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(54) Benævnelse: **Bioforligeligt vævstransplantatmateriale til implantering samt fremgangsmåde til dets fremstilling**

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DESCRIPTION

BACKGROUND

[0001] In treating many illnesses and injuries, it is often useful to replace or reinforce damaged or injured tissues with a biocompatible graft material. Examples of such graft materials are diverse and include, but are not limited to: coronary grafts, such as arteries, veins, and valves; structural tissues, such as ligaments and tendons, dura mater, and skin. The suitable graft materials may also be used for surgical procedures such as slings for the treatment of urinary incontinence, bulking agents for cosmetic or reconstructive surgery, heart valve replacements, pericardium repairs, arterial transplants, and surgical meshes for the repair of hernias, abdominal wall reconstructions, and pelvic floor reconstructions. Suitable graft materials may be derived from allogenic or exogenic sources. Furthermore, allogenic graft materials may further be derived from autologous or homologous sources and may even include cadaveric sources.

[0002] The use of biocompatible grafts is an important and sometimes indispensable part of a course of treatment. However, to avoid, dangerously adverse reactions in a patient being treated with a biocompatible graft, it is first necessary to treat a freshly harvested graft material before it may be used as intended. This is particularly true where graft materials are derived from exogenic and homologous sources. Typically autologous sources of graft material represent a much lower risk with regard to adverse reactions but treatment may still be desired for the graft material to further reduce the likelihood of adverse reactions.

[0003] Freshly harvested graft materials are treated to remove any type of reactive material that may be present in the graft material, such as antigens, viruses and prions. Once such reactive material is removed, the graft may be emplaced. Removal of reactive cellular materials leaves behind an immunologically inert structural component of the graft alone. The structural component of a graft is an extra cellular matrix comprised of collagen fibers that are by themselves typically biochemically inert. The failure to remove reactive cellular material from the extra cellular matrix can cause severe reactions to the graft material that can extend healing time or even result in the complete rejection of the graft material itself.

[0004] Much work has been done in the field of decellularizing human and animal tissue to yield an essentially inert extra cellular matrix useful as a graft material. Typically, other technologies essentially use crosslinking or alkylation to mask the antigens or enzymes or caustic solutions to remove the antigens. While these methods may produce useful biocompatible graft materials, these methods have limitations in terms of their complexity, their expense, their ability to remove (rather than mask) antigens, their ability to remove hair, or controlling the rate of absorption.

[0005] US 2005/0238688 A1 describes a method of preparing an immunologically inert graft material from body tissue and US 6,933,103 B1 discloses a method of preparing an immunologically inert collagenic graft material.

SUMMARY

[0006] The present invention provides a method of preparing an absorbable remodelable graft material that is antigen-free and immunologically inert in which an animal tissue is soaked in a bleach solution; washed in a detergent solution; rinsed to remove the detergent solution; configured to a desired physical form and thickness; soaked in an iodophor solution; rinsed to remove the iodophor solution; soaked in a hypertonic solution; and rinsed to remove the hypertonic solution; wherein the method comprises:

1. (a) agitating the animal tissue in a mixture of a caustic and peroxide solution to provide a substantially hair-free and antigen-free animal tissue; and
2. (b) rinsing the substantially hair-free and antigen-free animal tissue in water.

[0007] Also provided is a method of preparing an endotoxin-free, antigen-free and immunologically inert implantable material that is absorbable and remodelable comprising the steps of lysing tissue using an osmotic pressure gradient followed by removal of remaining immunological components by treating the tissue with a caustic peroxide solution followed by a rinse to remove residuals to provide a substantially hair-free implantable material.

[0008] Further provided is an implantable material obtained by a method according to the present invention, comprising:

a substantially hair-free, endotoxin-free and immunologically inert tissue material that has a thickness of about 0.02-0.1 inches,

and that is bioabsorbable and remodelable, wherein

the tissue material is dermal derived.

[0009] The invention also provides a sling, a mesh and bulking agent comprising said implantable material and an absorbable remodelable graft material obtained by the above process wherein the tissue comprises skin.

[0010] One embodiment of the present invention provides an endotoxin-free, antigen-free and immunologically inert implantable graft material that is configured to a shape and thickness to delay bioabsorption or remodeling and to increase resistance to enzymatic degradation.

