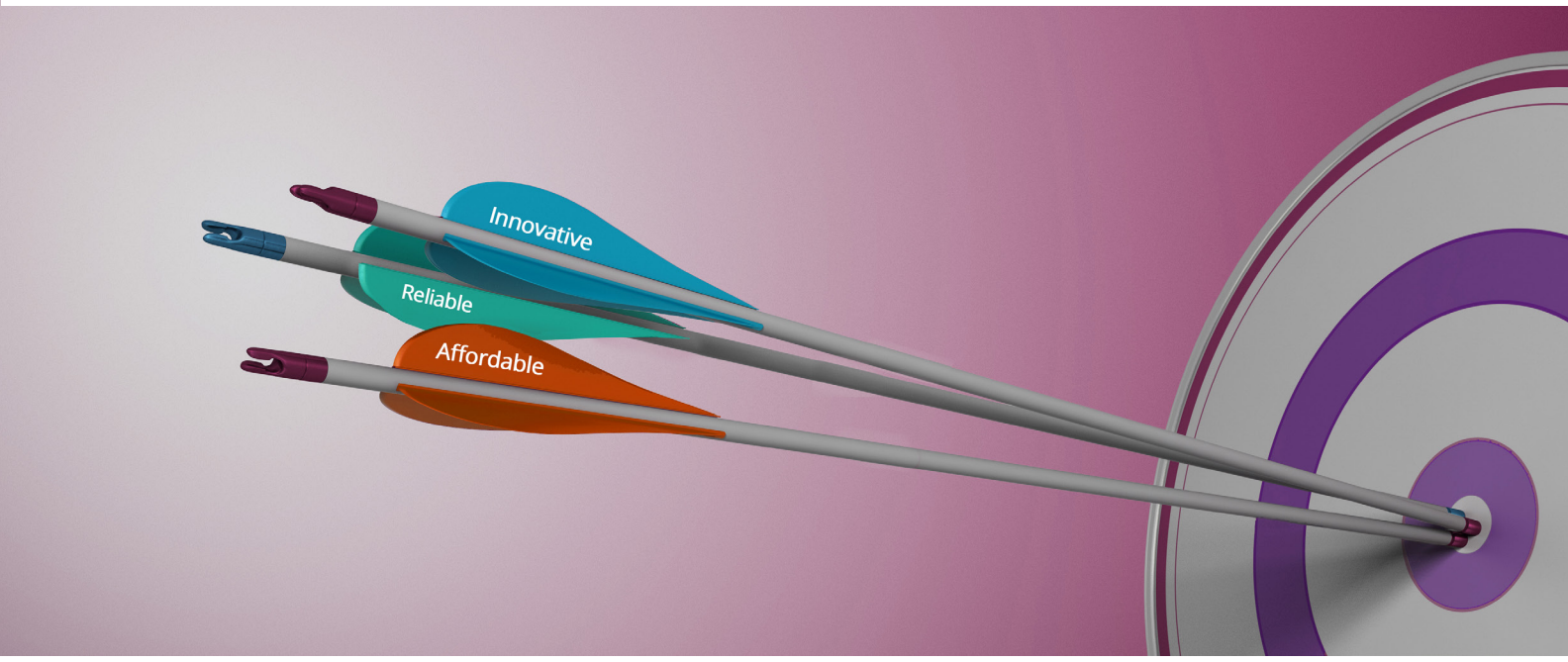
InnovaMatrix®
Platform Technology



A Targeted Approach to Material Selection

The InnovaMatrix® platform offers the first and only placental-derived extracellular matrix medical devices cleared by the FDA for wound management. Combining the inherent benefits of the placenta[1,2] with the reliability, reproducibility and safety profile of a medical device,[3,4] InnovaMatrix® products are next-generation technology for hard-to-heal wounds.

A New Category
of Advanced Biologic Wound Dressings

Until recently, clinicians who have wanted to utilize ECMs to treat their patients have been limited to choosing products from two categories: placental allografts (human cells, tissues, and cellular and tissue-based products or HCT/Ps) or xenograft-derived medical devices.

