

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization

International Bureau



(10) International Publication Number

WO 2018/140853 A1

(43) International Publication Date

02 August 2018 (02.08.2018)

(51) International Patent Classification:

A61L 27/18 (2006.01) *A61L 27/34* (2006.01)
A61L 27/24 (2006.01) *A61L 27/36* (2006.01)

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

(21) International Application Number:

PCT/US2018/015684

Published:

- with international search report (Art. 21(3))

(22) International Filing Date:

29 January 2018 (29.01.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/452,000 30 January 2017 (30.01.2017) US

(71) **Applicant:** LIFECELL CORPORATION [US/US]; One Millennium Way, Branchburg, NJ 08876-3876 (US).

(72) **Inventors:** CHEN, Yi; 62 Canal View Drive, Lawrenceville, NJ 08648 (US). COLLINS, Sean; 575 Sierra Vista Lane, Valley Cottage, NJ 10989 (US). HUANG, Li Ting; 405B Olive Street, Branchburg, NJ 08853 (US). STEC, Eric; 3 Washington Square Circle, Washington, NJ 07882 (US). XU, Hui; 10 Daisy Court, Plainsboro, NJ 08536 (US).

(74) **Agent:** VAN EMAN, Matthew R. et al.; McCarter & English, LLP, 265 Franklin Street, Boston, MA 02110 (US).

(81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) Title: TRANSGLUTAMINASE TREATED PRODUCTS

(57) **Abstract:** The present application relates to use of transglutaminases to treat various products, including medical devices such as tissue grafts, tissue matrices or other tissue-derived materials, and synthetics. The transglutaminases can be applied to the medical devices to provide advantages such as adhesion resistance or abrasion resistance.

TRANSGLUTAMINASE TREATED PRODUCTS

[0001] This application claims priority under 35 U.S.C. § 119 to US Provisional Application Number 62/452,000, filed January 30, 2017, the entire contents of which are incorporated herein by reference.

[0002] The present disclosure relates to tissue products, including tissue matrices that are treated with or incorporate a transglutaminase coating.

[0003] Various tissue-derived products are used to regenerate, repair, or otherwise treat diseased or damaged tissues and organs. Such products can include intact tissue grafts or acellular or reconstituted acellular tissues (e.g., acellular tissue matrices from skin, intestine, or other tissues, with or without cell seeding). Such products can also include hybrid or composite materials, e.g., materials including a synthetic component such as a polymeric mesh substrate with a coating or covering that includes materials derived from tissue.

[0004] Tissue products, including acellular tissue matrices, can be used for a variety of load bearing or regenerative applications. In many situations, the tissue matrices are subject to mechanical forces including bending, stretching, compression, or shear stress. These forces can lead to damage or degradation to the tissue products or to surrounding tissues that may rub against the implanted products. To prevent or reduce wear and damage to the implanted tissue products or surrounding tissues, it may be desirable to produce tissue products that have improved resistance to wear or damage (e.g., flaking or other damage), especially at the tissue surfaces.

[0005] Accordingly, the present application provides devices and methods that provide modified tissue products with transglutaminase coatings. The devices and methods can provide one or more of improved resistance to surface damage,

improved resistance to wear, resistance to formation of adhesions with surrounding tissues, or reduced friction when in contact with other materials.

SUMMARY

[0006] In one embodiment, a medical device is provided. The device can include an implant main body portion comprising a collagen-containing tissue matrix; and a transglutaminase coating disposed on at least a portion of the outer surface, wherein the coating provides at least one of an anti-adhesion or anti-abrasion property to the outer surface.

[0007] In another embodiment, a method of producing a tissue product is provided. The method can include selecting a collagen-containing tissue matrix; applying a composition comprising a transglutaminase enzyme to the collagen-containing tissue matrix; and allowing the transglutaminase to perform an enzymatic activity on the collagen-containing tissue matrix to produce a region of the collagen-containing tissue matrix having at least one of an anti-adhesion or anti-abrasion property.

[0008] In one embodiment, a medical device is provided. The device can include an implant main body portion comprising a collagen-containing tissue matrix; and a surface region comprising a portion that has been treated with a transglutaminase coating, wherein the surface region provides at least one of an anti-adhesion or anti-abrasion property to the outer surface.

[0009] Also provided are methods of treatment using the presently disclosed devices as well as tissue products produced according to the disclosed methods.

DESCRIPTION OF THE DRAWINGS

[0010] Fig. 1 provides a perspective view of a tissue product including a transglutaminase coating, according to various embodiments.

[0011] Fig. 2 provides a side end view of a tissue product including a transglutaminase coating, according to various embodiments.

