repopulation

Cell repopulation was mapped across the implant cross section, counting all cell nuclei, and evaluated by

Table 2. Tissue Attachment Results

| Condition | 4 weeks | | | | 12 weeks | | | |
|---------------|----------------------|--------------------|---------------------------------|---|----------------------|--------------------|---------------------------------|---|
| | Suture at Explant | Tissue Mobility | Mechanical Strength (N ± SD) | Primary Mechanical Failure Mechanism | Suture at Explant | Tissue Mobility | Mechanical Strength (N ± SD) | Primary Mechanical Failure Mechanism |
| Vicryl Rapide | Degraded | Highly Elastic | 2.13±0.93 | Tissue only | Degraded | Highly Elastic | 3.67±1.14 | Tissue only |
| Vicryl | Present | Stable | 8.76±1.36 | Suture broke | Degraded | Highly Elastic | 2.89±1.48 | Tissue only |
| Maxon | Present | Stable | 6.97±1.97 | Suture broke | Degraded | Moderately Elastic | 5.58±2.08 | Tissue only |
| PDS | Present | Stable | 8.04±3.62 | Suture pulled through muscle | Degraded | Moderately Elastic | 4.98±2.24 | Tissue only |
| Prolene | Present | Stable | 11.49±3.68 | Suture pulled through muscle | Present | Stable | 3.16**±1.87 | Tissue only* |
| BIO | Present | Stable | 15.23±2.82 | Tissue only† | Present | Stable | 12.88†±5.93 | Tissue only† |

*Suture knots were cut on the anterior side of the abdominal wall before testing at 12 weeks (but not 4).

†Suture knots were cut on the anterior side of the abdominal wall before testing at both 4 and 12 weeks.

grouping into regions. At the 4 week time point, more cells were present in the anterior third of the implant, closest to the abdominal wall, for all conditions except the BIO condition where cells were evenly distributed through the implant (Fig. 6). A trend of more cells with Vicryl Rapide and Vicryl than Maxon, PDS, and Prolene did not reach statistical significance. There were significantly fewer cells in the anterior third of Vicryl Rapide and Vicryl at 12 weeks compared with 4 weeks ($P < 0.05$, data not in figures). There were no significant differences between the distributions of cells comparing the middle of the implant (between the sutures) to the periphery of the implant (distal to the sutures) for any condition (Fig. 7). For all conditions except BIO there was a non-significant trend of increased cell quantity in the superficial portion of the implant (inclusive of anterior, posterior, and sides) compared with the deep (interior) implant (Fig. 8). For the BIO condition, the distribution was similar between deep and superficial portions of the implant (Fig. 8).

DISCUSSION

The goal of this study was to investigate the effects of polymer and fixation type on the strength of attachment and rate of cell repopulation of the matrix in an IAI model. Previous work with this model demonstrated that SurgiMend was adherent when placed in tight approximation with injured (de-epithelialized) host tissue, but not adherent in areas of loose approximation or when placed against intact, uninjured mesothelium.²¹ The qualities of this attachment, including the strength and effect on cell repopulation of the implant were characterized in this study.

By gross observation, blood vessels emanating from the abdominal wall into the matrix were more pronounced with degradable suture materials than permanent polypropylene sutures. By 12 weeks, the degradable sutures were either largely or totally gone, leaving only tissue connecting and affixing the matrix to the abdominal wall.

