

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 May 2001 (10.05.2001)

PCT

(10) International Publication Number
WO 01/32229 A1

- (51) International Patent Classification⁷: A61L 27/18, 27/38, A61F 2/08
- (21) International Application Number: PCT/GB00/04166
- (22) International Filing Date: 30 October 2000 (30.10.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
9926231.3 4 November 1999 (04.11.1999) GB
- (71) Applicant (for all designated States except US): SMITH & NEPHEW PLC [GB/GB]; Heron House, 15 Adam Street, London WC2N 6LA (GB).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): COTTON, Nicholas, John [GB/GB]; 21 Woolmoor Close, Thirsk, North Yorkshire YO7 1BY (GB).
- (74) Agent: SMITH & NEPHEW GROUP RESEARCH CENTRE; Group Patents & Trade Marks, York Science Park, Heslington, York YO10 5DF (GB).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 01/32229 A1

(54) Title: TISSUE REPAIR

(57) Abstract: The invention concerns implants for tissue repair and in particular for the repair or connective tissue such as ligament, cartilage, bone, meniscus, tendon and skin. It also concerns methods of manufacture of such implants and their use in methods of medical treatment. The implants themselves may comprise an implantable article itself comprising a first component and a second component coupled thereto, wherein the first component comprises a fabric and the second component comprises a material capable of being seeded with and supporting the growth of cells.

Tissue Repair

The present invention relates to an implantable article; to synthetic implants comprising the implantable article; to hybrid implants
5 generated by culturing cells within synthetic implants according to the invention; to methods of manufacture of implants according to the invention and to methods of treatment employing the implants according to the invention. Implantable articles, synthetic implants and hybrid implants according to the invention may be used for the
10 partial or total replacement of tissue, particularly connective tissue, such as ligament, cartilage, bone, meniscus, tendon, skin and the like.

Generally speaking, there are two types of treatment for injured
15 ligaments, such as cruciate ligaments, namely tissue grafting or replacement by a synthetic device. Ligament reconstruction with autograft tissue (derived from the patient) is the most common treatment, but the extent to which this may be practised is evidently limited by the amount of tissue available for grafting. In addition,
20 donor site morbidity and necrosis of the graft tissue following implantation are problems which have not yet been overcome. Use of allogenic or xenogenic tissue (derived from foreign tissue sources) is one possible alternative to the use of allograft, which eliminates the problems associated with the tissue harvesting
25 procedure in the patient. On the other hand, the perceived risk of disease transmission and immunogenic responses has limited the use of these types of tissue to a small fraction of ligament reconstructions.

It has been proposed in the prior art to employ single layer synthetic implants which encourage the ingrowth of tissue. Such is aimed at improving the properties, e.g. strength, of the repair devices. Where this has been done, however, tissue ingrowth has often been

5 disorganised and insufficient in quantity and quality.

Synthetic devices for the replacement of ligaments have generally failed to show successful long-term results, with failure commonly occurring over a 2-10 year period, due to synovitis, loosening or implant failure. Following implantation, continuous loading of the

10 device and abrasion against joint tissues causes wear, creep and fatigue of the device until it ultimately fails.

It is an object of the present invention to overcome the shortcomings of prior synthetic devices.

15 According to a first aspect of the invention, an implantable article is provided comprising a first component and a second component coupled thereto, wherein the first component comprises a fabric and the second component comprises a material capable of being

20 seeded with and supporting the growth of cells.

As used herein, the phrase "capable of being seeded with and supporting the growth of cells" means having a seeding efficiency of greater than 50% and preferably greater than 70%. Seeding

25 efficiency may be determined in the following way: a 2mm x 10mm disc comprising the second component is soaked overnight in foetal calf serum. It is then seeded with four million HuFF (human foreskin fibroblast) cells, suspended in 1ml of culture medium by pulling the cell suspension backwards and forwards through the disc five times,

30 using a 1ml. pipette. The proportion of cells adhering to the disc is determined (by DNA assay using Hoechst 33258™ dye) after which

the seeding efficiency may be calculated as the percentage of cells adhering to the disc in relation to the total number of cells.

It is not excluded from the ambit of the invention that the first
5 component also be capable of being seeded with and supporting the growth of cells, but in this event it is preferred that the second component have a higher seeding efficiency than the first component, according to the above definition of seeding efficiency.

10 According to this aspect of the invention, the second component may be incorporated within said first component, in which case it is preferably distributed evenly throughout. This has the advantage that cells, once seeded onto the second component, may proliferate evenly throughout the first component to generate a homogenous
15 matrix.

The first component typically comprises first and second surfaces. In this case, the second component may be attached to at least a portion of at least one of the first and second surfaces of said first
20 component. Such an arrangement may be employed if integration is a localised region is important.

In a preferred form, the second component is coupled to the first component so as to be co-extensive with one of the first and second
25 surfaces of the first component. More preferably, coupling is by physical attachment.

In a further alternative, the first component may be encased in the second component.

The first component according to the invention comprises a fabric. Fabrics which may be employed according to the invention are woven, non-woven, knitted, braided or crocheted materials or a mixture of these. If the first component comprises a woven or knitted material, it may comprise a spacer fabric. Such materials have an advantage that their three dimensional structure may be modified to give a specific architecture, allowing, in their turn, properties like percentage open volume, toughness and other characteristics to be accurately tailored to the specific application.

10

According to a preferred form of the first aspect of the invention, the first component comprises an elongate fabric tape comprising both warp and weft strands.

Advantageously, the tape comprises first elongate elements. The first elongate elements may comprise woven, non-woven, knitted, braided or crocheted material. Advantageously, the first elongate elements comprise braided material. Braided material has the advantage of a favourable load to elongation relationship, i.e. high strength incorporating sufficient elasticity. Single fibres, for example, frequently do not fulfil this criterion and can fatigue and break *in vivo*.

If the first elongate elements comprise braided material, the pick rate of the braided material may advantageously be in the range from 10 to 30 picks/cm and comprise between 4 and 64 yarns, preferably between 8 and 64 yarns. The number of filaments per yarn is advantageously in the range 30 to 150 and the filaments preferably have a diameter in the range 8 - 20 μ m.

30

The first elongate elements may be independently translatable in the warp direction with respect to each other and with respect to the weft strands but maintained in a spaced apart relationship with respect to each other in the weft direction.

5

The implantable article according to the invention may be heat sealed or sealed with a binder in order to prevent fraying at the edges. It is preferred to heat seal the implantable article if it comprises independently translatable first elongate elements to prevent them from becoming detached.

10

The first elongate elements may be maintained in a spaced apart relationship by the weft strands alone or, in addition, by non-translatable second elongate elements interspersed between the translatable first elongate elements. The second elongate elements may comprise chain stitched, woven, non-woven, knitted, braided or crocheted material. Advantageously, the second elongate elements comprise chain-stitched material. A line of chain stitches has the advantage of fulfilling the task of being a spacer element while not occupying much space itself.

15

20

According to a particularly preferred form of this aspect of the invention, the elongate fabric tape comprises an upper and a lower layer, each layer comprising an open mesh structure comprising warp and weft yarns, wherein the first elongate elements are laid into the structure.