[0011] While multiple embodiments are disclosed, still other embodiments of the present invention will become apparent to those skilled in the art from the following detailed description, which shows and describes illustrative embodiments of the invention.

[0012] Accordingly, the detailed description is to be regarded as illustrative in nature and not restrictive.

DETAILED DESCRIPTION

[0013] The present invention generally provides an implantable graft material that is endotoxin-free, antigen-free, and immunologically inert and is configured to a shape and thickness to delay bioabsorption or remodeling and to increase resistance to enzymatic degradation. Also methods for producing such a graft material are provided for. As used in this specification, "antigen-free" refers to tissue material in which antigens are entirely or substantially removed from the tissues. Other embodiments of the invention provide for an implantable graft material that is absorbable remodelable, collegenic graft material that is "substantially hair-free" and immunologically inert. As used in this specification, "remodelable" refers to a material that can be broken down and resorbed without giving rise to adverse reactions and that is capable of conforming to the body by promoting and controlling the re-vascularization, re-population and regeneration of new tissue. As used in this specification, "substantially hair-free" refers to graft material obtained by the method of the present invention. Unless otherwise specified, all stated percentages are given by weight (wt %).

[0014] The source of the animal tissue may be derived from an autologous, heterologous or allogenic source. The graft material may be made from tissue obtained from human or animals. Animals include pigs, sheep, cows, goats, horses or other such animals. The animal tissues used may include skin, artery, heart valve, bone pericardium, fascia or dura mater.

[0015] One embodiment of the present invention provides a method for producing collegenic graft material. The method includes the steps of isolating and treating the derma layers of porcine tissue and lysing non-collagenic cell material by using "osmotic pressure gradients." As used in this specification, the term "osmotic pressure gradients" refer to soaking tissues alternately in increasingly hypertonic and hypotonic solutions. The methods further include altering proteins and non-collagenic tissue by treating the graft material with a mixture of sodium hydroxide and hydrogen peroxide, and preparing the graft material for storage and/or use. Although the following description is directed toward porcine tissue or skin, embodiments of the present invention may be suitable for other types of graft material.

[0016] In certain embodiments, suitable porcine tissues are procured and after an initial washing, are soaked in sodium hypochlorite bleach solution for the purpose of destroying bacteria and viruses. The tissue may be soaked, for example, for 30-45 minutes. The tissues are then frozen. While this freezing step does help to burst cells within the extra cellular matrix, it is essentially one of convenience and can be omitted if so desired. It is, however, necessary to soak the porcine tissues in a bleach or equivalent solution to reduce the level of microbial agents present in the hides. Suitable alternatives to sodium hypochlorite that may be used in the first procurement step and in the freezing and thawing steps include hydrogen peroxide, calcium hypochlorite and iodophor solutions such as povidone-iodine.

[0017] The frozen porcine tissues are next placed in sodium hypochlorite bleach solution and thawed therein for approximately 12 to 16 hours. In certain embodiments, the tissues are placed in a 0.1 to 0.2% sodium hypochlorite solution.

[0018] The tissues are then configured to a desired size, shape and thickness. In one embodiment, the rinsed tissues are cut into strips of a suitable size.

[0019] The strips of porcine tissue are next placed in a detergent solution to remove fats and greases therefrom. This detergent solution may also remove the cellular membrane and proteins by disrupting lipids. Bleach may also be added to the detergent solution for the purposes of destroying bacteria and viruses. In one embodiment, the porcine tissue is preferably soaked in the aforementioned detergent solution for approximately one half hour. During soaking in the detergent solution, the porcine tissue may be shaved to remove exterior hair shafts.

[0020] The porcine tissue is next rinsed in purified or tap water for approximately two hours. During this rinsing step, the epidermis and dermis are removed from the tissue using a dermatome to obtain a suitable thickness. The thickness may vary depending upon the desired final thickness of the graft material. For example, tissue material may be prepared with thickness ranging between about 0.02 to about 0.1 inches. In one embodiment, the tissue material has a thickness of 0.035 to 0.048 inches. In another embodiment, the tissue material has a thickness between 0.07 to 0.1 inches.

[0021] Varying the thickness affects the rate of absorption within the body when the material is acted upon by degradation or enzymes such as collagenase.