In all conditions, with intact sutures, the implant remained stable and firmly fixed to the abdominal wall. However, once the polymer suture degraded, the remaining attachment was a thin, elastic, and compliant/stretchy connective tissue. This tissue attachment after suture degradation was characterized as loose, and the implant was mobile upon mechanical manipulation (Table 2). The direct measurement of the strength of these attachments at 4 weeks considered both the tissue formed around the suture, as well as the remaining strength of the suture, resulting in values between 2 and 8 Newtons for degradable sutures. By 12 weeks, only the strength of the tissue attachment was measured and remained in a similar range of ~3-6N. The strength of the attachment with a non-degradable suture (Prolene) is predicted to remain unchanged with time. In this study, the Prolene knot was cut on the anterior abdominal wall before testing at 12 weeks and therefore only tested the tissue attachment strength, which was notably lower. The biologic tissue attachment condition (after the Prolene stitch was cut) was twice as strong at 4 and 12 weeks than the

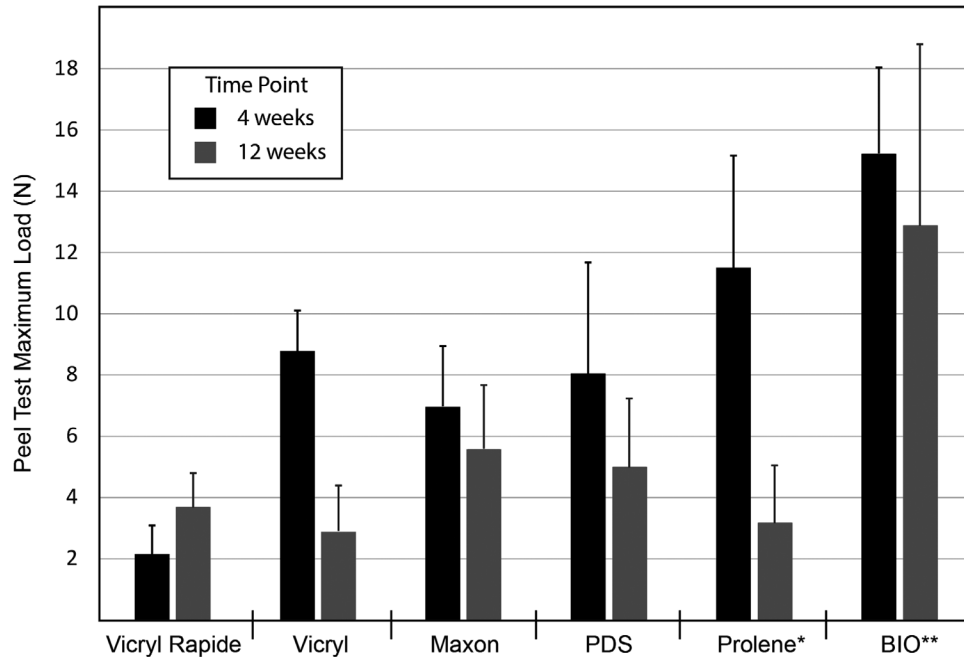


Fig. 3. Attachment mechanical properties: the average ultimate tensile load from the peel testing is reported for each of the conditions at 4 and 12 weeks. *Suture knots were cut on the anterior side of the abdominal wall before testing at 12 weeks (but not 4). **Suture knots were cut on the anterior side of the abdominal wall before testing at both 4 and 12 weeks.

other conditions, excluding intact permanent suture. In essence, once the polymer was degraded or the polymer stitch was cut, the strength of the remaining tissue was similar, regardless of polymer type, and lower than the strength of the biologic attachment.

Inflammation was directly associated with the suture material, being observed histologically in the immediate peri-suture regions. Inflammation was highest with Vicryl Rapide and Vicryl, and lowest with Prolene. These differences affected the magnitude, rate, and the spatial distribution of the cells repopulating the matrix. With increased inflammation, more cells were counted at the 4 week time point, particularly on the anterior surface of the implant closest to the abdominal muscle. This effect diminished with time, leaving fewer and more evenly distributed cells. However, with the lower inflammation Prolene condition, areas of the implant, particularly in the central third, were virtually cell free at 4 weeks and remained low at 12 weeks. Overall, a significant trend was seen with an outside-in repopulation with more cells in the superficial/exterior portions of the implant in all conditions except the biologic/de-epithelialization condition. In this condition (Prolene + abraded peritoneum), an even distribution of cells was found throughout the implant at both time points, in quantities significantly higher than with Prolene alone.