25

According to this particularly preferred form of the invention, the warp and weft strands of the upper and lower layers may cooperate to maintain the first elongate elements in a spaced relationship in the weft direction. This may be achieved by attaching weft strands of

30

the upper layer to corresponding weft strands of the lower layer at positions between adjacent first elongate elements moving along the weft. Attachment may be by various methods, for example spot fusing or by means of a warp strand linking the upper and lower weft strands.

The first component according to the invention may comprise bioresorbable materials or materials which do not resorb *in vivo*.

- 10 Reference herein to a material being bioresorbable means that it breaks down over a finite period of time due to the chemical/biological action of the body and the terms "resorption" and "resorb" are to be interpreted accordingly. Preferably, complete resorption occurs within about 5 years, more preferably within about
- 15 3 years. This breakdown is at a rate allowing the implantable medical article to maintain sufficient integrity while the tissue repairs: surgical repair devices formed of materials which are resorbed too quickly may fail when compressive, tensile or flexural loads are placed on them when the tissue has fully healed.
- 20 Advantages of using bioresorbable materials over materials which do not bioresorb include that they encourage tissue repair and further surgery is not required to remove them.

The first component may comprise bioresorbable polymers or

25 copolymers comprising the following monomers or mixtures of polymers and/or copolymers formed thereby: hydroxy acids, particularly lactic acid, glycolic acid; caprolactone; hydroxybutyrate; dioxanone; orthoesters; orthocarbonates; aminocarbonates.

- 30 Preferred bioresorbable materials according to the invention include poly(lactic acid), poly(glycolic acid), polydioxanone,

polyhydroxybutyrate and poly(trimethylene carbonate) or mixtures thereof. It is particularly preferred to use poly(lactic acid). This material has the advantage that it has good mechanical strength and does not resorb too quickly *in vivo* allowing this strength to be
5 retained for a sufficient time for tissue repair to occur at which point the repaired tissue can take over load-bearing functions.

Appropriate non-bioresorbable materials according to the invention include polyesters, particularly aromatic polyesters, such as
10 polyalkylene terephthalates, like polyethylene terephthalate and polybutylene terephthalates; polyamides; polyalkenes such as polyethylene and polypropylene; poly(vinyl fluoride), polytetrafluoroethylene carbon fibres, silk (natural or synthetic) and mixtures of these materials.

15

The second component according to the invention advantageously comprises a solid material. Advantageously, the second component comprises a fabric, such as a woven or non-woven (fleece) material, a foams, a sponge or a mixture of these.

20

The second component may comprise bioresorbable polymers or copolymers comprising the following monomers, or mixtures of the polymers and/or copolymers formed thereby: hydroxy acids, particularly lactic acid, glycolic acid; caprolactone; hydroxybutyrate;
25 dioxanone; orthoesters; orthocarbonates; aminocarbonates.

Preferred bioresorbable materials according to the invention comprise poly(lactic acid), poly(glycolic acid), polydioxanone, polyhydroxybutyrate, polyaminocarbonates and poly(trimethylene
30 carbonate). It is particularly preferred to use poly(glycolic acid). This material has the advantage that it has a relatively high resorption

rate allowing rapid tissue regeneration in those areas where it is present.

Appropriate non-bioresorbable materials according to the invention
5 include polyesters, particularly aromatic polyesters, such as
polyalkylene terephthalates, like polyethylene terephthalate and
polybutylene terephthalates; polyamides; polyalkenes such as
polyethylene and polypropylene; poly(vinyl fluoride),
polytetrafluoroethylene carbon fibres, silk (natural or synthetic) and
10 mixtures of these materials.

Preferably, the second component comprises a non-woven material.
The nonwoven material may be dry laid, wet laid, spun laid or melt
blown. Advantageously, the fibres are needed to give a random
15 entanglement providing a large surface area for cell
attachment/capture. The void fraction of the nowoven may be in the
range 50 to 99%, but is preferably in the range 90 to 99%. Typically,
the nonwoven will have a density in the range 25 to 100 g/m² and
staple fibre lengths in the range 40-50mm, though values outside
20 these ranges may also be employed. The nonwoven is typically
used in thicknesses of 0.25 to 5mm and preferably in thicknesses of
0.5 to 2 mm, though again, the thickness according to the invention
is not limited to these ranges.

25 The seeding efficiency of the second component may be an inherent
property of the material selected or may be the result of an
additional treatment step. Treatment steps which may be employed
according to the invention to achieve the requisite seeding
efficiency include those of surface-modification by application of a
30 material, such as serum, fibronectin or RGD peptide; by a chemical
method, such as acid hydrolysis, or by plasma treatment.

Appropriate methods according to the invention for coupling the second component to the first component are by stitching, preferably crocheting, by means of a binder, an adhesive or by heat
5 sealing.

The implantable article according to the invention is suitable for implantation into tissue defects. According to a second aspect of the invention, synthetic implants are provided, the synthetic implants
10 comprising an implantable article according to the first aspect of the invention.

The synthetic implants according to the second aspect of the invention may comprise unmodified sections of implantable article,
15 though cut, if necessary, to a suitable shape, such as a quadrilateral, a circle, a triangle or other appropriate form.

Alternatively, the synthetic implants according to the second aspect of the invention may be presented in a modified form suitable for
20 different surgical applications.

A first alternative form of synthetic implant according to the second aspect of the invention comprises a plurality of superimposed, mutually connected implantable articles, as defined above, also cut
25 to a relevant shape, if appropriate. Suitable methods according to the invention for attaching the superimposed layers to one another include those methods detailed above for coupling of the second component to the first component.

30 A second alternative form of the synthetic implant according to the second aspect of the invention comprises a spirally wound (i.e. a

“Swiss Roll”-type of arrangement) implantable article. According to a modification of the second alternative, the synthetic implant may comprise a plurality of superimposed implantable articles which is then spirally wound to form a “Swiss Roll”. According to a further
5 modification of the second aspect, the synthetic implant may comprise a plurality of “Swiss Rolls” aligned longitudinally, parallel to one another, plaited or twisted together.

A third alternative form of the synthetic implant according to the
10 second aspect of the invention comprises a serpentine or “concertina”-type of arrangement of an implantable article, wherein, in each case, juxtaposed curves of the “concertina” are affixed to one another. According to a modification of the third alternative, the synthetic implant may comprise a plurality of superimposed
15 implantable articles, which is then formed into a serpentine arrangement.

A fourth form according of the synthetic implant according to the second aspect of the invention comprises a tube of the implantable
20 article attached together along an edge or a plurality of mutually connected concentric tubes of this type.

In a preferred form, the synthetic implant comprises an implantable article which has been spirally wound into a “Swiss Roll”. In this
25 embodiment, the windings may be interconnected to prevent unravelling by means of stitching, by impregnation with a binder, by use of an adhesive or by heat sealing. The “Swiss Roll”-type arrangement is a procedurally efficient way of ensuring that the second component of the implantable article within which cells may
30 be seeded is present throughout the synthetic implant.

Advantageously, according to this form of the invention, the second

component of the implantable article is coupled by physical attachment to the first component of the implantable article so as to be co-extensive with one of the surfaces of the first component.