[0022] Collagenases are a class of enzymes that break down the native collagen that holds animal tissues together and are made by a variety of microorganisms and by many different animal cells. Collagenase is one of the body's natural mechanisms for absorbing and remodeling collagen. Hence, collagenase can be used to determine the rate of break down or absorption of a material by a mammalian host.

[0023] The porcine tissue is next transferred to a first iodophor solution. In one embodiment, a 7.5% povidone-iodine was used and the porcine tissue allowed to soak for approximately 2 hours. In other embodiments, the porcine tissue, as strips were removed temporarily from the iodophor scrub solution so that additional hair stubble may be removed by shaving. When the porcine tissue strips have been soaked for a sufficient amount of time in the first iodophor scrub solution the tissue is then rinsed in water and transferred to another iodophor solution, for example, 10% povidone-iodine, for approximately one half hour to further reduce the bioburden level of non-collagenic cellular materials present in the porcine tissue samples. After this second iodophor solution soak, the porcine tissue strips are again rinsed in water, this time for approximately 3 hours. After rinsing, the porcine tissues are trimmed to their final dimensions.

[0024] In an alternate embodiment, the porcine tissue may be treated with a bleach solution containing sodium hypochlorite or calcium hypochlorite.

[0025] The portions of porcine tissue are next measured and sorted into batches of known surface area. Each batch of porcine tissue may optionally be treated with an antibiotic solution to remove unwanted bacteria. In one embodiment, the porcine tissue is treated with a concentration of an antibiotic solution of approximately 2000 milliliters for every 5 square feet of porcine tissue. Antibiotics that may be used include 0.05% kanamycin sulfate in a 0.9% saline solution. Other suitable antibiotics include neomycin, bacitracin, tetracycline and other antibiotics.

[0026] After treatment with antibiotics, the respective batches of porcine tissue are then soaked alternately in increasingly hypertonic and hypotonic solutions for 2-hour intervals. In one embodiment, the hypertonic solutions include 2%, 4%, 6%, 8%, 10% and 12% sodium chloride in purified water. The hypotonic solution may include purified water. Each treatment consists of a 2-hour soak with or without agitation. Therefore, this step in the production of an immunologically inert graft material requires 12 two-hour treatments for a total of approximately 24 hours. For example, a batch of porcine tissue is placed in the hypertonic 2% saline solution for two hours. Thereafter this batch of porcine tissue is placed in the hypotonic purified water for two hours and then into a hypertonic 4% saline solution for two hours. This process continues through the 12% saline solution.

[0027] The treatment of the porcine tissue batch with alternating hypertonic and hypotonic solutions acts to rupture cellular membranes by creating an osmotic pressure gradient across the cellular membranes. The cyclic nature of raising and lowering osmotic pressures using hypertonic and hypotonic solutions has been found very effective in lysing the cells present in the tissue. Gradually increasing the concentration of the hypertonic solutions is a preferred means of increasing this lysing action.

[0028] In some embodiments, the concentration of the hypertonic solutions may include 1%, 3%, 5%, 7%, 9%, and 11% solutions and other series of increasingly concentrated solutions. Any ionic aqueous solution that is compatible with the intended use of the porcine tissue will be suitable for use as a hypertonic solution in this treatment. Similarly, any non-ionic aqueous solution that is compatible with the intended use of the porcine tissue will be suitable for use as a hypotonic solution in this treatment.

[0029] Following the last hypotonic solution rinse, the porcine tissue is then placed in a mixture of a caustic and peroxide solution. In one embodiment, a 1N sodium hydroxide solution and a 3% solution of hydrogen peroxide is used for approximately

two hours. In some embodiments the ranges of sodium hydroxide that may be used are from 0.1N to 5N, and ranges for hydrogen peroxide include between about 0.1 and 20%. In other embodiments the ranges of sodium hydroxide that may be used are from 0.25-3N, and ranges for hydrogen peroxide include between about 0.75%- 10%. In still other embodiments, the peroxide solution concentration used is between 1-3 %. Alternate embodiments of this step may involve treating the porcine tissue with functional equivalents of sodium hydroxide, for example, potassium hydroxide, ammonium hydroxide, calcium hydroxide, sodium dodecylsulfate, urea, phenol, or formic acid. Alternative or functional equivalents of hydrogen peroxide, for example, include peracetic acid, perbenzoic acid, benzoyl peroxide, sodium peroxide, or potassium permanganate.

