

## Tissue Augmentation with OPEN DERMAL MATRIX™ Technology

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### Objectives

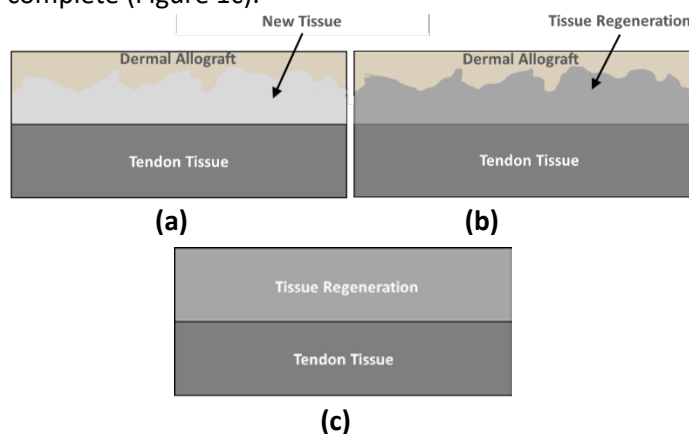
OPEN DERMAL MATRIX™ Technology (ODM) describes a decellularized dermal allograft processed using a proprietary method resulting in an open (i.e. porous) structure. Dermal allografts have been successfully used for tissue augmentation.<sup>1,2</sup> In this paper, we describe tissue augmentation with ODM Allograft.

Specifically, the objectives of this study are to characterize the integration of ODM Allograft compared to traditional dermal allografts and to illustrate how integration of dermal allografts with host tissue could lead to tissue regeneration.

We hypothesize that the use of ODM Allograft may expedite the process of dermal allograft integration, as a porous dermal allograft could lead to faster tissue regeneration by providing more channels for host cells to penetrate and ultimately form new tissue.

### Methods

Integration is defined as the formation of new tissue from the host tissue into the dermal allograft (Figure 1a). Tissue regeneration is initiated when the newly formed tissue is remodeled to a host-like tissue (Figure 1b). Once the dermal allograft has been completely replaced by host-like tissue, the tissue regeneration process is complete (Figure 1c).



**Figure 1.** A schematic illustrating the process of tissue regeneration. Tendon tissue is used as an example of host tissue. (a) An integrated human dermis (formation of new tissue into the dermal allograft). (b) Initiation of the tissue regeneration process (new tissue remodeled to tendon-like tissue). (c) Completion of the tissue regeneration process (dermal allograft has completely been replaced by tendon-like tissue).

To illustrate the mechanism of ODM Allograft integration with host tissue, we conducted a preclinical study to observe the integration of ODM Allografts compared to traditional dermal allografts. The results from the preclinical study were considered along with the existing scientific literature to better understand both the timing of dermal allograft integration with tendon tissue and the timing of tissue regeneration.

- **Pre-clinical study: ODM Allograft vs. traditional dermal allograft**

A pre-clinical, Good Laboratory Practice (GLP) study was conducted to assess the local tissue response and integration of dermal allograft with host tissue following dermis implantation at 1, 6, and 12 wks.<sup>3</sup>

Subcutaneous pockets (implant sites) were created on the back of 15 athymic (immunocompromised) rats. For each animal, two subcutaneous pockets were created – one cranial and the other caudal – on each side of the spinal column. Each pocket was implanted with an ODM Allograft [Custom Mitek - custom dermis processed for Mitek Sports Medicine (freeze dried); Coll-E-Derm™<sup>§</sup> (frozen), Parametrics Medical, Leander, TX] or traditional dermal traditional dermal allografts [GraftJacket™ (freeze dried dermis), Wright Medical, Memphis, TN; ArthroFLEX® (wet dermis), Arthrex, Naples, FL; MemoDerm™ (freeze dried), Stryker, Allendale, NJ]. The 15 rats were assigned to implant schemes 1 through 5 (3 rats/scheme) (Table 1). Throughout the study, assessments of general health and body weight measurements were performed.

		Subcutaneous Implant Sites			
		Left Side		Right Side	
		Cranial	Caudal	Cranial	Caudal
Implant Scheme	1	Coll-E-Derm	ArthroFLEX	Custom Mitek	GraftJacket
	2	ArthroFLEX	GraftJacket	MemoDerm	Custom Mitek
	3	GraftJacket	Custom Mitek	Coll-E-Derm	MemoDerm
	4	Custom Mitek	MemoDerm	ArthroFLEX	Coll-E-Derm
	5	MemoDerm	Coll-E-Derm	GraftJacket	ArthroFLEX

§: The current product commercialized under the Coll-E-Derm trademark is different than the product used in this study. Therefore, the results reported here related to Coll-E-Derm are not applicable to the current product commercialized under the Coll-E-Derm trademark.