5 In a particularly preferred form, the synthetic implant according to the invention comprises an implantable article comprising:

- (a) a first component comprising an elongate fabric tape
- (b) a second component comprising a non-woven felt,

10

the second component being attached to one of the surfaces of the first component so as to be co-extensive with said surface, the implantable article being spirally wound into a "Swiss Roll" with the free end being secured to prevent unravelling. Advantageously,

15 according to this form of the invention, the first component comprises poly(lactic acid) fibres and the second component comprises poly(glycolic acid) fibres.

Suitably, synthetic implants in the form of a "Swiss Roll" have a
20 diameter in the range 5-15 mm. Advantageously, the end regions will have a reduced diameter in the range 9-11 mm, to enable them to be located within a bone tunnel, which will generally have a diameter in this range. Alternatively, a plurality of "Swiss Rolls" of smaller diameter may be employed. In this case, they may be
25 longitudinally aligned and plaited or arranged in a twisted fashion.

Optionally, the synthetic implant according to the invention may be received within a porous sleeve comprising a resorbable material. Appropriate resorbable materials are those listed above in relation
30 to the first and second components of the implantable article. The sleeve may comprise a fabric, such as a knitted, woven, crocheted

or braided material. Preferably, it is a braided material. This has the advantage of preventing abrasion damage when the implantable article is *in vivo*. In the event that a porous sleeve is present, then it is preferred that it be shorter than the "Swiss Roll" or the plurality of "Swiss Rolls", so that its or their ends protrude from the sleeve at one or both ends thereof.

Synthetic implants according to the invention may comprise cells. Incorporation of cells may be carried out either before or after implantation, but is preferably carried out prior to implantation. If carried out before implantation, tissue growth may be carried out exclusively *in vivo* but may also be preceded by *in vitro* tissue culturing. Preferably there is a stage of *in vitro* tissue growth prior to implantation.

15

The cells are normally incorporated into synthetic implants according to the invention by means of a carrier medium. The carrier medium may be a medium which is retained by the implantable medical article, for example a hydrogel, or one which substantially passes through the implantable medical article, such that, after seeding, it is substantially no longer present therein - the cells remaining within the article, particularly within the second component. Examples of this type of carrier medium are cell culture media. Preferably, a cell culture medium is employed to seed the cells, for example DMEM (DULBECO'S™ Modified Eagle's Medium containing 10% calcium).

If the carrier medium is a hydrogel it may be incorporated within and/or on and/or around at least the second component. Preferably, the carrier medium is incorporated at least within the second component, since this efficiently utilises the available open volume

30

for cellular growth. More preferably, the carrier medium occupies the entire open volume of the second component. Hydrogels which may be used as carrier media according to the invention comprise positively charged, negatively charged and neutral hydrogels which may be saturated or unsaturated. Examples of hydrogels which may be used according to the invention are TETRONICS™ and POLOXAMINES™, which are poly(oxyethylene)-poly(oxypropylene) block copolymers of ethylene diamine; polysaccharides, chitosan, poly(vinyl amines), poly(vinyl pyridine), poly(vinyl imidazole), polyethylenimine, poly-L-lysine, growth factor binding or cell adhesion molecule binding derivatives, derivatised versions of the above, e.g. polyanions, polycations, peptides, polysaccharides, lipids, nucleic acids or blends, block-copolymers or combinations of the above or copolymers of the corresponding monomers; agarose, methylcellulose, hydroxypropylmethylcellulose, xyloglucan, acetan, carrageenan, xanthan gum/locust beangum, gelatine, collagen (particularly Type 1), PLURONICS™, POLOXAMERS™, POLY(N-isopropylacrylamide) and N-isopropylacrylamide copolymers.

The cells with which synthetic implants according to the invention may be seeded comprise cells which are terminally differentiated or capable of undergoing phenotypic change e.g. stem cells, pluripotent cells and other precursor cells. More specifically, mesenchymal, tenocytes, ligamentous and chondrocytic cells may be seeded into the synthetic implants according to the invention.

As stated above, it is preferred to seed the synthetic implants and to at least partially grow tissue therein *in vitro* prior to implantation. With this in mind, in a preferred form of the second aspect of the invention, the synthetic implant additionally comprises a third

component, wherein the third component comprises biological tissue.

In the event that the implantable medical article is seeded with cells and biological tissue is grown *in vitro*, then, if one or both of the first and second components comprises a resorbable material, then one or both of said first and second components, as the case may be, may be resorbed prior to implantation. Preferably, the second component is resorbable and is substantially resorbed prior to implantation. This leads to a third aspect of the invention:

According to a third aspect of the invention, a hybrid implant is presented comprising a first component and a third component, coupled thereto, wherein the first component comprises a fabric and the third component comprises biological tissue generated by culturing a cell-seeded synthetic implant according to the second aspect of the invention, such that the second component has substantially resorbed.

As employed herein, the term "culturing" means supplying with nutrients and maintaining conditions (e.g. temperature, pH) which propagate cell growth.

According to a fourth aspect of the invention, a method of making an implantable article according to the first aspect of the invention is presented, the method comprising the steps of manufacturing a first component comprising a fabric having first and second surfaces; encasing the first component in, or incorporating within the first component, or attaching to at least a portion of at least one of the opposing surfaces of the first component a second component

15

which comprises a material capable of being seeded with and supporting the growth of cells.

According to a fifth aspect of the invention, a method of making
5 synthetic implants is presented, the method comprising the step of forming an implantable article made according to the fourth aspect of the invention by applying the step of:

- (a) cutting the implantable article to the desired shape, or
- 10 (b) superimposing a plurality of implantable articles, securing them to one another and, optionally, cutting to a desired shape, or
- (c) spirally winding an implantable article or a plurality of superimposed implantable articles, or
- 15 (d) arranging an implantable article or a plurality of superimposed implantable articles in a serpentine fashion such that juxtaposed curves are affixed to one another, or
- (e) arranging an implantable article as a tube or a plurality of mutually connected concentric tubes.

20

According to a sixth aspect of the invention, a method of making hybrid implants is presented, the method comprising the step of seeding a synthetic implant made according to the fifth aspect of the invention with cells and culturing said seeded synthetic implant
25 under conditions conducive to the growth of cells for a sufficient period of time to permit growth of a biological tissue.

In the event that one or both of the first and second components of the implantable article comprised within the synthetic implant
30 comprises a resorbable material, then one or both of said first and second components, as the case may be, may be resorbed prior to

implantation. In a preferred form of the sixth aspect of the invention,
the second component comprises a resorbable material and
becomes resorbed during the growth of the biological tissue to
generate a hybrid implant according to the third aspect of the
5 invention.

According to a seventh aspect of the invention, a synthetic implant
according to the second aspect of the invention or a hybrid implant
according to the third aspect of the invention is implanted into an
10 wound site in a mammalian organism in clinical need thereof.

As used herein, the term "wound site" means any site where a
change in the tissue from its normal condition has occurred, for
example a change as a result of traumatic insult or degenerative
15 changes.