[0030] The treatment of the porcine tissue with the mixture of a caustic and peroxide solution removes the epidermis from the tissue and the majority of any remaining hair stubble that may be contained or trapped in the pores of the porcine tissue as well as destroys the non-collagenus material, for example, antigens. The porcine tissue is also bleached. This step may be performed under agitation in a reaction chamber as disclosed in U.S. patent 6,933,103.

[0031] The porcine tissue is agitated during this soaking step with a paddle mixer of known type running at approximately 120 rotations per minute. After the porcine tissue has been treated for its allotted time in the sodium hydroxide and hydrogen peroxide solution, the porcine tissue is then placed in water and agitated using a paddle mixer running at approximately 120 rotations per minute. This water rinse is essentially a polishing step that is a continuation of the sodium hydroxide and hydrogen peroxide treatment of the previous step due to the carryover of hydroxide ions from that previous step. Typically the pH of the purified water rinse will rise and become highly caustic but less caustic than the first sodium hydroxide solution. This slightly lower pH is less destructive to the collagen of the porcine tissue's extra cellular matrix, but will continue to remove non-collagenic cellular material from the extra cellular matrix.

[0032] Upon removal from the reaction chamber, the porcine tissue is rinsed in water for approximately one hour. This rinsing step may be carried out multiple times. This rinsing step removes pyrogens and hydrogen peroxide and hydroxyl ion carryover from the extracellular matrix of the porcine tissue. At this stage the porcine tissue has had substantially all of the non-collagenic cellular material, such as antigens, removed from the extra cellular matrix thereof.

[0033] In an optional step, after the water rinses, the resulting immunological inert porcine tissue may be chemically cross-linked with a cross-linking agent.

[0034] Aldehydes and other cross-linking agents have been used in tissue implants to cross-link and bind antigens as a means of reducing antigenicity. Oftentimes the undesirable side-effect of binding antigens is cross-linking the tissue to such a degree that adversely delays or prevents absorption by the body. Furthermore, when a cross-linking agent is used to mask or sequester antigens, any spontaneous breakage of the sequestration bond releases the antigen and causes localized antigenic responses which may cause implant failure. In the present invention, the cross-linking agent is not necessary for reducing antigenicity because the tissue is already antigen-free. Therefore, the cross-linking agent can be used solely for the purpose of controlling the rate of absorption by the body.

[0035] Depending upon the degree of cross-linking desired, the cross-linking treatment used is in the range between about 0.01 to 5 %. In one embodiment gluteraldehyde is used at a 1.5 % concentration. Other suitable cross-linking agents that may be used include aldehyde, formaldehyde, dialdehydes, dialdehyde starch, carodiamides, epoxides and isoycanates.

[0036] The cross-linked tissue is then rinsed in water and further subjected to an optional solution of hydrogen peroxide for an additional one hour. This step bleaches the tissue to a nearly white color.

[0037] In some embodiments, after the final water rinses, in either the cross-linked or non-cross-linked tissue, the tissue is soaked in a 0.9% saline solution for approximately half an hour to stabilize the porcine tissue and make it isotonic with respect to a recipient of the graft.

[0038] The porcine tissue is now an antigen-free and immunologically inert graft material that is ready for implantation. The porcine graft material may then be packaged, labeled and sterilized and conserved for future use. One alternative to standard packaging and sterilization is to freeze dry the porcine graft material.

[0039] As indicated above, a graft material produced according to the method of the present invention includes a collagenic extra cellular matrix from which substantially all of the bioreactive cellular material has been removed. The graft materials produced by the method of the present invention may be used for surgical procedures such as slings for treatment for urinary incontinence, surgical meshes for repair of hernias, bulking agents for cosmetic or reconstructive surgery, abdominal wall

reconstructions, pelvic floor reconstructions, heart valve replacements, pericardium repairs, or arterial transplants.