We hypothesized that increasing localized inflammation would increase the magnitude of cell repopulation and the strength of the tissue attachment. While inflammation did appear to affect the magnitude and distribution of cells, this ultimately did not translate to an effect on the strength of the tissue attachment. The resulting

tissue that encapsulated the polymer until it degraded was stretchy, elastic, and of similar strength regardless of the polymer biochemistry or degradation rate. The strongest attachment with most rapid and even repopulation of the deeper matrix regions was found with the addition of biologic attachment (ie, abrasion of peritoneum) despite the use of the least inflammatory suture fixation material.

There are several limitations to the study. The revascularization of the implant was evaluated both by gross observation and histology, but was not directly quantified, instead using cell numbers as a proxy. Future work will utilize perfusion imaging modalities to capture quantitative, as well as functional, information on revascularization. Furthermore, only total cell numbers were evaluated, not cell type or morphology. The various cells recruited and/or their differentiation within the implant may provide significant information, and therefore warrants further investigation, and is a key element of our future research work. Further, only one ECM biomaterial was used in the experiment. With the widely disparate post-implantation properties of these materials resulting from source and processing variables,¹ the applicability of these results to other ECM biomaterials may be limited.

Unlike permanent materials that are encapsulated with a thin layer of fibrous connective tissue, or degradable synthetic polymers that resorb via hydrolysis, ECM biomaterials are assimilated and remodeled in a cell-dependent manner. This difference is acutely transparent in this model system, where the ECM biomaterial was not associated with a classic foreign body response (Fig. 5). Instead, localized inflammation is seen around the polymeric