20 As stated in the introduction synthetic implants and hybrid implants
according to the invention may be used for the partial or total
replacement of tissue, particularly connective tissue such as
ligament, cartilage, bone, meniscus, tendon, skin and the like.
Ligaments which may be totally or partially replaced include the
25 medial and lateral collateral ligaments, the anterior and posterior
cruciate ligaments (ACL and PCL respectively) and ligaments and
tendons of the elbow and hand. Tendons which may be totally or
partially replaced include the achilles tendon and patellar tendon.
The present invention finds particularly effective application in total
30 or partial ACL-replacement and in the total or partial replacement

of the rotator cuff of the glenohumeral joint. Reference hereinafter to "implants" includes reference to both synthetic and hybrid implants.

The rotator cuff comprises four tendons, the supraspinatus, 5
infraspinatus, teres minor and subcapularis. Ruptures to the supraspinatus are the most common problem encountered. For rotator cuff applications, an implant manufactured from the implantable article according to the invention may be shaped in a generally triangular configuration, as shown in EP 0 7 44 165 or in 10
the short or long Y shape as utilised in the RCR™ device commercially available from Merck Biomaterial, France.

Alternatively, if reinforcement is the issue, an implant comprising a strip of implantable article may suffice. Rotator cuff implants may be 15
secured in place by any conventional means known to those skilled in the art, e.g. suturing, suture anchors, bone fixation devices and bone screws.

Implants according to the present invention may also be used to 20
partially/totally replace or augment other tissues such as the achilles tendon, medial collateral ligament (MCL), posterior cruciate ligament (PCL), patella tendon, lateral collateral ligament (LCL) and ligaments and tendons of the elbow and hand.

Implants described herein can be used to repair a patellar tendon 25
harvest site. Typically, when the patellar tendon is harvested from a patient, a portion of the tendon (e.g., the middle one third of the tendon) is harvested with patella and tibial bone plugs integrally attached thereto. The use of the harvested patellar tendon for reconstruction of ligaments is considered advantageous because 30
the tissue is derived from the host patient and the implanted tendon readily allows rapid tissue ingrowth. However, studies have shown

that after a patellar tendon autograft, the tissue that replaces the harvested patellar tendon often does not have the histological characteristics of a normal patellar tendon. Moreover, even after healing, patients often experience discomfort and pain at the
5 patellar tendon harvest site.

To repair the patellar tendon harvest site, an implant according to the invention is implanted into the site following harvesting of the bone-patellar-tendon-bone graft and secured, e.g., by fixing the
10 implant into the site. In one embodiment, the implant is disposed along the length of the patellar tendon and the implant is secured to the remaining natural patellar tendon, e.g., by suturing opposite sides of the implant to the tendon. In another embodiment, the implant is secured to the tibia and patella, e.g., by cementing,
15 suturing, stapling or fixing with one or more screws.

Implants according to the invention may also be used to repair a ruptured or torn Achilles tendon. For example, the implant can be used to repair tears that occur within the Achilles tendon itself,
20 severing the tendon, or the implant can be used to repair ruptures, which result from the tendon tearing off of the calcaneus.

For Achilles tendon repair, the implant may be composed of elements that have load-bearing properties similar to the naturally
25 occurring Achilles tendon and is designed so as to allow new Achilles tendon growth on the implant. The implant preferably comprises a bioresorbable material that has the property of resorbing slowly in the body, e.g., PLA. The slow resorption allows retention of the mechanical properties of the implantable material
30 until a time when the newly reconstructed Achilles tendon can take over the load-bearing functions of the implant.

To repair a torn or ruptured achilles tendon, standard surgical methods of identifying and locating the torn tendon can be used. Briefly, a longitudinal incision is made just medial to the Achilles tendon and the severed end(s) of the ruptured tendon identified. 5 Where the Achilles tendon is severed from within, the opposite ends of the implant are attached to each of the torn tendon ends, e.g., by suturing the first end of the implant to the first end of the torn Achilles tendon and suturing the second end of the implant to the 10 second end of the torn Achilles tendon, thereby reattaching the first and second ends. Alternatively, where the Achilles tendon is torn away from the calcaneus, the surgical method includes attaching a first end of the implant to the calcaneus and the second end of the implant to the torn end of the Achilles tendon, e.g., by suturing, 15 thereby reattaching the Achilles tendon to the calcaneus.

Reference is made to the embodiments shown in the figures. Other features and advantages will become apparent from the following description and from the claims. 20

Figure 1 illustrates a synthetic implant according to an embodiment of the invention.

Figs.2-4 illustrate front and back views, made by SEM, of an implantable article made according to Example 1. 25

Figure 5 shows a synthetic implant according to Example 2, 3 months after implantation into an ovine stifle joint.

30 Figure 6 illustrates a biochemical analysis of synthetic implants, harvested after implantation, as described in Example 3. In

particular, it compares the amount of DNA and GAG present in the harvested synthetic implants with that in a natural ACL.

Figure 7 illustrates a biochemical analysis of synthetic implants,
5 harvested after implantation, as described in Example 3. In this case, it compares the amount of collagen and tissue found in the harvested synthetic implant as compared with a natural ACL.

Figure 8 is an H&E section through the femoral aspect of a synthetic
10 implant harvested after implantation, as described in Example 3.

Figure 9 is a transverse H&E section through an aspect of a
synthetic implant harvested after implantation, as described in
Example 3, at higher magnification than the view shown in Figure 8.
15

Figure 10 illustrates a knee joint in which an implant comprising an implantable article has been implanted during an anterior cruciate ligament (ACL) reconstruction procedure.

20 With reference to Fig.1, a synthetic implant according to an embodiment of the invention is illustrated comprising an implantable article, in which the second component (1) is attached to the first component (2) so as to be co-extensive with one of the opposing surfaces of the first component, the implantable article being spirally
25 wound to form the synthetic implant. The first component (2) may, for example, comprise an elongate fabric tape comprising poly(lactic acid) fibres and the second component (1) may comprise a non-woven felt comprising poly(glycolic acid) fibres. As can be seen from the figure, the second component is stitched onto one of the
30 opposing surfaces of the first component.

EXAMPLE 1: MANUFACTURE OF IMPLANTABLE ARTICLE

PLA yarn (90 filament) is twisted at 200 turns/metre "S" direction, wound onto 16 braider spools and braided at 1680 picks per metre.

- 5 PLA yarn (40 filament) is twisted at 200 turns/metre "S" direction and wound onto 11 knitting spools, and two weft spools.

The implantable article is manufactured as follows.

- 10 Bar 1 Eleven ends of yarn at one per guide knitting 01/01/01/01/ at 4 gauge (needles/cm)

Bar 2 One end of yarn laying in at $1, 1/1, 1/(n+2), (n+2)/(n+2), (n+2)$
Where n = Number of braids.

- 15 Bar 3 Ten braided ends of PLA Laying in at 00/00/00/00/ at one end per tube.

Bar 4 As bar 2 but in opposition.

Bar 5 A specially constructed unit laying in 1mm thick PGA felt (density - 45mg/cm^3) behind the last guide bar.

- 20 Courses/metre are set at 535. The felt is cut slightly too wide to insert into the knitting and the sides of the tape are trimmed later.