**Table 1.** Animal Implant Scheme Assignment

At 1, 6, and 12 weeks post-implantation, one animal from each implant scheme was arbitrarily selected and euthanized (5 animals/time point; N = 4/test article). The implant sites were photographed and macroscopically examined for infection, appearance, redness, discoloration, and signs of encapsulation. Each implant site as well as out-of-package samples (non-implanted samples) were fixed in 10% neutral buffered formalin. After fixation, samples were processed for histological assessment, sectioned, and stained with hematoxylin and eosin (H&E).<sup>3,4</sup> The excised implants were microscopically scored by a NAMSA certified pathologist for integration (ingrowth) using the grading criteria shown in Table 2.

Grade	Description
0	No ingrowth
1	Poor, inconsistent or limited focal penetration of the article by individual cells or by very fine strands of fibroplasia or fibrous tissue
2	Fair, multifocal or diffuse penetration of the article by individual cells or thin bands of fibroplasia or fibrous tissue
3	Good, consistent deep penetration of the article by bands of fibroplasia or fibrous tissue
4	Excellent, article completely penetrated by bands of fibroplasia or fibrous tissue

**Table 2.** Integration Grading Criteria

In addition to integration, local reactivity, encapsulation, penetration of the article by blood vessels, extracellular material remaining, remodeling, and evidence of immune response were examined.

The actual number of sites evaluated microscopically at 1 and 12 weeks was reduced because in some instances, the implant was not in the sectioning plane or it had migrated. At the 1-week time point, sample size was reduced from 4 to 3 for GraftJacket, ArthroFLEX, and Coll-E-Derm. At the 12-week time point, sample size was reduced from 4 to 3 for Custom Mitek, ArthroFLEX, and Coll-E-Derm. The study was not powered for statistical significance.

- **Existing literature summary: traditional dermal allograft**

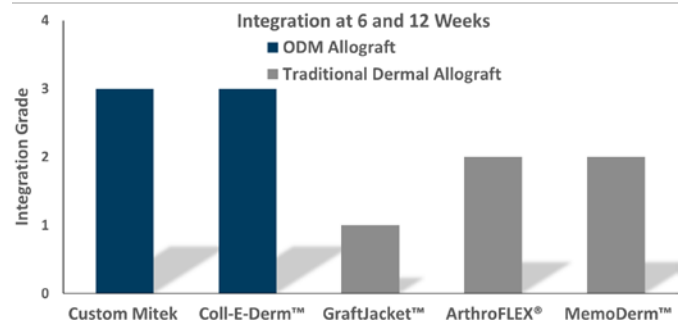
A literature search was conducted to identify peer reviewed clinical studies that assessed human dermis integration with tendon tissue.

## Results

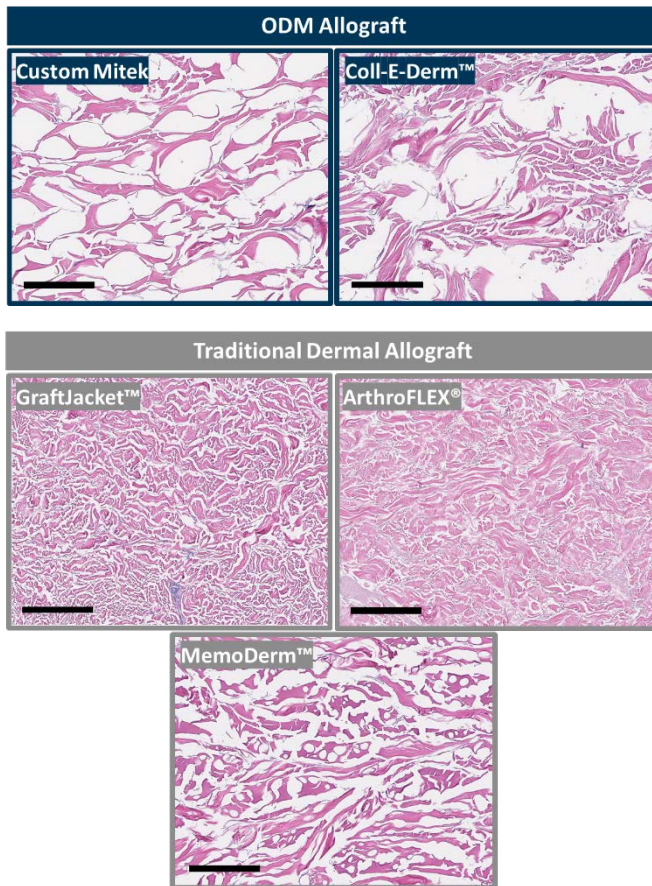
- **Pre-clinical study: ODM Allograft vs. traditional dermal allograft**