[0040] Some embodiments of the present disclosure are summarized as follows:

1. 1. A method of preparing an absorbable remodelable graft material that is antigen-free and immunologically inert in which an animal tissue is soaked in a bleach solution; washed in a detergent solution; rinsed to remove the detergent solution; configured to a desired physical form and thickness; soaked in an iodophor solution; rinsed to remove the iodophor solution; soaked in a hypertonic solution; rinsed to remove the hypertonic solution; wherein the method comprises:
    1. (a) agitating the animal tissue in a mixture of a caustic and peroxide solution to provide an antigen-free animal tissue; and
    2. (b) rinsing the substantially hair-free and antigen-free animal tissue in water.
2. 2. The method of item 1 wherein the animal tissue is from an autologous, heterologous or allogenic source and derived from a porcine, bovine, equine, rodent or human tissue.
3. 3. The method of item 1, wherein the mixture of a caustic and peroxide solution comprises a sodium hydroxide solution having a concentration between about 0.1-5N and the peroxide solution having a concentration between about 0.1-20 wt %.
4. 4. The method of item 3, wherein the mixture of a caustic and peroxide solution comprises a sodium hydroxide solution having a concentration between about 0.25-3N and the peroxide solution having a concentration between about 0.75-10 wt %.
5. 5. The method of item 1 wherein the graft material is further soaked in a saline solution after step (b).
6. 6. The method of item 1, wherein the graft material is further chemically cross-linked, after step (b).
7. 7. The method of item 1, wherein the graft material is hairless.
8. 8. An implantable material obtained by the method according to items 1 to 7 comprising:

    a substantially hair-free, endotoxin-free and immunologically inert tissue material that has a thickness of about 0.02-0.1 inches, and that is bioabsorbable and remodelable, wherein the tissue material is dermal derived.

9. 9. The implantable material of item 8, wherein the tissue material is chemically cross-linked to delay bioabsorption or remodeling and to increase resistance to enzymatic degradation.
10. 10. A sling, a mesh and bulking agent comprising the implantable material of item 8.
11. 11. A method of preparing an absorbable remodelable graft tissue material that is hairless and immunologically inert comprising the steps of:
    1. (a) soaking an animal tissue in a bleach solution;
    2. (b) washing the animal tissue in a detergent solution;
    3. (c) rinsing the animal tissue to remove the detergent solution;
    4. (d) configuring the animal tissue to a desired physical form and thickness;
    5. (e) soaking the animal tissue in an iodophor solution;
    6. (f) rinsing the animal tissue to remove the iodophor solution;
    7. (g) soaking the animal tissue in a hypertonic solution;
    8. (h) rinsing the animal tissue to remove the hypertonic solution;
    9. (i) agitating the animal tissue in a mixture of a caustic and peroxide solution; and
    10. (j) rinsing the animal tissue in water to remove the mixture of caustic and peroxide solution.
12. 12. The method of item 11, wherein the step of soaking the animal tissue in a hypertonic solution further comprises the steps of:

    soaking the animal tissue in a series of increasingly hypertonic solutions; and

    rinsing the animal tissue after each soaking in a hypotonic solution to remove the hypertonic solution.

13. 13. The method of item 11, wherein the mixture of a caustic and peroxide solution comprises a sodium hydroxide solution having a concentration between about 0.1-5N and the peroxide solution having a concentration between about 0.1-20 wt %.
14. 14. The method of item 13, wherein the mixture of a caustic and peroxide solution comprises a sodium hydroxide solution having a concentration between about 0.25-3N and the peroxide solution having a concentration between about 0.75-10 wt %.
15. 15. The method of item 11, wherein the tissue material is soaked in a saline solution after step (j).
16. 16. The method of item 11, wherein the tissue material is chemically cross-linked, after step (j).
17. 17. A method of preparing an endotoxin-free, antigen-free and immunologically inert implantable material that is absorbable and remodelable comprising the steps of lysing tissue using an osmotic pressure gradient followed by removal of remaining immunological components by treating the tissue with a caustic peroxide solution followed by a rinse to remove residuals to

provide a substantially hair-free implantable material.

18. 18. A method of item 17, wherein the tissue comprises skin, artery, heart valve, bone pericardium fascia, or dura mater.
19. 19. A method of item 17, wherein the implantable material is chemically cross-linked.
20. 20. A method of item 17, wherein the implantable material has a thickness of about 0.02-0.1 inches.

