ARTICLE REVIEW

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Macrophage phenotype as a predictor of constructive remodeling following the implantation of biologically derived surgical mesh materials.

Brown BN, Londono R, Tottey S, Zhang L, Kukla KA, Wolf MT, Daly KA, Reing JE, Badylak SF†. Acta Biomater. 2012 Mar; 8(3):978-87.

Key Findings

The study evaluated the relationship between macrophage phenotype and host response for 14 different extracellular matrix (ECM) devices within a rat injury model. The MatriStem UBM™ (Urinary Bladder Matrix) technology group demonstrated increased numbers of M2 macrophages and higher M2:M1 macrophage ratios within the site of remodeling at both 14 and 35 days. Implant devices associated with an early, elevated presence of the M2 macrophage phenotype were correlated with a site-appropriate tissue remodeling response (which the authors defined as constructive remodeling).

The peer-reviewed data presented within this Article Review was conducted on a small animal model not pursuant to Good Laboratory Practices (GLP). Many of the products reported are no longer made commercially available by the respective manufacturers. The preclinical results may not directly reflect outcomes in human patients.

Introduction

Macrophages are a type of white blood cell that play a role in wound healing by clearing damaged tissue or foreign material from the site of injury and by facilitating tissue remodeling. Immature macrophages are recruited from the blood stream in response to injury, infectious microorganisms, or foreign objects such as medical devices. Research has shown that these immature macrophages generally polarize toward two main phenotypes referred to as type 1 (M1) and type 2 (M2)[1,2]. The M1 phenotype is considered pro-inflammatory and is characterized by secretion of inflammatory signaling factors, production of reactive oxygen species, antigen presentation, and fibrosis. In contrast, the M2 phenotype is considered anti-inflammatory and is associated with secretion of anti-inflammatory, pro-remodeling signaling factors and new tissue deposition.

Study Design

A 1 cm^2 defect was created in the external and internal oblique muscles of rats and repaired with one of 14 different commercially available ECM devices. Tissue biopsies taken at days 14 and 35 post-surgery were used to assess the tissue remodeling outcomes. Histological scoring was assigned based on cellular infiltration, the presence of multinucleated giant cells, vascularity, connective tissue organization, encapsulation, product degradation, and the presence of muscle cells. Macrophage presence and phenotype within and surrounding the implant sites was also examined through immunohistochemical staining for cell surface markers associated with M1 and M2 macrophage phenotypes. An M2:M1 ratio was calculated for each device by quantifying positive staining for M2 and M1 macrophages within tissue samples.

Results

Although the 14 ECMs showed varying degrees of cellular infiltration, vascularization, connective tissue deposition, and tissue remodeling, they were able to be semi-quantitatively categorized into one of three groups:

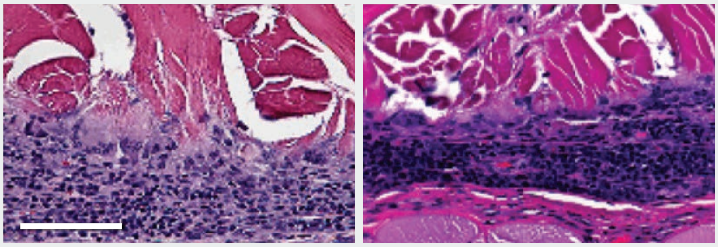
GROUP 1 **Encapsulation**	GROUP 2 **Integration**	GROUP 3 **Site-Appropriate Tissue Remodeling**
Chronic inflammation and foreign body response.	Early immune cell infiltration with decreased cellularity and little evidence of site-specific cells at later time points.	Early infiltration by immune cells and signs of site-specific cells at later time points.

Histological Sampling Testing

The representative photomicrographs from the histological staining in Figure 1 and the histological score chart in Figure 2 summarize the results of the histological sampling testing.