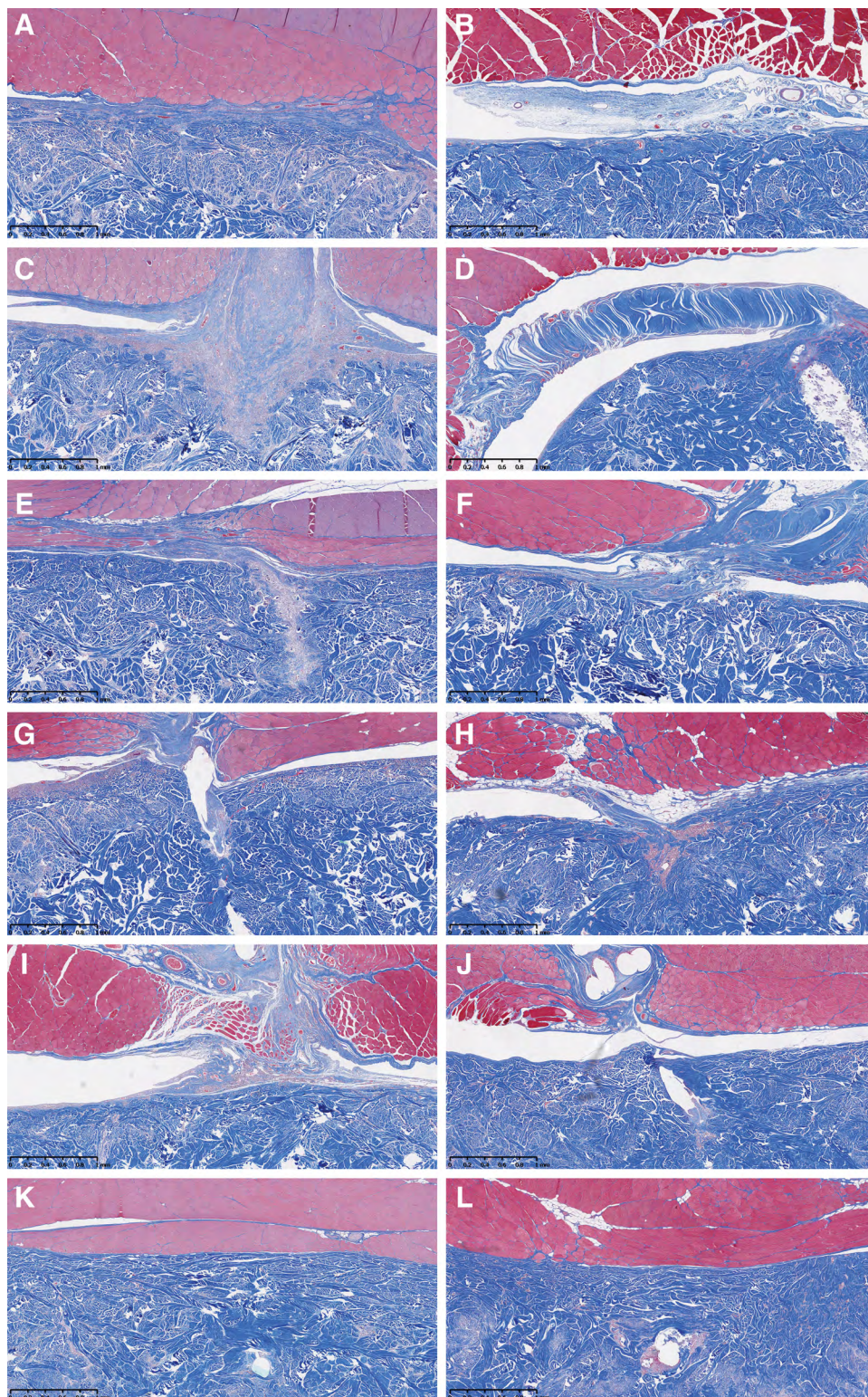


Fig. 4. Histology of the attachments: representative images of Masson's Trichrome stained sections at the interface of the muscle and implant in the region nearest the suture material at 4 weeks (A,C,E,G,I, and K) and 12 weeks (B,D,F,H,J, and L) are shown for Vicryl Rapide (A,B), Vicryl (C,D), Maxon (E,F), PDS (G,H), Prolene (I,J), and BIO (K,L).

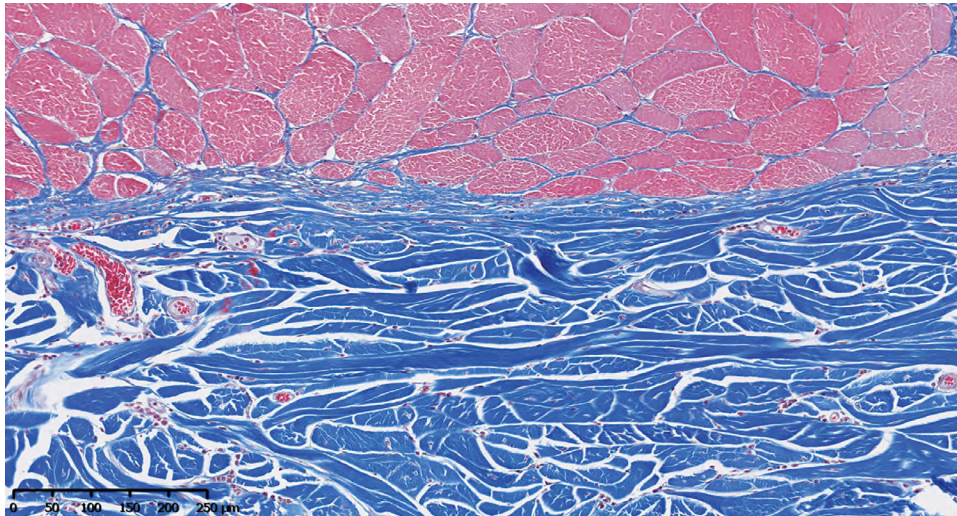


Fig. 5. High magnification (x20) image of the muscle-to-implant interface in BIO condition with Masson's trichrome staining at 12 weeks. Notably absent is a foreign body encapsulation response at the muscle-to-implant interface.