- 25 With reference to Figs.2-4, Fig.2 illustrates a view of one side of the implantable article, with the PGA-felt being visible on the far side of the fabric tape. Fig.3 is a more magnified version of part of Fig.2.

Fig.4 illustrates the opposing side of the implantable medical article, showing the PGA-felt and the stitching attaching it to the PLA-tape.

EXAMPLE 2: MANUFACTURE OF SYNTHETIC IMPLANT

The implantable article made according to Example 1 was cut into the 280mm lengths and held at both ends of the outer braid. The outer braid was twisted so that the scaffold rolled over itself to form a spiral section structure. The lip formed by this process was
5 attached to the rest of the scaffold by stitching PLA fibre through the scaffold and lip along the entire length of the device.

EXAMPLE 3: IMPLANTATION OF SYNTHETIC IMPLANT OF
EXAMPLE 2 FOR ACL REPAIR

10

5 Female sheep, approximately 2 years old, weighing between 55 and 80kg were used for this investigation.

Implantation

15

Long acting amoxicillin (Clamoxyl LA 150mg/ml; Pfizer Ltd) was administered by intramuscular injection, at a dose of approximately 15mg/kg bodyweight at the time of surgery and two days post surgery. Anaesthesia was induced with injectable 5% Thiopentone
20 sodium (Intraval Sodium; Rhone Merieux Ltd) administered 'to effect' by rapid intravenous injection at an approximate dose of 15mg/kg. Following induction the animals were intubated with an appropriately sized endotracheal tube. Anaesthesia was maintained using a halothane/oxygen/nitrous oxide mixture.

25

The lateral parapatellar incision was used to expose the joint. The patella was dislocated medially. The stifle joint was assessed visually to ensure the absence of gross pathology e.g. degenerative joint disease. The stifle joint was flexed to expose the anterior
30 cruciate ligament which was resected as close to its origin and

insertion sites as possible. All visible particulate matter was be removed from the joint and flushed with sterile physiological saline.

Using an adapted, standard orthopaedic drill guide, a Kirschner wire
5 (K-wire) was inserted from the medial border of the proximal tibia
(approximately 1cm distal to the joint surface and midway between
anterior and posterior aspects of the tibia) and directed in to the
joint at the point of insertion of the resected anterior cruciate
ligament. An appropriately designed drill bit was slipped over the K-
10 wire and a suitable bone tunnel, extending into the joint, was
created. All resultant visible debris was removed and the articular
borders of the bone tunnel smoothed to reduce abrasion of the
device.

15 An orthopaedic cruciate 'hook' was inserted from between the
femoral condyles and directed posteriorly towards the caudo-lateral
aspect of the lateral condyle to exit lateral and proximal to the lateral
fabella. The 'hook' was used to guide a graft passer into the joint
from the lateral aspect of the lateral condyle, around the posterior of
20 the lateral condyle to exit in the inter-condylar space. Using the
graft passer the synthetic implant was inserted from the anterior
aspect of the inter-condylar space, between the condyles and
around the caudo-lateral aspect of the lateral condyle to exit at the
disto-lateral femur. The femoral end of the synthetic implant was
25 anchored to the disto-lateral femur with standard orthopaedic
screws and washers. Using a graft passer the tibial end of the
synthetic implant was passed from the joint space into and through
the tibial tunnel. The tibial end of the synthetic implant was
tensioned to ensure it has been inserted fully and was then
30 anchored with standard orthopaedic RCI (round head cannulated

inside-out) screws inserted into the tunnel from the medial aspect of the tibia and directed towards the joint.

5 The patella was relocated and the limb manipulated through the full range of normal motion approximately five times. The intra-articular portion of the ligament was assessed for tautness. Following implantation to the satisfaction of the surgeon excess length of synthetic implant was removed from the medial aspect of the tibia. The patella was relocated and the incisions sutured in the standard
10 surgical manner. Robert-Jones type dressings were applied and maintained for approximately 7 days post surgery. Analgesia (buprenorphine - Vetergesic; Animalcare) was administered at completion of surgery and maintained for a minimum of 48 hours post surgery. Antibiotic cover was maintained for 4 days.

15 Following recovery from the surgical procedures the animals were individually housed for a minimum of 7 days and then group housed until return to pasture at approximately 5 weeks post surgery. All skin sutures (including resorbable sutures) were removed at 10 to
20 14 days post surgery or once healing has occurred. Animals were clinically observed during the recovery period. Recovery was uneventful in all cases.

Harvest

25 Animals were terminated and tissue biopsied at 13 weeks (+/- 1 week) from the date of surgery. The stifle joint was examined for gross pathology and then analysed histologically and biochemically

Biochemistry

30 All sections of the synthetic implant, native tissue samples and controls were freeze dried overnight, then papain digested at 60°C.

The papain solution containing digested sample was separated from the residual scaffold material and used for the following analyses: total collagen, sulphated glycosaminoglycans (GAG) and DNA.

5 Histology

Samples were fixed in 10% formalin and embedded in paraffin. The samples were sectioned (approximately 6µm) and stained with picrosirrus red and haematoxylin and eosin (H&E).

10

Results

Gross pathology.

15 Figure 5 shows the intact ACL scaffold at 3 months. Tissue can be seen completely encapsulating the synthetic implant, indicated by pointer (3).

Biochemistry

20

Figure 6 illustrates the DNA and GAG assay results. They show that the native ACL has low levels of DNA, as it is composed largely of extra cellular matrix and is generally acellular. The slightly higher levels in the implanted synthetic implants represent cells invading the device upon implantation. On the other hand, the GAG levels in the devices are comparable to that found in the natural ACL.

25

Figure 7 shows the collagen and % dry weight of tissue results found in the implanted synthetic implants. Even at this early time point, the synthetic implants already contained approximately half the level of collagen of the natural ACL.

30

Histology

5 Within the bone tunnel, the synthetic implant was infiltrated with cellular fibrous tissue; alignment of collagen extending between braids and surrounding the braid was also observed when visualised under polarised light. The arrangement of the braids was open allowing optimum incorporation of tissue.

10 Within the articular region (figures 8-9), the braid (4) was incorporated with tissue which in many areas was very dense and ligamentous-like in appearance. This tissue also stained intensely with picro-sirius red suggesting that the major component was collagen (5). In Figure 9, the individual fibres (6) are visible,
15 surrounded by ingrown tissue.

In summary, the synthetic implant has been shown to support tissue ingrowth and it was apparent that the tissue was beginning to mature into a dense, ligamentous tissue.

20

EXAMPLE 4: ROTATOR CUFF REPAIR

Implants were generated by cutting implantable articles, manufactured as in Example 1, into 20 x 15 mm lengths (of 1mm
25 thickness).