Graft inconsistency has long been an issue for ECMs due to:

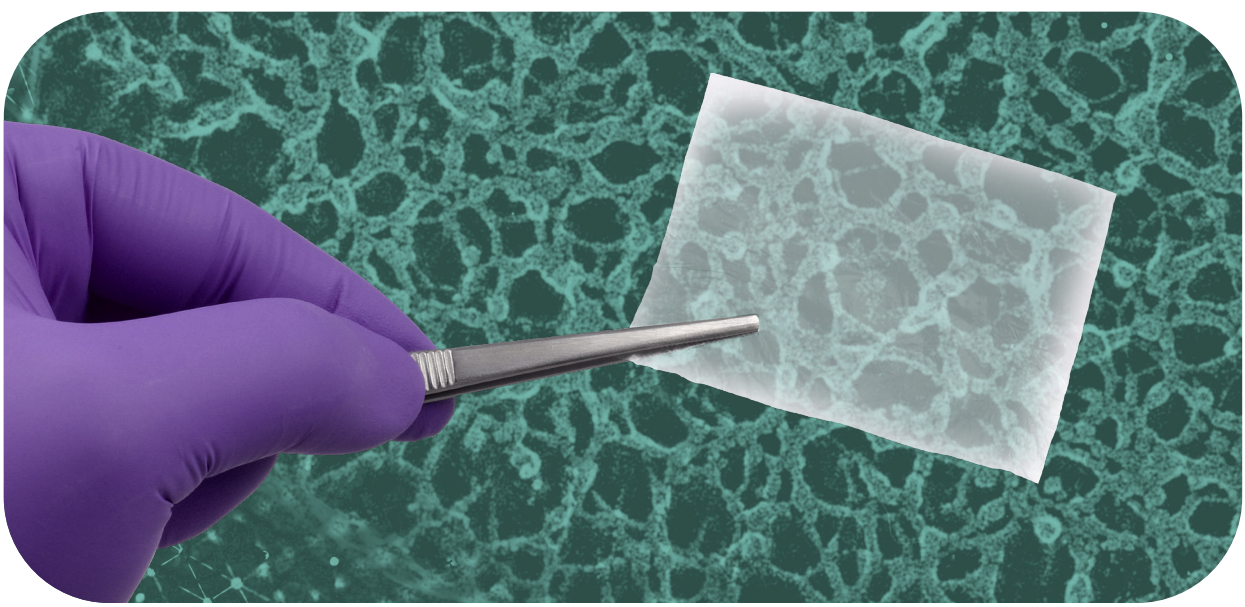
- Variability of human donated placentas[5,6]
- Limitations to processing of the membrane[7]
- Cellular remnants and debris remain in the ECM[4]
- Age of the source tissue[8]

The porcine placenta source is an ideal material for ECMs because it supports fetal growth and development and is a relatively young organ whose age corresponds to the gestation period. In addition, a significant number of scientific studies support its use as a wound dressing.[9-11]

The placenta contains a unique and high component combination of functional ECM molecules. It is inherently young tissue that provides protection and regenerative properties during human fetal development, including:

- Elastin[9]
- Hyaluronic Acid[10]
- Sulfated GAGs[10]
- Laminin and Fibronectin[11,12]

The InnovaMatrix® technology platform gives clinicians a new, next-generation option for managing complex surgical, traumatic and hard-to-heal wounds. InnovaMatrix® products feature the benefits of the placenta[1,2] along with the reliability, reproducibility and safety profile of a medical device.[3,4]



Processing Matters

The state-of-the-art TriCleanse™ Process was developed and has been validated to sterilize tissue, inactivate viruses and thoroughly decellularize the ECM while maintaining the structural components of the ECM.[3,4,13,14] The combination of the inherent advantages of the placenta[1,2] and thorough decellularization[4] via the TriCleanse™ Process yields the first-ever placental-derived medical devices for wound management.

Processing for ECM membranes has evolved over time and is performed by numerous tissue bank processors. It is essential to understand that not all processes are similar.