Preparation of Tissue Material

[0041] Three versions of mesh were made, by the methods described herein, for testing differing rates of absorption. The first version was made using porcine skin cut at a thickness of 0.035 inches to 0.048 inches. The second version was made using porcine skin cut at a thickness of 0.070 inches to 0.100 inches. The third version was made using porcine skin cut at a thickness of 0.035 inches to 0.048 and subsequently treated with glutaraldehyde at a concentration of 1.5%.

[0042] Treatment with collagenase was used to simulate absorption by the body of a collagen implant. The collagenase used was a type 1A obtained from Sigma Aldrich, catalogue number C-2674. After sterilization, each of the versions were placed in a 20 mg/mL collagenase solution at the rate of 0.89 mL collagenase solution per square centimeter of tissue. The different versions of tissues were incubated at 35° C for 48 hours.

Measure of Pull and Tensile Strength

[0043] A snapshot in time of the strength of a porcine dermis after reaction with a known amount of collagenase at constant temperature is determined by measuring pull and tensile strength. Pull and tensile strength is used as a measure of collagen integrity, thus absorption. The relative strength of porcine dermis at any given time is equivalent to relative time required to retain any given strength. In this manner, one can use the presented data as a representation of the relative absorption rates of treated porcine dermis by the body.

[0044] To measure the pull strength of the tissue samples, the samples were cut in the shape of an hourglass. The dimensions of the neck or narrow region of the hourglass-shaped tissue samples were approximately 0.5 inches by 0.5 inches. The thicknesses of the samples were also measured in this region. The samples were placed in an Instron® or similar measurement device and stretched to the point of failure. The maximum force (in pounds) required to tear apart the tissue was recorded. The force (in pounds) divided by the width (in inches) results in the pull strength in pounds/linear inch.

[0045] The measure of tensile strength was determined by dividing the force by the thickness (in inches) resulting in the tensile strength in pounds/ square inch.

Example 1

[0046] The following table shows the results of subjecting different versions of treated porcine dermis with collagenase.

Test No.	Version	Collagenase	Pull Strength Lbs/in	Tensile Strength Lbs/in^2
1	Thin	collagenase @ 20 mg/mL	2.76	71.6
2	Thick	collagenase @ 20 mg/mL	46.68	258.5
3	Thin with Glutaraldehyde	collagenase @ 20 mg/mL	51.76	956.8
4	Thin - Control	none	84.34	1500.0

[0047] This table shows the porcine tissue control (material made according to this patent) is initially very strong - 84.34 lbs/in pull strength (Test 4). When implanted the porcine implant will be absorbed and remodeled by the body. In the presence of collagenase the thin porcine implant is broken down, absorbed, as evident by the reduced pull and tensile strengths - 2.76 and 71.6 lbs/in respectively (Test 1). By increasing the thickness the implant retained substantial strength as seen by Test 2-46.68 lbs/in compared with 2.76 for the thin version. By treating the thin version with glutaraldehyde the rate of break down or absorption is further reduced as is evident by Test 3 - 51.76 lbs/in. In this manner, the desired absorption can be adjusted by

changing the thickness and/or cross-linking of the implant.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US20050238688A1 **[0005]**
- US6933103B1 **[0005]**
- US69331038 **[0030]**

PATENTKRAV

1. Fremgangsmåde til fremstilling af et absorberbart omformeligt transplantatmateriale, der er antigenfrit og immunologisk indifferent, ved hvilken et dyrisk væv gennemvædes i en blegeopløsning; vaskes i en vaskemiddelopløsning; skylles for at fjerne vaskemiddelopløsningen; konfigureres til en ønsket fysisk form og tykkelse; gennemvædes i en iodophoropløsning; skylles for at fjerne iodophoropløsningen; gennemvædes i en hypertonisk opløsning; og skylles for at fjerne den hypertoniske opløsning; idet fremgangsmåden omfatter:

(a) bevægelse af det dyriske væv i en blanding af ætsemiddel og peroxidopløsning for at tilvejebringe et i det væsentlige hårfrit og antigenfrit dyrisk væv; og
(b) skylning af det i det væsentlige hårfrie og antigenfrie dyriske væv i vand.

2. Fremgangsmåde ifølge krav 1, ved hvilken det dyriske væv stammer fra en autolog, heterolog eller allogen kilde og er afledt af svine-, okse-, heste-, gnaver- eller menneskevæv.