Ten matched pairs of fresh shoulders from Merino sheep were dissected to expose the infraspinatus tendon and its insertion. The tendon was carefully detached from its insertion using sharp
30 dissection. The insertion site was measured (average 19.0 x 13.3mm). Using an 8mm square template, four MITEK GII™ suture anchors were used to reattach the infraspinatus tendon using simple

stitches #2 ETHIBOND™. In half the samples, the repair was reinforced with an implant, as defined above, placed on the top of the tendon. Sutures were passed through the tendon and implant using standard simple suturing technique. A bone trough 4 x 15mm was prepared using a rongeur in the juxta-articular portion of the greater tuberosity. Three #5 ETHIBOND™ sutures were then passed through the trough and through two drill-holes 5mm apart placed 10mm distal to the tip of the greater tuberosity. In half of the matched specimens the sutures were reinforced by passage through the scaffold. The ends were tied to form a loop 10 cm long.

EXAMPLE 5: Use of an implant comprising the biocompatible, implantable material to repair the ACL

Implants comprising implantable articles described herein may be used for reconstructing a torn anterior cruciate ligament (ACL). Referring to Fig.10, a knee joint is shown in which an implant (7) has been implanted during an ACL reconstruction procedure. For ACL reconstruction, the implant (7) comprises elements that have load-bearing properties similar to the naturally occurring ACL. An implant (7) for an ACL repair is designed to be porous so as to allow new ACL tissue growth thereon/therewithin. It is important that the porosity does not collapse or decrease significantly when implant (7) is extended longitudinally.

25

The implant (7) preferably comprises the bioresorbable material PLA, which has two key features: PLA resorbs slowly, and it has load-bearing properties similar to the naturally occurring ACL. The slow resorption is important so as to allow retention of the mechanical properties until a time when the newly reconstructed ACL can take over load-bearing functions.

30

Prior to surgically implanting the implant (7), the surgeon removes the torn ACL stump from the intercondylar notch and clears the ligament. A notchplasty procedure is preferably performed to
5 expand the intercondylar notch (8) of the femur (an example of such a notchplasty procedure is described in U.S. Patent 5,139, 520, the contents of which are incorporated herein by reference). A femoral tunnel (9) for receiving one end of the implant (7) and a tibial tunnel (10) for receiving the other end of implant (7) are drilled. The two
10 tunnels should be formed so that they enter the joint at the proper anatomic attachment points. These points are preferably on the knee joint surfaces where the original ACL was attached. The procedure for providing the femoral tunnel (9) and tibial tunnel (10) is described in greater detail in U.S. Patent 5,306,301, the contents
15 of which are incorporated herein by reference.

The implant (7) is inserted through the femoral tunnel (9) and exits an opening in the femur (11). The femoral end of the implant (7) is attached to the femur by any of a number of different procedures
20 known in the art, e.g., cementing, suturing, stapling, or fixing with a screw. The tibial end of implant (7) is then passed from the joint space into the tibial tunnel (10). The tibial end of the implant (7) is tensioned and attached within the tibial tunnel, e.g., by cementing, suturing, stapling, or fixing with a screw. Once the implant (7) is
25 secured in place in the tibia, it is viewed arthroscopically and is assessed for tightness. The knee is also moved through its normal range of motion to assure that impingement of implant (7) does not occur. Following implantation to the satisfaction of the surgeon, excess length of implant (7), if necessary, is removed from
30 the tibia.

Other embodiments are within the scope of the following claims:

5

10

15

20

25

30

CLAIMS

1. Implantable article comprising a first component and a second component coupled thereto, wherein the first component
5 comprises a fabric and the second component comprises a material capable of being seeded with and supporting the growth of cells.
2. Implantable article according to claim 1, wherein the first component comprises a woven, non-woven, knitted, braided or
10 crocheted material or a mixture of these.
3. Implantable article according to claim 1 or claim 2, wherein the second component comprises a woven or non-woven material, a foam, a sponge or a mixture of these.
15
4. Implantable article according to any one of the preceding claims, wherein either or both of the first and second components comprise bioresorbable or non-bioresorbable materials.
- 20 5. Implantable article according to claim 4, wherein the bioresorbable materials comprise bioresorbable polymers or copolymers comprising hydroxy acids, glycolic acid; caprolactone; hydroxybutyrate; dioxanone; orthoesters; orthocarbonates; aminocarbonates.
25
6. Implantable article according to claim 5, wherein the bioresorbable material comprises polylactic acid, polyglycolic acid or a mixture of these.
- 30 7. Implantable article according to claim 4, wherein the non-bioresorbable materials comprise polyesters; polyamides;

polyalkenes; poly(vinyl fluoride); polytetrafluoroethylene; carbon fibres; natural or synthetic silk and mixtures of these materials.

8. Implantable article according to claim 7, wherein the non-
5 bioresorbable material comprises a polyester selected from polyethylene terephthalate and polybutylene terephthalate.
9. Implantable article according to any one of the preceding
10 claims, wherein the first component comprises first and second surfaces.
10. Implantable article according to claim 9, wherein the second
component is attached to at least one of the first and second
surfaces of said first component.
15
11. Implantable article according to claim 10, wherein the second
component is co-extensive with one of the surfaces of the first
component.
- 20 12. Synthetic implant comprising an implantable article according to any one of the preceding claims.
13. Synthetic implant comprising an implantable article according to claim 11.
25
14. Synthetic implant according to claim 12 or 13, wherein the implantable article is spirally wound.
15. Synthetic implant according to any one of claims 12 to 14,
30 wherein the first component of the implantable article comprises

braided material and the second component of the implantable article comprises a non-woven material.

16. Synthetic implant according to claim 15, wherein the braided
5 material comprises polylactic acid yarns and the non-woven material comprises polyglycolic acid fibres.

17. Synthetic implant according to any one of claims 12 to 16,
which is seeded with cells.

10

18. Synthetic implant according to claim 17, wherein the cells
comprise mesenchymal, tenocytes, ligamentous and chondrocytic
cells or mixtures of these.

15 19. Method for the total or partial replacement of connective
tissue in a mammalian patient comprising the step of implanting a
synthetic implant as defined in any one of claims 12 to 18.

20. A method of supporting tissue growth at a selected site in a
20 body, comprising: providing an implantable article comprising a first
component and a second component coupled thereto, wherein the
first component comprises a fabric and the second component
comprises a material capable of being seeded with and supporting
the growth of cells; and implanting the implantable article at the
25 selected site.

21. The method of claim 20 wherein the implanting includes
attaching the implantable article to a tissue at the selected site.

30 22. The method of claim 21 wherein the tissue to which the
implantable article is attached is a connective tissue.

23. The method of claim 22 wherein the connective tissue is a ligament, tendon or muscle.
24. The method of claim 21 wherein the attaching is performed
5 by cementing the implantable article to the tissue.
25. The method of claim 21 wherein the attaching is performed by suturing the implantable article to the tissue.
- 10 26. The method of claim 21 wherein the attaching is performed by fixing the implantable article to the tissue with at least one screw.
27. The method of claim 20 wherein the implanting includes attaching a first portion of the implantable article to a first support
15 structure and attaching a second portion of the implantable article to a second support structure, such that the implantable article connects the first support structure to the second support structure.
28. The method of claim 27 wherein the first and second support
20 structures are a tibia and a femur, said attaching further comprising attaching the first and second portions of the implantable article to regions of the tibia and femur, respectively, proximate attachment regions of a natural cruciate ligament.
- 25 29. The method of claim 27 wherein the first and second support structures are a tibia and a femur, said attaching further comprising attaching the first and second portions of the implantable article to regions of the tibia and femur, respectively, proximate attachment sites of a natural collateral ligament.