FIGURE 1*
Representative Photomicrographs at 14 Days and 35 Days

Collamend - Crosslinked Porcine Dermis

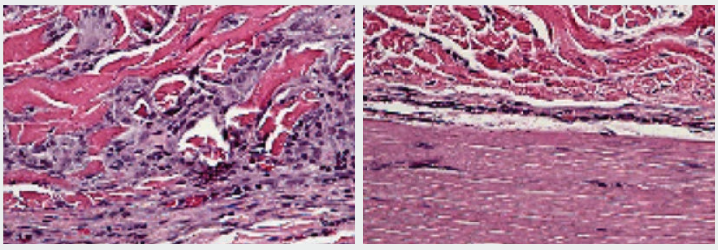


14 Days | 35 Days

Group 1 (Encapsulation) ECMs had:

- Little to no cellular infiltration or vasculature
- Dense fibrous capsule surrounding implant
- Little to no device degradation
- No muscle ingrowth

InteXen - Porcine Dermis

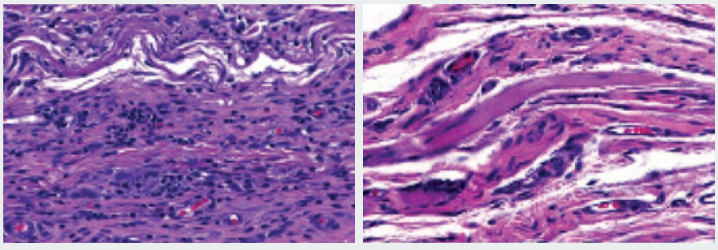


14 Days | 35 Days

Group 2 (Integration) ECMs had:

- Limited vascularization
- Dense infiltration of mononuclear cells
- Limited device degradation or tissue deposition
- No obvious fibrous encapsulation

MatriStem UBM



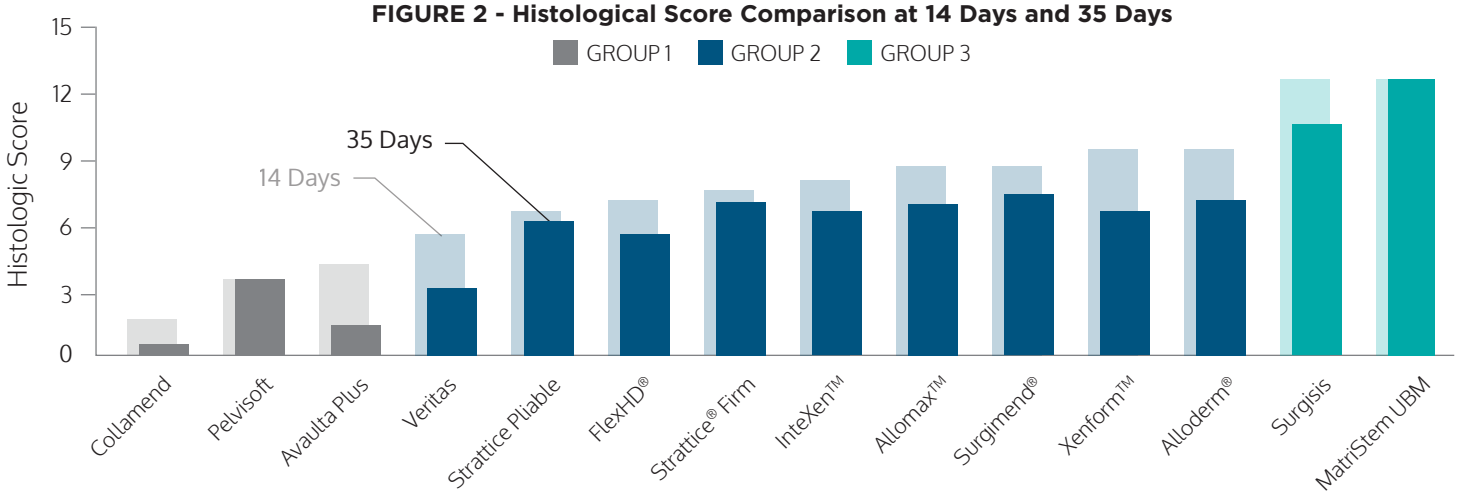
14 Days | 35 Days

Group 3 (Site-Appropriate Tissue Remodeling) ECMs had:

- Dense cellular infiltration, vasculature present throughout the device
- Organized connective tissue deposition
- Rapid device degradation
- Islands of skeletal muscle at the surgical site