Process variables can include:

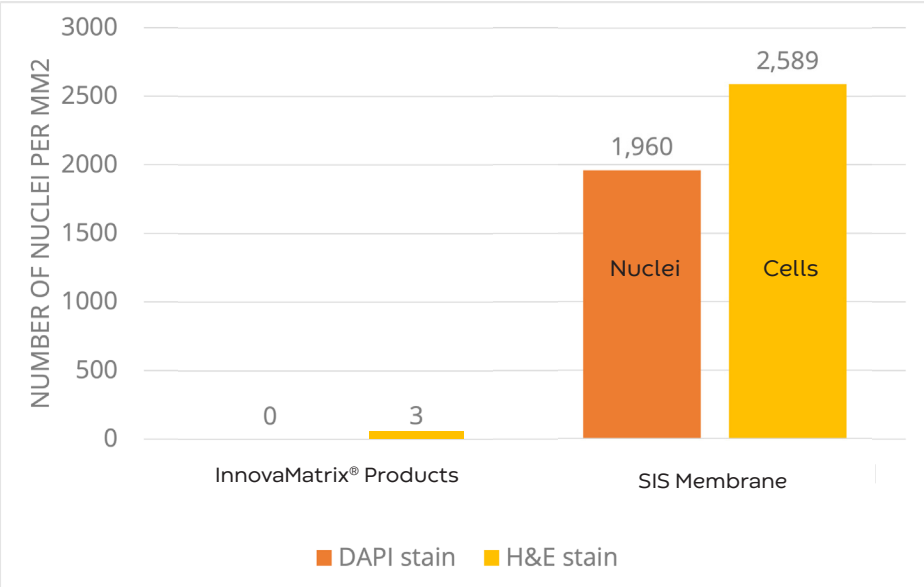
- Heated drying
- Antibiotics
- Fixation chemicals
- Oxidizing agents

These variables may affect the processed tissue in multiple ways, including residuals from the processing chemicals, presence of antibiotics, and moisture content. Those variations can impact performance and safety of the device. Our proprietary TriCleanse™ Process thoroughly decellularizes the ECM while leaving the structural and functional proteins intact in the final product.

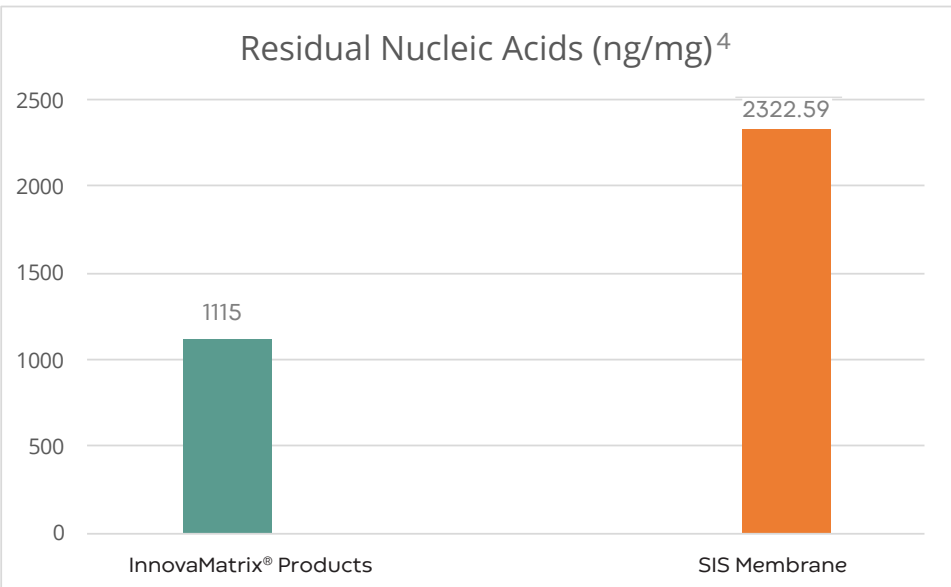
Balancing Decellularization Efficiency and the Denaturing of ECM Proteins

As placental medical devices processed with the proprietary TriCleanse™ Process, InnovaMatrix® products were biochemically characterized extensively to identify and quantify the different structural and functional proteins. These results were then compared to a SIS membrane device as a base line for comparison.