30. The method of claim 27 wherein the first and second support structures are a humerus and a rotator cuff muscle, said attaching comprising attaching the first and second portions of the implantable article to regions of the humerus and the rotator cuff muscle, respectively, thereby reattaching the rotator cuff muscle to the humerus.

31. The method of claim 27 wherein the first support structure is a first portion of a torn Achilles tendon and the second support structure is a second portion of the torn Achilles tendon, said attaching further comprising attaching the first portion of the implantable article to the first portion of the torn Achilles tendon and the second portion of the implantable article to the second portion of the torn Achilles tendon, thereby reattaching the portions.

32. The method of claim 27 wherein the first and second support structures are a tibia and a patella, said attaching further comprising attaching the first and second portions of the implantable article to regions of the tibia and patella, respectively, proximate attachment sites of a natural patellar tendon.

33. A method of supporting growth of a knee ligament, comprising:
providing an implantable article comprising a first component and a second component coupled thereto, wherein the first component comprises a fabric and the second component comprises a material capable of being seeded with and supporting the growth of cells; attaching a first portion of the implantable article to a first support structure of the knee; and attaching a second portion of the implantable article to a second support structure of the knee.

34. The method of claim 33 wherein the first and second support structures are a tibia and a femur, said attaching comprising attaching the first and second portions of the implantable article to
5 regions of the tibia and femur, respectively, proximate attachment regions of a natural cruciate ligament.

35. The method of claim 33 wherein the first and second support structures are a tibia and a femur, said attaching comprising
10 attaching the first and second portions of the implantable article to regions of the tibia and femur, respectively, proximate attachment regions of a natural collateral ligament.

36. A method of supporting growth of a rotator cuff, comprising:
15 providing an implantable article comprising a first component and a second component coupled thereto, wherein the first component comprises a fabric and the second component comprises a material capable of being seeded with and supporting the growth of cells;
and attaching a first portion of the implantable article to a first
20 support structure of the shoulder; and attaching a second portion of the implantable article to a second support structure of the shoulder.

37. The method of claim 36 wherein the first and second support structures are a humerus and a rotator cuff muscle, said attaching
25 comprising attaching the first and second portions of the implantable article to regions of the humerus and rotator cuff muscle, respectively, thereby reattaching the rotator cuff muscle to the humerus.

30 38. A method of supporting growth of an Achilles tendon, comprising: providing an implantable article comprising a first

component and a second component coupled thereto, wherein the first component comprises a fabric and the second component comprises a material capable of being seeded with and supporting the growth of cells; and attaching a first portion of the implantable
5 article to a first support structure of an ankle; and attaching a second portion of the implantable article to a second support structure of the ankle.

39. The method of claim 38 wherein the first support structure is a
10 first portion of a torn Achilles tendon and the second support structure is a second portion of the torn Achilles tendon, said attaching further comprising attaching the first portion of the implantable article to the first portion of the torn Achilles tendon and the second portion of the implantable article to the second portion of
15 the torn Achilles tendon, thereby reattaching the portions.

40. A method of treating a tissue harvest site, comprising: providing an implantable article comprising a first component and a second component coupled thereto, wherein the first component comprises
20 a fabric and wherein the second component comprises a material capable of being seeded with and supporting the growth of cells; and implanting the implantable article at the harvest site.