3. Fremgangsmåde ifølge krav 1 til fremstilling af et absorberbart omformeligt transplantatvævsmateriale, der er hårfrit og immunologisk indifferent, omfattende følgende trin:

(a) gennemvædning af et dyrisk væv i en blegeopløsning;
(b) vask af det dyriske væv i en vaskemiddelopløsning;
(c) skylning af det dyriske væv for at fjerne vaskemiddelopløsningen;
(d) konfigurering af det dyriske væv til en ønsket fysisk form og tykkelse;
(e) gennemvædning af det dyriske væv i en idophoropløsning;
(f) skylning af det dyriske væv for at fjerne iodophoropløsningen;
(g) gennemvædning af det dyriske væv i en hypertonisk opløsning;
(h) skylning af det dyriske væv for at fjerne den hypertoniske opløsning;
(i) bevægelse af det dyriske væv i en blanding af et ætsemiddel og en peroxidopløsning; og
(j) skylning af det dyriske væv i vand for at fjerne blandingen af ætsemiddel og peroxidopløsning for at tilvejebringe det hårfrie transplantatvævsmateriale.

4. Fremgangsmåde ifølge krav 3, ved hvilken trinnet til gennemvædning af det dyriske væv i en hypertonisk opløsning endvidere omfatter følgende trin:

gennemvædning af det dyriske væv i en række tiltagende hypertoniske opløsninger; og skylning af det dyriske væv efter hver gennemvædning i en hypotonisk opløsning for at fjerne den hypertoniske opløsning.

5. Fremgangsmåde ifølge krav 1 eller 3, ved hvilken blandingen af ætsemiddel og peroxidopløsning omfatter en natriumhydroxidopløsning med en koncentration mellem ca. 0,1 og 5 N og en peroxidopløsning med en koncentration mellem ca. 0,1 og 20 vægt%.

6. Fremgangsmåde ifølge krav 5, ved hvilken blandingen af ætsemiddel og peroxidopløsning omfatter en natriumhydroxidopløsning med en koncentration mellem ca. 0,25 og 3 N og en peroxidopløsning med en koncentration mellem ca. 0,75 og 10 vægt%.

7. Fremgangsmåde ifølge krav 1 eller 3, ved hvilken vævsmaterialet gennemvædes i en saltopløsning efter trin (b) hhv. trin (j).

8. Fremgangsmåde ifølge krav 1 eller 3, ved hvilken vævsmaterialet tværbindes kemisk efter trin (b) hhv. trin (j).

9. Fremgangsmåde til fremstilling af et endotoxinfrit, antigenfrit og immunologisk indifferent implanterbart materiale, der er absorberbart og omformeligt, omfattende de trin at lysere væv under anvendelse af en gradient af osmotisk tryk efterfulgt af fjernelse af resterende immunologiske komponenter ved behandling af vævet med en kaustisk peroxidopløsning efterfulgt af skylning for at fjerne rester til tilvejebringelse af et i det væsentlige hårfrit implanterbart materiale.

10. Fremgangsmåde ifølge krav 9, ved hvilken vævet omfatter hud, arterie, hjerteklap, knogle, pericardium fascia eller dura mater.

11. Fremgangsmåde ifølge krav 9, ved hvilken det implanterbare materiale er kemisk tværbundet.

12. Fremgangsmåde ifølge krav 9, ved hvilken det implanterbare materiale har en tykkelse på ca. 0,02-0,1 inches.

13. Implanterbart materiale opnået ved en fremgangsmåde ifølge krav 1 til 12 omfattende:
et i det væsentlige hårfrit, endotoxinfrit og immunologisk indifferent vævsmateriale, der har en tykkelse på ca. 0,02-0,1 inches, og som er bioabsorberbart og omformeligt, idet vævsmaterialet er afledt af hud.

14. Implanterbart materiale ifølge krav 13, hvor vævsmaterialet er kemisk tværbundet for at forhale bioabsorption eller omformning og for at forøge bestandighed over for enzymatisk nedbrydning.

15. Slynge, net og fyldmateriale omfattende det implanterbare materiale ifølge krav 13.

16. Absorberbart omformeligt transplantatmateriale opnået ved fremgangsmåden ifølge krav 9, hvori vævet omfatter hud.