[0012] Fig. 3 provides a side end view of a tissue product including a transglutaminase coating and a supportive substrate material, according to various embodiments.

[0013] Fig. 4 is a cross-sectional view of an abdominal wall treated using tissue products of the present disclosure.

DESCRIPTION OF CERTAIN EXEMPLARY EMBODIMENTS

[0014] Reference will now be made in detail to certain exemplary embodiments according to the present disclosure, certain examples of which are illustrated in the accompanying drawings. Wherever possible, the same reference numbers will be used throughout the drawings to refer to the same or like parts.

[0015] In this application, the use of the singular includes the plural unless specifically stated otherwise. In this application, the use of “or” means “and/or” unless stated otherwise. Furthermore, the use of the term “including”, as well as other forms, such as “includes” and “included”, is not limiting. Any range described herein will be understood to include the endpoints and all values between the endpoints.

[0016] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in this application, including but not limited to patents,

patent applications, articles, books, and treatises, are hereby expressly incorporated by reference in their entirety for any purpose.

[0017] Various human and animal tissues can be used to produce products for treating patients. For example, various tissue products for regeneration, repair, augmentation, reinforcement, and/or treatment of human tissues that have been damaged or lost due to various diseases and/or structural damage (e.g., from trauma, surgery, atrophy, and/or long-term wear and degeneration) have been produced. Such products can include, for example, acellular tissue matrices, tissue allografts or xenografts, and/or reconstituted tissues (i.e., at least partially decellularized tissues that have been seeded with cells to produce viable materials).

[0018] A variety of tissue products have been produced for treating soft and hard tissues. For example, ALLODERM® and STRATTICE™ (LIFECELL CORPORATION, Branchburg, NJ) are two dermal acellular tissue matrices made from human and porcine dermis, respectively. Although such materials are very useful for treating certain types of conditions, it may be desirable to modify the tissue matrices or other tissue products to alter the surface mechanical properties, to improve resistance to wear or damage, to prevent development of adhesions with surrounding tissues, or to reduce friction when the tissue products are in contact with other materials such as body tissue.

[0019] Accordingly, in one embodiment, a medical device is provided. The device can include an implant main body portion comprising a collagen-containing tissue matrix; and a transglutaminase coating disposed on at least a portion of the outer surface, wherein the coating provides at least one of an anti-adhesion or anti-abrasion property to the outer surface.

[0020] In another embodiment, a method of producing a tissue product is provided. The method can include selecting a collagen-containing tissue matrix; applying a composition comprising a transglutaminase enzyme to the collagen-containing tissue matrix; and allowing the transglutaminase to perform an enzymatic activity on the collagen-containing tissue matrix to produce a region of the collagen-containing tissue matrix having at least one of an anti-adhesion or anti-abrasion property.

[0021] In one embodiment, a medical device is provided. The device can include an implant main body portion comprising a collagen-containing tissue matrix; and a surface region comprising a portion that has been treated with a transglutaminase coating, wherein the surface provides at least one of an anti-adhesion or anti-abrasion property to the outer surface.

[0022] Also provided are methods of treatment using the presently disclosed devices as well as tissue products produced according to the disclosed methods.

[0023] Transglutaminases are enzymes expressed in bacteria, plants, and animals that catalyze the binding of gamma-carboxamide groups of glutamine residues with amino groups of lysine residues or other primary amino groups. Transglutaminases are used in the food industry for binding and improving the physical properties of protein rich foods such as meat, yogurt, and tofu. Transglutaminases are also currently being explored for use in the medical device industry as hydrogels and sealants. See Aberle, T. et al., "Cell-type Specific Four Component Hydrogel," PLoS ONE 9(1): e86740 (Jan. 2004).

[0024] Fig. 1 provides a perspective view of a tissue product including a transglutaminase coating, according to various embodiments. Fig. 2 provides a side end view of a tissue product including a transglutaminase coating, according to

various embodiments. Fig. 3 provides a side end view of a tissue product including a transglutaminase coating and a supportive substrate material, according to various embodiments.

[0025] As shown, the tissue products 10, 10' can include a sheet of material, but the tissue products can include any shape, size, or configuration selected based on a desired use or clinical indication. For example, the sheets 10, 10' can be useful for surgical treatment of a variety of conditions such as abdominal wall treatment, breast augmentation or reconstruction, skin treatment (e.g., for burn or ulcer treatment), urologic treatment, orthopedic treatment (e.g., tendon, ligament, bone, cartilage, or connective tissue treatment), neurological treatment (e.g., as dura replacement), thoracic wall treatment, or other soft tissue treatment. In addition, other shapes such as irregular or bulk-like masses (e.g., for soft tissue regeneration, fistula treatment, or bone defect filling) can be used. Whatever the shape, the tissue product will include a main body portion 12, 12' including a collagen-containing tissue product (discussed below) with one or more surfaces 14, 16 (i.e., a top surface 14 or bottom surface 16 if in a sheet like configuration) that can be treated to include a region 18, 18', 20, 20' having a transglutaminase coating or section of matrix that has been treated to enzymatically alter the tissue matrix.