The GLP study indicates that ODM Allografts integrates in a markedly different manner than traditional dermal allografts (Figure 2). Specifically, at both 6 and 12-weeks, “Good” integration of the ODM Allografts was observed<sup>3</sup> (Custom Mitek: 3-Good; Coll-E-Derm: 3-Good). By contrast, “Poor” or “Fair” integration grades was recorded for each of the traditional dermal allografts (GraftJacket: 1-Poor; ArthroFLEX: 2-Fair; MemoDerm: 2-Fair). The results also show that more blood vessels penetrate into the ODM Allografts than into traditional dermal allografts at both 6 and 12 weeks. All tested articles scored “Poor” or “Fair” for integration at 1 week. This was expected, as this is an early time point in the integration process. No substantial differences between ODM Allografts and traditional dermal allografts for any other assessed parameter at any time point was noted.<sup>3</sup>

Histological images of out-of-package samples (non-implanted samples) clearly show that the ODM Allografts have more openings than the traditional dermal allografts<sup>4</sup> (Figure 3).



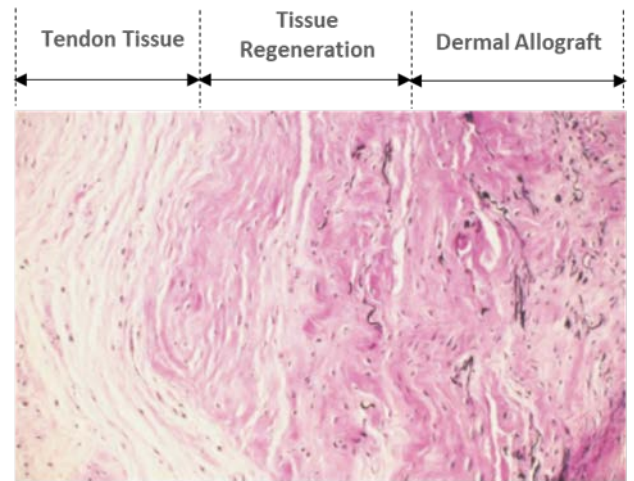
**Figure 2.** Integration grades. For all the tested articles, the same integration grade was reported at both 6 and 12 weeks. 6 weeks sample size: Custom Mitek - N = 4; Coll-E-Derm - N = 4; GraftJacket - N = 4; ArthroFLEX - N = 4; MemoDerm - N = 4. 12 weeks sample size: Custom Mitek - N = 3; Coll-E-Derm- N = 3; GraftJacket - N = 4; ArthroFLEX - N = 3; MemoDerm - N = 4.



**Figure 3.** Histological images of out-of-package samples (non-implanted samples). Scale bar: 200 microns.

- **Existing literature summary: traditional dermal allograft**

Peer reviewed clinical studies have reported the integration of traditional dermal allografts with tendon tissue when used for Achilles tendon augmentation<sup>5,6</sup> as well as for rotator cuff augmentation.<sup>7</sup> The results show that traditional dermal allograft integration occurs by 2 months.<sup>5</sup> At the 3-month time point, the integration process has advanced to a level that the new tissue formed into the traditional dermal allograft has remodeled to a tendon-like tissue, which is strongly suggestive of tissue regeneration (Figure 4).<sup>7</sup>



**Figure 4.** A histological image showing that a portion of the implanted dermal allograft has been replaced by tendon-like tissue indicative of tissue regeneration. Histological image was adapted from Snyder *et al.* 2009.<sup>7</sup>

## Conclusion

Reports in the scientific literature provide strong support for the idea that rotator cuff augmentation with a traditional dermal allograft is likely to reduce the incidence of rotator cuff re-tears.<sup>1,2</sup> However, it is unclear how augmentation with human dermis could reduce the incidence of rotator cuff re-tears. One possible explanation is that augmentation with human dermis results in a more robust rotator cuff via the process of dermal allograft integration.

According to the literature summary, traditional dermal allograft integrates with host tissue and remodels to tendon-like tissue, which is strongly suggestive of tissue regeneration.<sup>7</sup> The process of integration leads to an increase in tissue thickness. We surmise that because thicker tissue is stronger than thinner tissue, it is less prone to tears. As most rotator cuff re-tears are initiated in the tendon tissue<sup>8</sup>, tendon augmentation with human dermis may reduce the risk of rotator cuff re-tears.

Our results also show that, in an animal model, there are clear differences in integration between ODM Allografts and traditional dermal allografts. Specifically, ODM Allografts integrate better than the tested traditional dermal allografts at 6- and 12-weeks post-implantation.

Both the literature summary and our preclinical study provide support for the idea that the beneficial effects of traditional dermal allograft augmentation<sup>1,2</sup> may be more pronounced when an ODM Allograft is used. Note that the pre-clinical data presented here may not be representative of the findings for human clinical use as presented in the literature summary findings synopsis.

## References

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