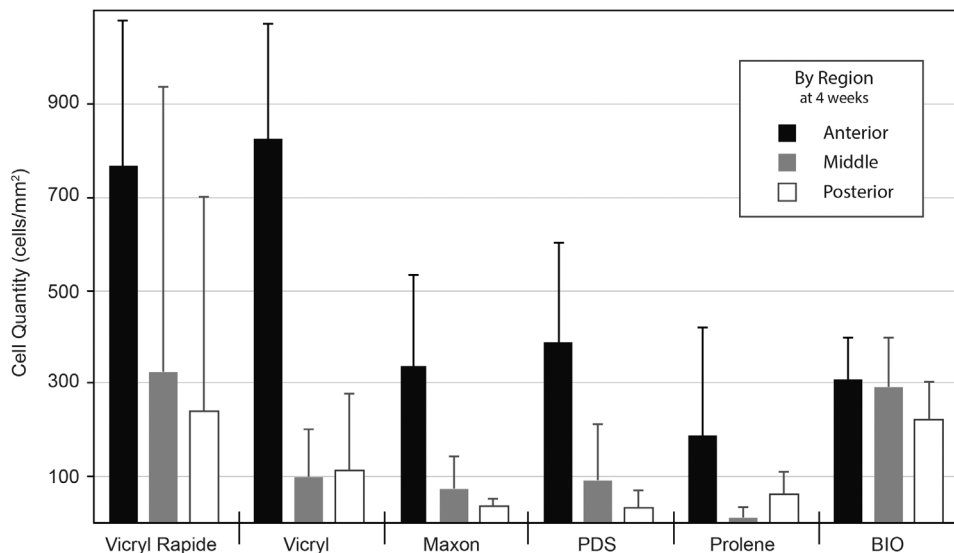


Fig. 6. Cell repopulation of implant by region (anterior, middle, and posterior) at 4 weeks: The average cell density in cells per mm were measured via whole slide imaging in geographic regions (see Fig. 1) representing the anterior (side against the abdominal muscle) 1/3rd, middle 1/3rd, and posterior (side facing the viscera) 1/3rd. More cells were seen early in the anterior region with degradable polymers while the most consistent and uniform population at both early and late timepoints were seen with the BIO condition.

suture materials within the implant. This matrix can be repopulated with host cells but is not associated with rapid degradation. Furthermore, unlike the synthetic polymers that predictably resorb, leaving a thin, elastic, and mechanically weak capsule tissue, the assimilation and remodeling response with SurgiMend is dictated most strongly by environmental cues. This response appears to have more similarities to homeostatic tissue remodeling, as seen during skin expansion or during developmental growth, than to a synthetic material with a foreign body response.²³

CONCLUSIONS

Localized inflammation varied by suture type affecting the magnitude and distribution of cells repopulating the matrix, but ultimately did not affect the strength of the tissue attachment to the abdominal wall. The resulting tissue that encapsulated the polymer sutures was stretchy and of similar strength regardless of degradation rate or polymer type. The strongest attachment, most rapid repopulation of the deep matrix regions, and the most uniform distribution of cells were found with the addition of biological attachment (ie, abrasion of peritoneum). Improved