Cellular Debris Comparison[4]

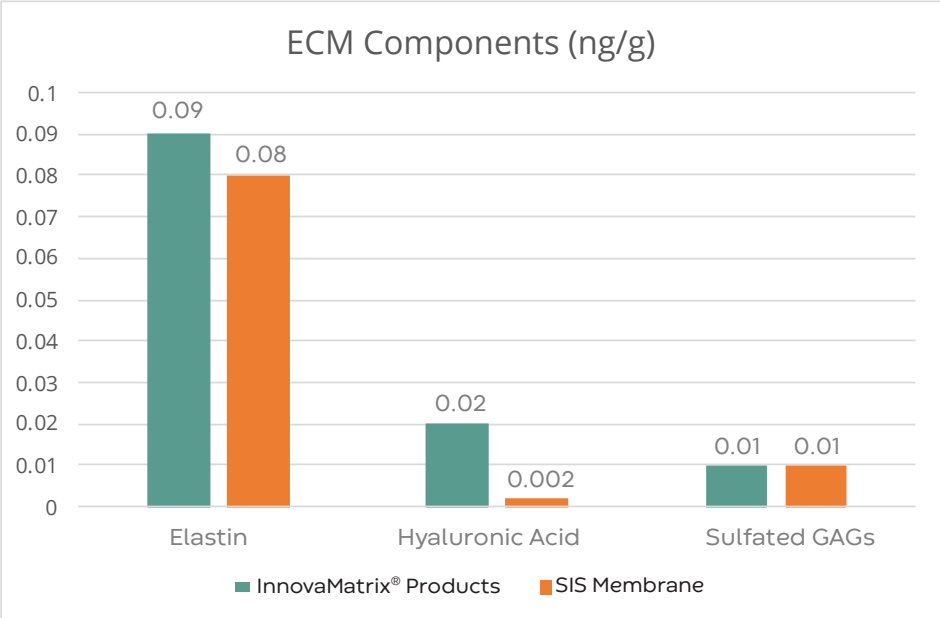


The presence of intact cells and nuclei creates an immunogenic response as cellular antigens are recognized as foreign by the host's immune system.

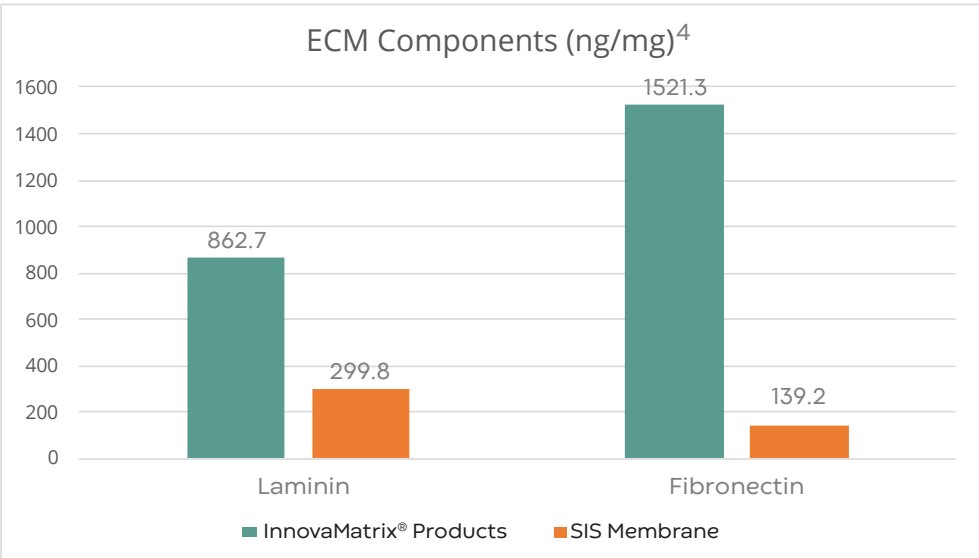


The immune system has the innate capability to recognize nucleic acids not contained within the nucleus via pattern recognition receptors and mount an inflammatory response to their presence.[15,16]

Naturally Occurring Proteins Content[4]