[0026] The transglutaminase coating region or region that has been treated (regions 18, 18', 20, 20') can be formed in a variety of suitable ways. For example, the transglutaminase can be provided in a solution or formed into a solution from a stored form (e.g., a dry powder or other suitable storage form). The solution can include any suitable buffer such as phosphate buffered saline or other biologically compatible buffer material that will maintain or support enzymatic activity and will not damage the enzyme or tissue product.

[0027] A variety of transglutaminases can be used including any that are biologically compatible, can be implanted in a patient, and have sufficient activity to provide desired catalytic results within a desired time frame. Transglutaminases are known and can include microbial, plant, animal, or recombinantly produced enzymes. Depending on the specific enzyme used, modifications such as addition of cofactors, control of pH, or control of temperature or other environmental conditions may be needed to allow appropriate enzymatic activity. Microbial transglutaminases can be effective because they may not require the presence of metal ions, but any suitable transglutaminase may be used.

[0028] The enzymatic solution can be applied to the surface of the tissue products 10, 10' using any suitable mechanical means. For example, the enzyme can be applied by simple brushing, spraying, dipping, rolling, syringe spackling, or any other suitable process. The enzyme can be applied to one or more than one surface. For example, for a sheet product, the enzyme can be applied to one side of the tissue product, allowed to dry, and then applied to the other side. Alternatively, the enzyme can be applied to more than one side (e.g., by dipping), and the product can be allowed to dry by hanging or any other suitable process.

[0029] After application of the transglutaminase to the tissue product, the enzyme may be allowed to cause enzymatic changes for a desired period of time. The specific time during which the enzyme is applied and allowed to cause enzymatic changes will depend on the concentration and amount of enzyme, the specific tissue, and/or other factors such as temperature and pH that may affect the enzymatic reaction.

Next, the tissue product may be treated to inactivate and/or dry the composition. The transglutaminase can be inactivated, for example, by heating. The heat can be

selected to deactivate the enzymes without causing undesired alteration in the tissue underlying the coating. For example, to deactivate the enzyme, the tissue can be heated to about 80 °C or other temperatures depending on the specific enzyme being used. After deactivation, the tissue can be dried, e.g., by freeze drying or air drying.

[0030] Alternatively or in addition to deactivation, the enzymes may be washed from the tissue product after causing changes in the tissue composition. For example, the enzymes can be washed using aqueous solutions such as saline (e.g., phosphate buffered saline) or other solutions that do not damage the product.

[0031] The tissue product used to produce the devices described herein can include a variety of materials. Generally, the tissue products 10, 10' will include a collagen-containing tissue matrix having amino acid residues that can be acted on by the transglutaminase coating, and which can form a suitable material for tissue treatment, e.g., for tissue repair or regeneration.

[0032] The tissue product 10, 10' can include a tissue matrix, such as a decellularized or partially decellularized tissue matrix. Examples of tissues that may be used can include, but are not limited to, skin, parts of skin (e.g., dermis), fascia, muscle (striated, smooth, or cardiac), pericardial tissue, dura, umbilical cord tissue, placental tissue, cardiac valve tissue, ligament tissue, tendon tissue, blood vessel tissue (such as arterial and venous tissue), cartilage, bone, neural connective tissue, urinary bladder tissue, ureter tissue, and intestinal tissue. For example, a number of biological scaffold materials that may be used for the first component are described by Badylak *et al.*, "Extracellular Matrix as a Biological Scaffold Material: Structure and Function," *Acta Biomaterialia* (2008), doi:10.1016/j.actbio.2008.09.013.

[0033] The tissue product, in addition or alternatively to using an intact acellular tissue matrix sheet or other form, can include a tissue matrix that is processed and reformed into a sponge or similar material incorporating particulate or reconstituted tissue matrix. For example, a tissue matrix sponge can be formed by cutting, grinding, or chopping tissue matrix to produce particles or fragments. The particles or fragments can then be formed into a slurry by addition of water and cast in a container (e.g., as a sheet or other shape) or applied to a substrate before drying (e.g., by air or freeze drying). Optionally stabilization steps can be performed to cross-link or otherwise stabilize the particle or fragment material. Exemplary tissue products including a sponge or coating for use with or without a polymeric substrate are disclosed in US Patent Number 9,382,422, which issued on July 5, 2016 to LifeCell Corporation.