* Photomicrograph images are at 40x magnification. Scale bars = 100 µm

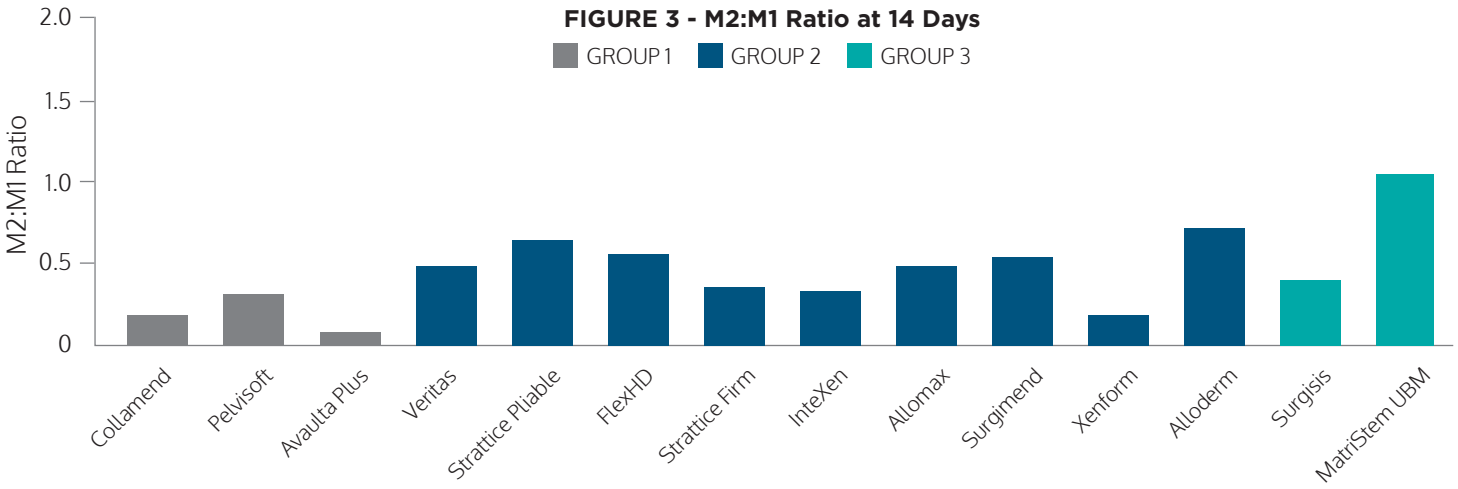
FIGURE 2 - Histological Score Comparison at 14 Days and 35 Days



Macrophage Phenotype Testing

Macrophage phenotype cell staining at 14 days showed Group 1 ECMs were associated with a predominantly M1 phenotype, Group 2 were associated with a mix of M1 and M2 phenotypes, and Group 3 were associated with a mix of M1 and M2 phenotypes, but with an increased M2 phenotype at the periphery of the remodeling site. The study found a strong, statistically significant correlation between the histologic scores and macrophage phenotype (both the number of M2 cells and the ratio of M2:M1 cells) at 14 days, suggesting that early phenotype distribution could be a predictor for long-term remodeling outcomes. Figure 3 shows the ratio of M2:M1 expressing cells at 14 days. Quantitative results are presented as the mean for each sample type (n=2).

FIGURE 3 - M2:M1 Ratio at 14 Days



Study Discussion and Conclusion

This study showed that the body responds in dramatically different ways to various ECM materials. The authors stated that the macrophage phenotypic response was likely due to multiple aspects of the implanted material, such as surface topology, available ligands, processing and/or degradability. The ECMs categorized into Group 1 were predominantly chemically crosslinked materials. ECMs in Group 2 were predominantly dermis-derived materials, which generally require a more robust process for decellularization due to their density. The MatriStem UBM technology from Group 3 utilizes minimal processing, which may support the early strong M2 macrophage phenotype and positive host tissue response with evidence of site-specific tissue remodeling. Authors noted that more research into macrophage polarization patterns would be beneficial for better understanding the role of macrophages in tissue remodeling post device placement.

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