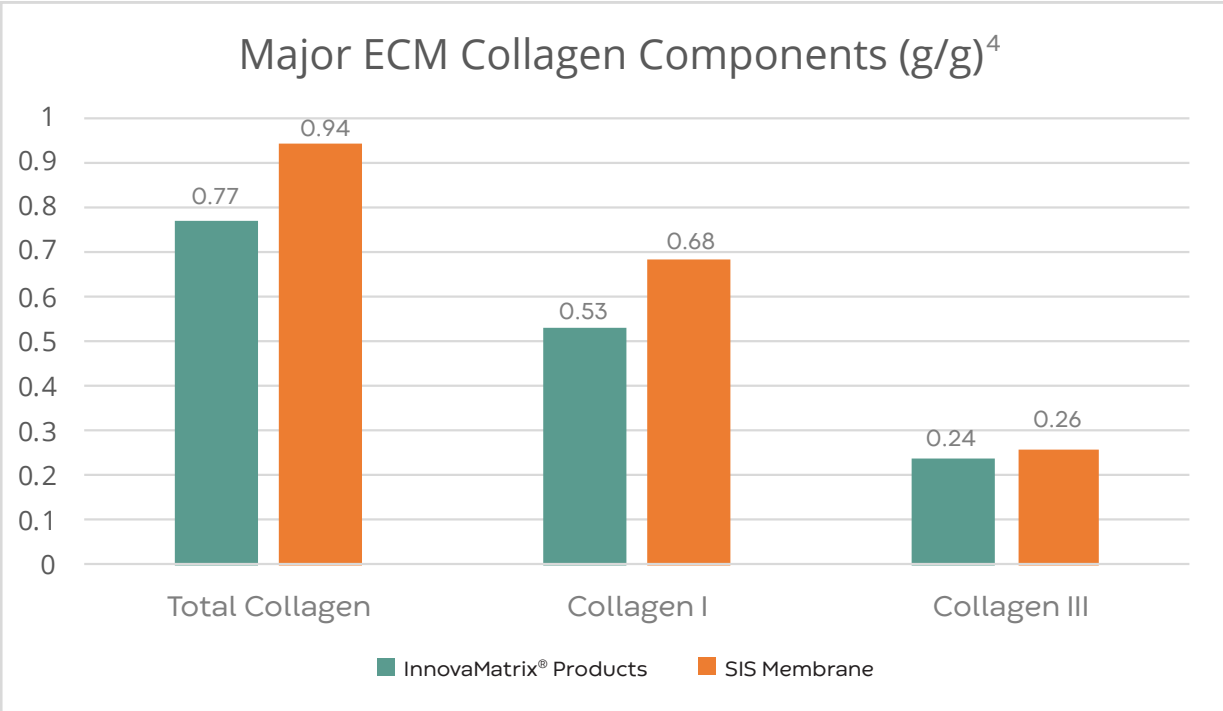
Functional ECM molecules have an active role in wound healing. Hyaluronic Acid has been demonstrated to play an important role in all stages of wound healing.[17]



Laminin, a basement membrane protein, plays a critical role in the regulation of cell adhesion, motility, survival, and differentiation and is therefore critical for wound healing.[18]

Fibronectin, an adhesive glycoprotein, plays a crucial role in wound healing, particularly during ECM formation and re-epithelialization.[19]

Collagen Content



Collagen is an important structural protein in ECM materials, but lower collagen content allows for higher content of other molecules.[4]

Conclusion

This comparison demonstrates that InnovaMatrix® products and the SIS membrane device have similar biochemical constituents, but the quantities of those constituents vary between the two products. While the SIS membrane contains slightly greater quantities of Collagen I, it also contains a slightly more denatured collagen than the InnovaMatrix® devices. In addition, InnovaMatrix® devices have 10 times the amount of Hyaluronic Acid, approximately 3 times the amount of Laminin, and 11 times the amount of Fibronectin than that of the SIS membrane.

In addition to these varying quantities of proteins, the amount of cellular debris and nucleic acid found in the two ECMs also varies greatly. The SIS-based device, despite claiming decellularization, has 2 times the amount of nucleic acid debris and more than 1,000 times more cells and cellular debris than that found in InnovaMatrix® products. The comparison found that InnovaMatrix® products contain virtually no intact cells or cellular debris and very little remaining nucleic acid, which demonstrates the decellularization efficiency of Convatec's proprietary TriCleanse™ Process.

Based on this comparison, InnovaMatrix® devices have slightly less denatured collagen and a more thoroughly decellularized scaffold, as well as containing higher amounts of functional proteins. This evidence indicates that InnovaMatrix® medical devices make excellent wound scaffolds that could support the host to heal the wound.

Process Flow Chart

Material Source

Production begins with a carefully selected tissue that is sourced from a highly controlled, monitored, and exclusive facility. The site is certified to ISO 13485:2016 and ISO 9001:2015 standards and compliant with the FDA's Good Manufacturing Practices in 21 CFR 820. In addition, the raw placental tissues are compliant with ISO 22442-2 standards.