[0034] As noted, the tissue product can include a substrate material that is coated with or encased with a tissue matrix. An exemplary product including a substrate layer 22 is illustrated in Fig. 3. The product 10' is similar to those discussed above, including the tissue product 12' and surfaces 14', 16' but further including a synthetic or biologic supporting substrate 22. The substrate 22 can include suitable polymeric materials including, for example, a mesh 24 formed of filaments, such as polypropylene. In one aspect, the substrate can be substantially non-absorbable or non-biodegradable. In another aspect, the substrate can be absorbable. The absorbable mesh can be a polymer selected from the group consisting of polyhydroxyalkanoate, polyglycolic acid, poly-L-lactic acid, polylactic/polyglycolic acid (PLGA), polygalactin 910, and carboxymethyl cellulose. The polymer can include poly-4-hydroxybutyrate. The substrate can be a synthetic substrate; the synthetic substrate can include polypropylene.

[0035] In some embodiments, a tissue matrix sponge is formed from adipose tissue. Suitable adipose tissues are described generally in US Patent Publication Number 2012/0310367 A1 (United States Patent Application Number 13/483,674, filed May 30, 2012, to Connor). Such adipose materials can be formed generally by mechanical homogenization, washing, resuspension, and stabilization of the material. The material may be dried (e.g. by freeze drying before or after stabilization), and stabilization can further be used to bond or attach the sponge to the other material. In addition, the sponge may be sterilized before or after joining to the intact tissue matrix. Sterilization may be performed after the components of the devices described herein are joined. Further, the sponge may be formed while in contact with the intact acellular tissue matrix components or may be formed separately prior to joining.

[0036] The tissue products and their methods of production can be used for the treatment of a variety of conditions. For example, Fig. 4 is a cross-sectional view of an abdominal wall 150 treated using tissue products 10 of the present disclosure. As shown, the tissue product 10 can be used to reinforce abdominal fascia but could also be used for other aspects such as closure of a skin incision 151, closure of other fascia layers, and use for other non-abdominal indications. The tissue products discussed here can be useful for treatment of any tissue site where it may be desirable to provide a tissue product with increased resistance to abrasion or adhesion. Such tissues can include connective tissue (e.g., tendon, ligaments, or other tissues within or near joints, surrounding muscles, or connecting tissues).

Claims:

1. A medical device, comprising:
 - an implant main body portion comprising a collagen-containing tissue matrix; and
 - a transglutaminase coating disposed on at least a portion of the outer surface of the implant main body portion, wherein the coating provides at least one of an anti-adhesion or anti-abrasion property to the outer surface.
2. The medical device of claim 1, wherein the implant main body portion comprises a sheet of collagen-containing tissue matrix.
3. The medical device of either of claims 1 or 2, wherein the collagen-containing tissue matrix comprises an acellular tissue matrix.
4. The medical device of any one of claims 1–3, wherein the collagen-containing tissue matrix is produced from tissue derived from a tissue selected from fascia, adipose, pericardial tissue, dura, umbilical cord tissue, placental tissue, cardiac valve tissue, ligament tissue, tendon tissue, arterial tissue, venous tissue, neural connective tissue, urinary bladder tissue, ureter tissue, muscle, and intestinal tissue.
5. The medical device of any one of claims 1–3, wherein the collagen-containing tissue matrix is produced from tissue derived from skin.
6. The medical device of any one of claims 1–3, wherein the collagen-containing tissue matrix comprises a dermal tissue matrix.
7. The medical device of any of claims 1–6, wherein the transglutaminase coating comprises a deactivated transglutaminase enzyme.

8. The medical device of any of claims 1–7, wherein the device is dry.
9. The medical device of any one of claims 1–8, wherein the collagen-containing tissue matrix comprises a collagen region that has been enzymatically treated with the transglutaminase.
10. The medical device of any one of claims 1–9, further comprising a synthetic substrate, wherein the collagen-containing tissue matrix is in contact with the a synthetic substrate.
11. The medical device of claim 10, wherein the synthetic substrate comprises a synthetic mesh.
12. The medical device of either of claims 10 or 11, wherein the synthetic substrate comprises polypropylene filaments.
13. The medical device of any one of claims 1–12, wherein the collagen-containing tissue matrix comprises a particulate acellular tissue matrix.
14. The medical device of claim 13, wherein the particulate acellular tissue matrix has been suspended and stabilized to produce a stable three-dimensional shape.
15. The medical device of claim 14, wherein the three-dimensional shape is in the form of a sheet.
16. The medical device of claim 1, wherein the collagen-containing tissue matrix comprises a particulate acellular tissue matrix and a synthetic mesh substrate, wherein the particulate acellular tissue matrix forms a covering over the synthetic mesh substrate, and the transglutaminase coating is disposed

along an outer surface of the tissue matrix to form a treated tissue region having increased resistance to adhesion or abrasion when implanted in a patient.