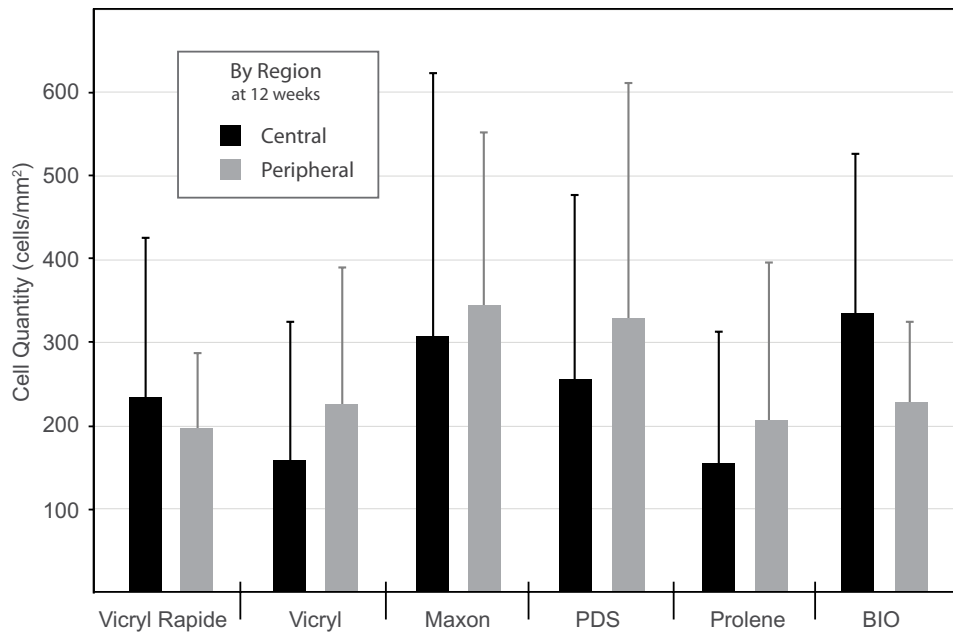


Fig. 7. Cell repopulation of implant by region (central versus peripheral): the average cell density in cells per mm were measured via whole slide imaging in geographic regions (see Fig. 1) representing the central (middle 1/3rd of the cross section) and the peripheral (outer 1/3rd on either side of the implant). No significant differences were seen suggesting an even distribution longitudinally through the implant.

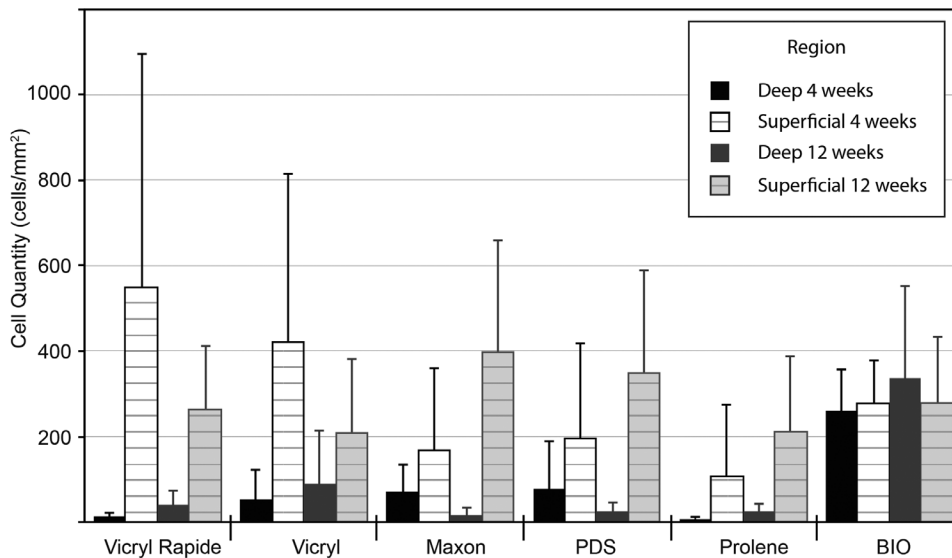


Fig. 8. Cell repopulation of implant by region (interior versus exterior): the average cell density in cells per mm were measured via whole slide imaging in geographic regions (see Fig. 1) representing the interior (middle portions) versus the exterior (top, bottom, and sides of the cross section) at both 4 and 12 weeks. More cells were seen in the exterior regions than the interior. The most consistent and uniform population at both early and late timepoints were seen with the BIO condition.

understanding of these parameters could potentially impact surgical decisions to improve patient outcomes when using ECM biomaterials for soft tissue reinforcement. For instance, a combination of suture materials and tissue conditions may ultimately lead to a proper balance of integration and remodeling. This concept deserves

further testing in animal models and may ultimately lead to changes in practice when using these materials in patients.

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