Physical Processing

The placental tissue undergoes thorough bulk washing, which removes surface contaminants, residual blood, and amniotic fluid.

TriCleanse™ Process

The placental tissue is subjected to a series of chemical baths and washes that disinfect and decellularize the tissue.

Preservation

The tissue is dried.

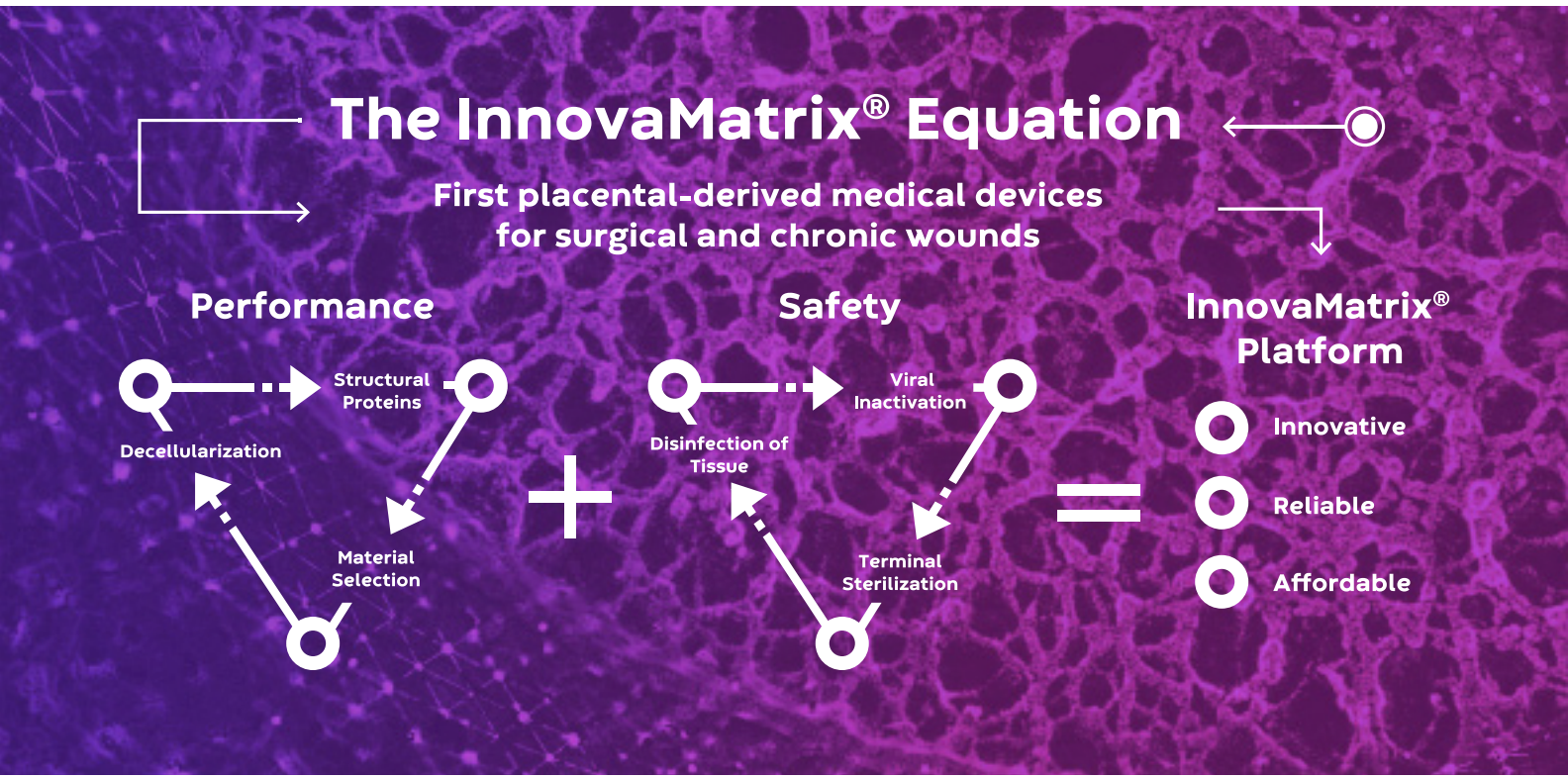
Final Processing

The dried tissue is processed to its final configuration.