17. A method of producing a tissue product, comprising:
selecting a collagen-containing tissue matrix;
applying a composition comprising a transglutaminase enzyme to the collagen-containing tissue matrix; and
allowing the transglutaminase to perform an enzymatic activity on the collagen-containing tissue matrix to produce a region of the collagen-containing tissue matrix having at least one of an anti-adhesion or anti-abrasion property.

18. The method of claim 17, wherein the composition comprises an aqueous solution.

19. The method of either of claims 17 or 18, further comprising deactivating the transglutaminase enzyme.

20. The method of claim 19, wherein the enzyme is deactivated by heating.

21. The method of any one of claims 17–20, wherein the collagen-containing tissue matrix is a sheet.

22. The method of any one of claims 17–21, wherein the collagen-containing tissue matrix comprises an acellular tissue matrix.

23. The method of any one of claims 17–22, wherein the collagen-containing tissue matrix is produced from tissue derived from a tissue

selected from fascia, adipose, pericardial tissue, dura, umbilical cord tissue, placental tissue, cardiac valve tissue, ligament tissue, tendon tissue, arterial tissue, venous tissue, neural connective tissue, urinary bladder tissue, ureter tissue, muscle, and intestinal tissue.

24. The method of any one of claims 17–22, wherein the collagen-containing tissue matrix is produced from tissue derived from skin.
25. The method of any one of claims 17–22, wherein the collagen-containing tissue matrix comprises a dermal tissue matrix.
26. The method of any one of claims 17-25, wherein the method includes attaching the collagen-containing tissue matrix to a synthetic substrate prior to applying the composition comprising a transglutaminase to the collagen-containing tissue matrix.
27. The method of claim 26, wherein the collagen-containing tissue matrix is a particulate matrix, and wherein attaching the collagen-containing tissue matrix to the synthetic substrate comprises applying a slurry of the collagen-containing tissue matrix to the synthetic substrate.
28. The method of claim 27, further comprising stabilizing the slurry.
29. The method of claim 27, further comprising drying the slurry.
30. The method of either of claims 28 and 29, wherein the composition comprising the transglutaminase is applied after stabilizing or drying.
31. The method of claim 30, further comprising drying the composition comprising the transglutaminase.

32. The method of any of claims 17–31, further comprising washing the composition to remove the transglutaminase.

33. A tissue product produced according to the method of any one of claims 17–32.

34. A medical device, comprising:

an implant main body portion comprising a collagen-containing tissue matrix; and

a surface region comprising a portion that has been treated with a transglutaminase coating, wherein the surface region provides at least one of an anti-adhesion or anti-abrasion property to the outer surface.

35. The medical device of claim 34, wherein the implant main body portion comprises a sheet of collagen-containing tissue matrix.

36. The medical device of either of claims 34 or 35, wherein the collagen-containing tissue matrix comprises an acellular tissue matrix.

37. The medical device of any one of claims 34–36, wherein the collagen-containing tissue matrix is produced from tissue derived from a tissue selected from fascia, adipose, pericardial tissue, dura, umbilical cord tissue, placental tissue, cardiac valve tissue, ligament tissue, tendon tissue, arterial tissue, venous tissue, neural connective tissue, urinary bladder tissue, ureter tissue, muscle, and intestinal tissue.

38. The medical device of any one of claims 34–36, wherein the collagen-containing tissue matrix is produced from tissue derived from skin.

39. The medical device of any one of claims 34–36, wherein the collagen-containing tissue matrix comprises a dermal tissue matrix.
40. The medical device of any of claims 34–39, wherein the device is dry.
41. The medical device of any one of claims 34–40, further comprising a synthetic substrate, wherein the collagen-containing tissue matrix is in contact with the synthetic substrate.
42. The medical device of claim 41, wherein the synthetic substrate comprises a synthetic mesh.
43. The medical device of either of claims 41 or 42, wherein the synthetic substrate comprises polypropylene filaments.
44. The medical device of any one of claims 34–43, wherein the collagen-containing tissue matrix comprises a particulate acellular tissue matrix.
45. The medical device of claim 44, wherein the particulate acellular tissue matrix has been suspended and stabilized to produce a stable three-dimensional shape.
46. The medical device of claim 45, wherein the three-dimensional shape is in the form of a sheet.
47. The medical device of claim 1, wherein the collagen-containing tissue matrix comprises a particulate acellular tissue matrix and a synthetic mesh substrate, wherein the particulate acellular tissue matrix forms a covering over the synthetic mesh substrate, and an outer surface of the tissue matrix has increased resistance to adhesion or abrasion when implanted in a patient.

48. A method of treatment, comprising implanting a medical device or tissue product of any one of claims 1–16 and 34–47 into or on an anatomic site.

1/4

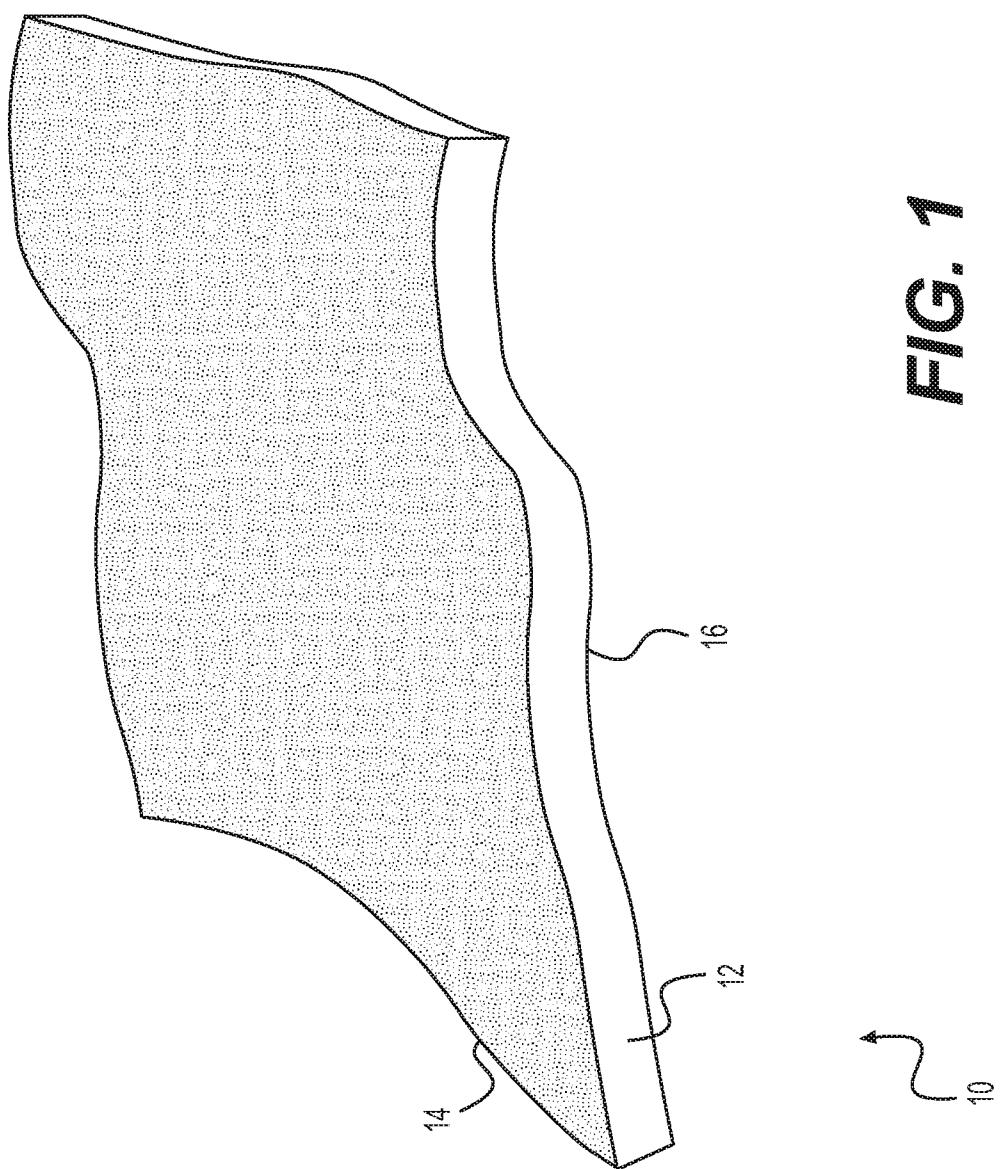
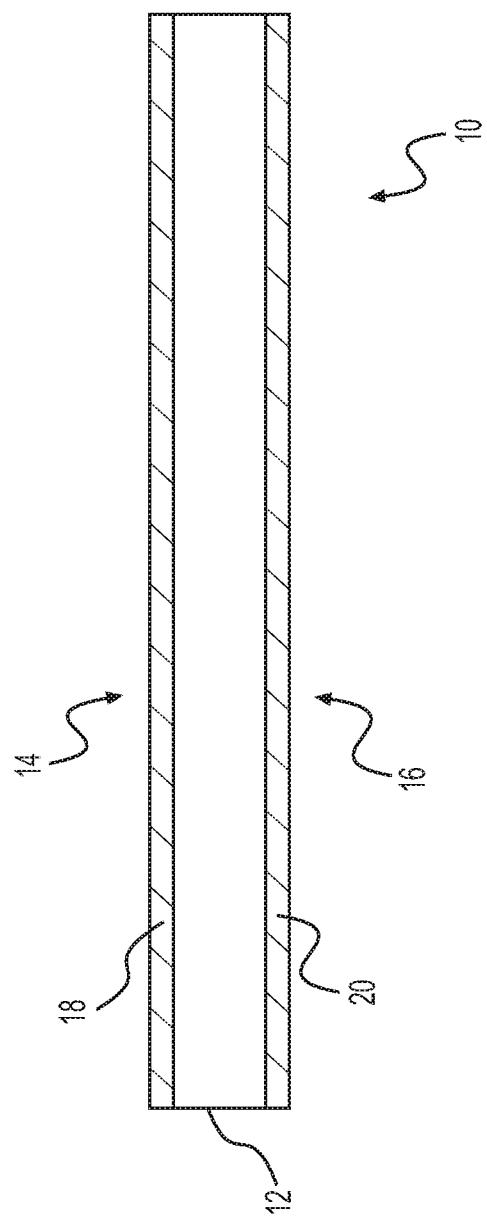