Sterilization

The tissue is terminally irradiated to a SAL 10^{-6}.

1. Shaifur Ra, M., Islam, R., Asaduzzama, S.M., & Shahedur R, M. (2015). Properties and Therapeutic Potential of Human Amniotic Membrane. Asian Journal of Dermatology, 7(1), 1-12. doi: 10.3923/ajd.2015.1.12 **2.** Fairbairn, N. G., Randolph, M. A., & Redmond, R. W. (2014). The clinical applications of human amnion in plastic surgery. Journal of Plastic, Reconstructive & Aesthetic Surgery, 67(5), 662-675. **3.** K193552 510(k) Summary **4.** Data on file - RDR-002 **5.** Cardinal, L. J. (2015). Central tendency and variability in biological systems. J Community Hosp Intern Med Perspect, 5(3), 27930. doi:10.3402/jchimp.v5.27930 **6.** O'Huallachain, M., Karczewski, K. J., Weissman, S. M., Urban, A. E., & Snyder, M. P. (2012). Extensive genetic variation in somatic human tissues. Proc Natl Acad Sci U S A, 109(44), 18018-18023. doi:10.1073/pnas.1213736109 **7.** https://www.fda.gov/regulatory-information/search-fda-guidance-documents/regulatory-considerations-human-cells-tissues-and-cellular-and-tissue-based-products-minimal **8.** Collier, A. C., Tingle, M. D., Paxton, J. W., Mitchell, M. D., & Keelan, J. A. (2002). Metabolizing enzyme localization and activities in the first trimester human placenta: the effect of maternal and gestational age, smoking and alcohol consumption. Hum Reprod, 17(10), 2564-2572. doi:10.1093/humrep/17.10.2564 **9.** Hieber AD, Corcino D, Motosue J, Sandberg LB, Roos PJ, Yu SY, Csiszar K, Kagan HM, Boyd CD, Bryant-Greenwood GD. Detection of elastin in the human fetal membranes: proposed molecular basis for elasticity. Placenta. 1997 May;18(4):301-12. doi: 10.1016/ s0143-4004(97)80065-3. PMID: 9179924. **10.** Steele VS, Froseth JA. Effect of gestational age on the biochemical composition of porcine placental glycosaminoglycans. Proc Soc Exp Biol Med. 1980 Dec;165(3):480-5. doi: 10.3181/00379727-165-41008. PMID: 7465562 **11.** Wewer U, Albrechtsen R, Manthorpe M, Varon S, Engvall E, Ruoslahti E. Human laminin isolated in a nearly intact, biologically active form from placenta by limited proteolysis. J Biol Chem. 1983 Oct 25;258(20):12654-60. PMID: 6415055 **12.** Isemura M, Yamaguchi Y, Munakata H, Aikawa J, Kan M, Yamane I, Yosizawa Z. Isolation and characterization of human placenta fibronectin. J Biochem. 1984 Jul; 96(1):163-9. doi: 10.1093/oxfordjournals.jbchem.a134808. PMID: 6436230. **13.** Data on file - TR-0103 **14.** Final Report: Evaluation of the host response to wound care products in a chronic wound model **15.** Gürtler C, Bowie AG. Innate immune detection of microbial nucleic acids. Trends Microbiol. 2013 Aug;21(8):413-20. doi: 10.1016/j.tim.2013.04.004. Epub 2013 May 29. PMID: 23726320; PMCID: PMC3735846. **16.** Schlee M, Hartmann G. Discriminating self from non-self in nucleic acid sensing. Nat Rev Immunol. 2016 Sep;16(9):566-80. doi: 10.1038/nri.2016.78. Epub 2016 Jul 25. PMID: 27455396; PMCID: PMC7097691 **17.** Litwiniuk M, Krejner A, Speyrer MS, Gauto AR, Grzela T. Hyaluronic Acid in Inflammation and Tissue Regeneration. Wounds. 2016 Mar;28(3):78-88 **18.** Malinda KM, Wysocki AB, Koblinski JE, Kleinman HK, Ponce ML. Angiogenic laminin-derived peptides stimulate wound healing. Int J Biochem Cell Biol. 2008;40(12):2771-80 **19.** Grinnell F, Billingham RE, Burgess L. Distribution of fibronectin during wound healing in vivo. J Invest Dermatol. 1981 Mar;76(3):181-9



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