FIG. 1

2/4

**FIG. 2**

3/4

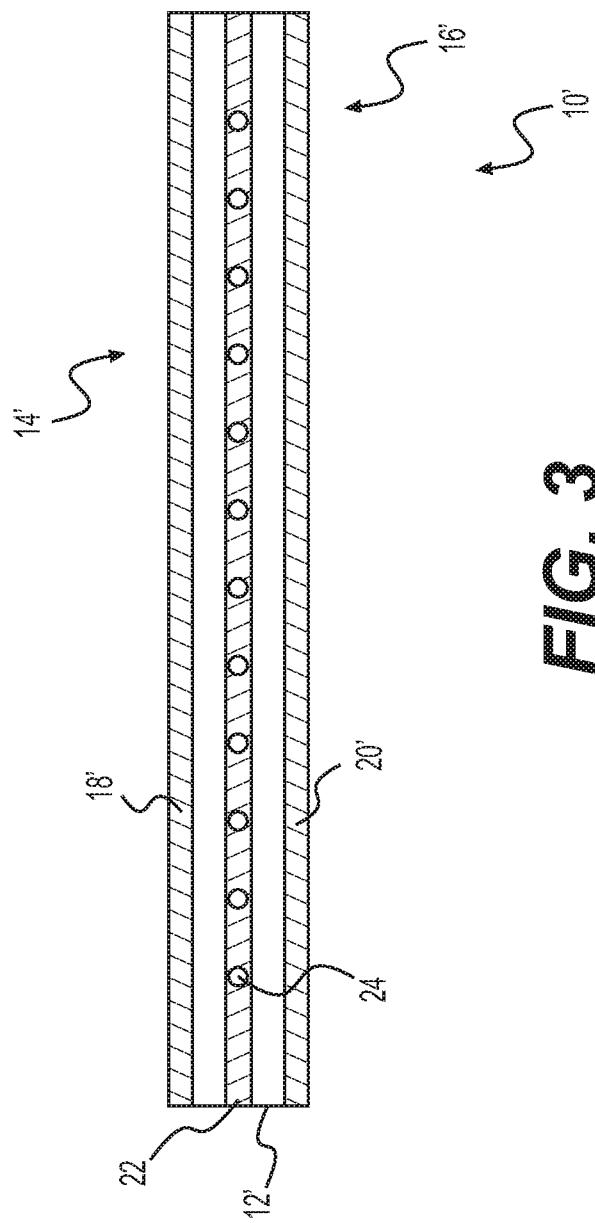


FIG. 3

4/4

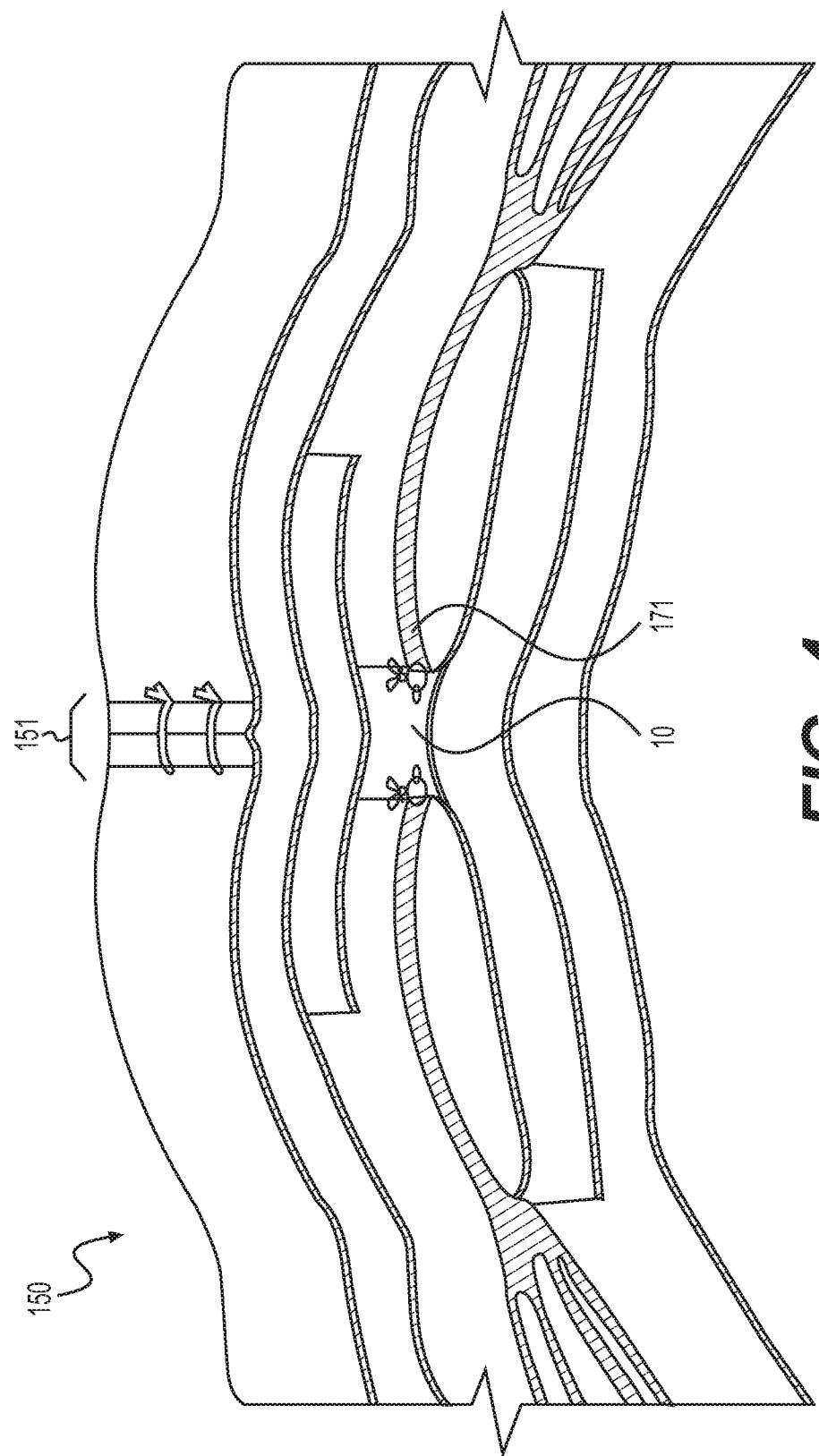


FIG. 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/015684

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61L27/18 A61L27/24 A61L27/34 A61L27/36
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94/28949 A1 (ORTHogene INC [US]) 22 December 1994 (1994-12-22) the whole document -----	1-48
L	COLLIGHAN R J ET AL: "Transglutaminase 2 cross-linking of matrix proteins: biological significance and medical applications", AMINO ACIDS ; THE FORUM FOR AMINO ACID AND PROTEIN RESEARCH, SPRINGER-VERLAG, VI, vol. 36, no. 4, 4 November 2008 (2008-11-04), pages 659-670, XP019723338, ISSN: 1438-2199 the whole document -----	1-48



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 April 2018	07/05/2018
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Derrien, Anne-Cécile

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2018/015684

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9428949	A1 22-12-1994	AT 234643	T	15-04-2003
		AU 7051194	A	03-01-1995
		AU 8305598	A	29-04-1999
		CA 2163250	A1	22-12-1994
		DE 69432300	D1	24-04-2003
		DE 69432300	T2	12-02-2004
		EP 0702572	A1	27-03-1996
		ES 2194869	T3	01-12-2003
		JP 3483255	B2	06-01-2004
		JP H08510943	A	19-11-1996
		TW 404836	B	11-09-2000
		US 5549904	A	27-08-1996
		US 5736132	A	07-04-1998
		WO 9428949	A1	22-12-1994