41. The method of claim 39 wherein the tissue harvest site is at a
25 patellar tendon.

42. The method of claim 39 wherein the tissue harvest site is at a semitendinosus.

Fig.1

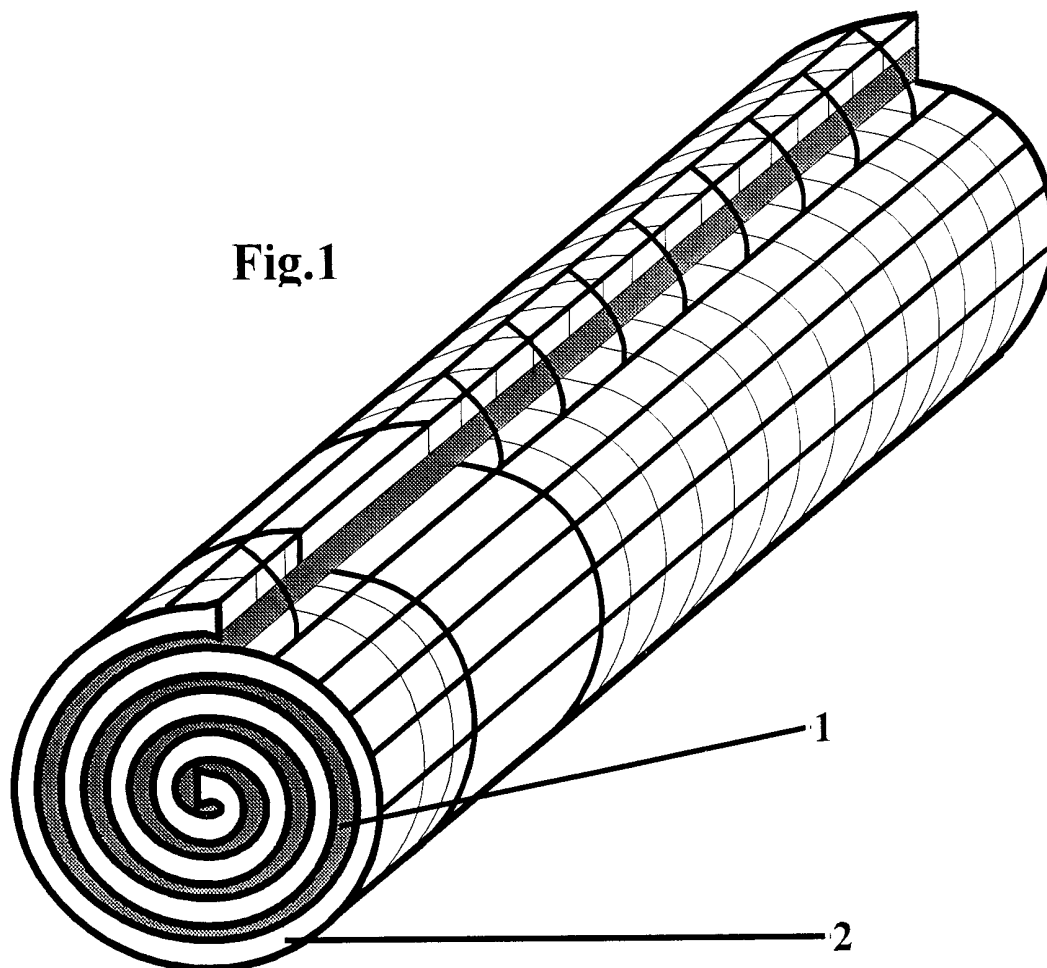


Fig.2

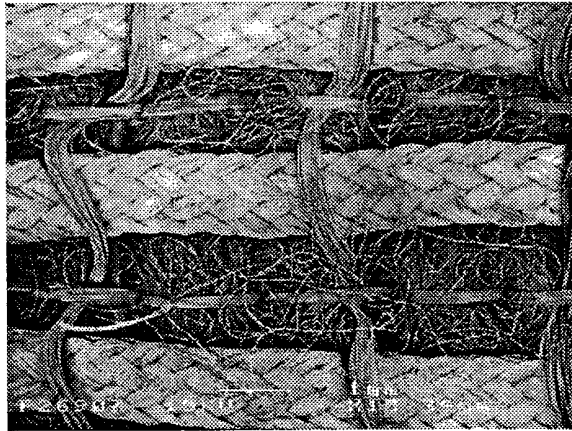


Fig.3

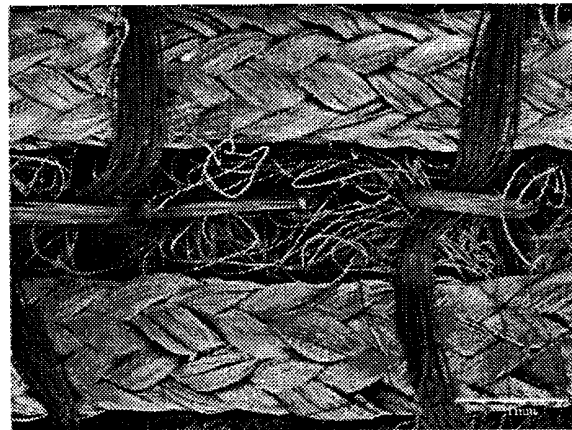


Fig.4

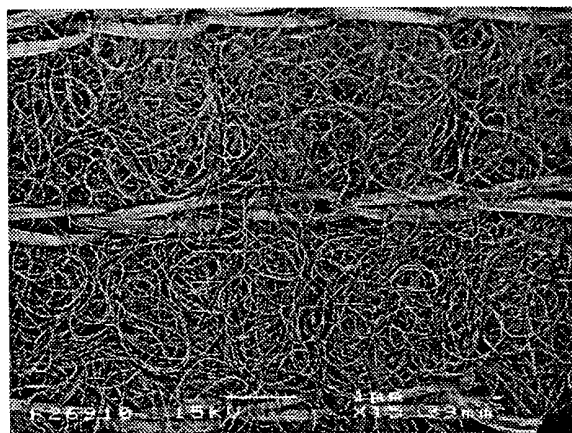


Fig.5

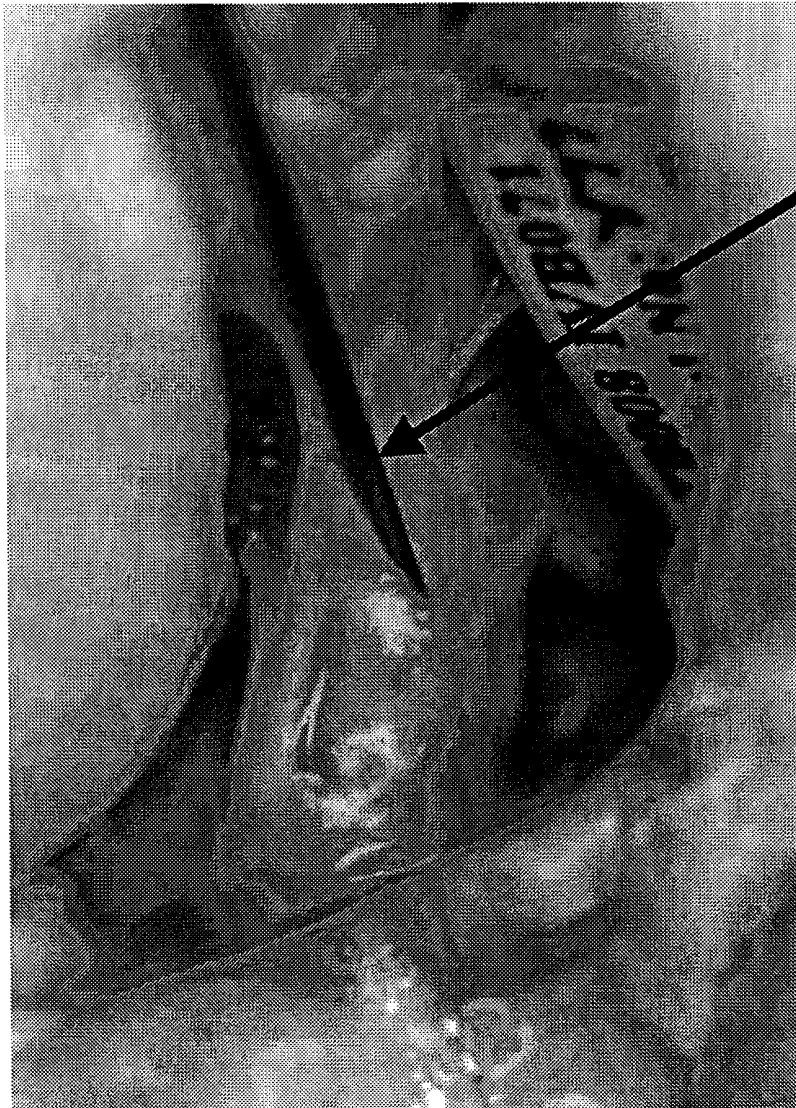


Fig.6

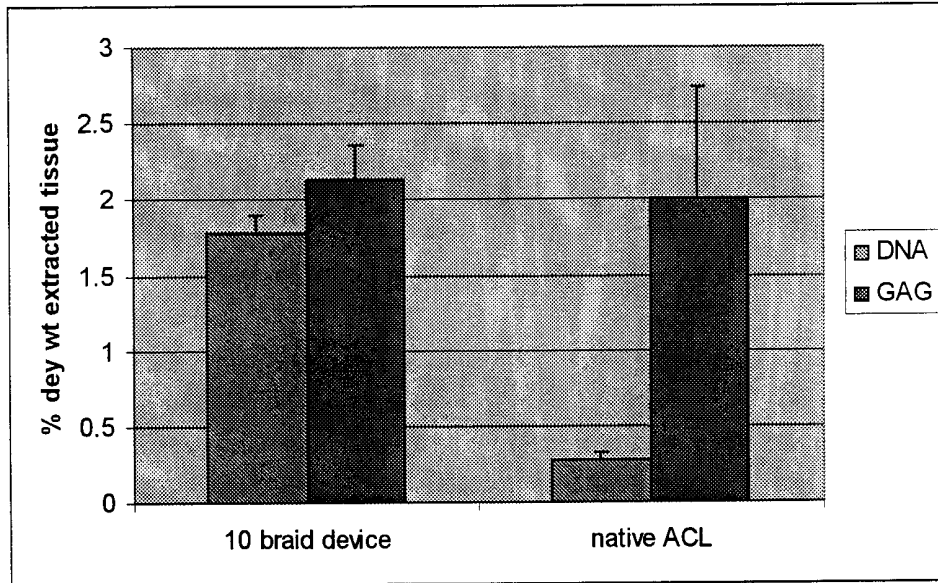


Fig.7

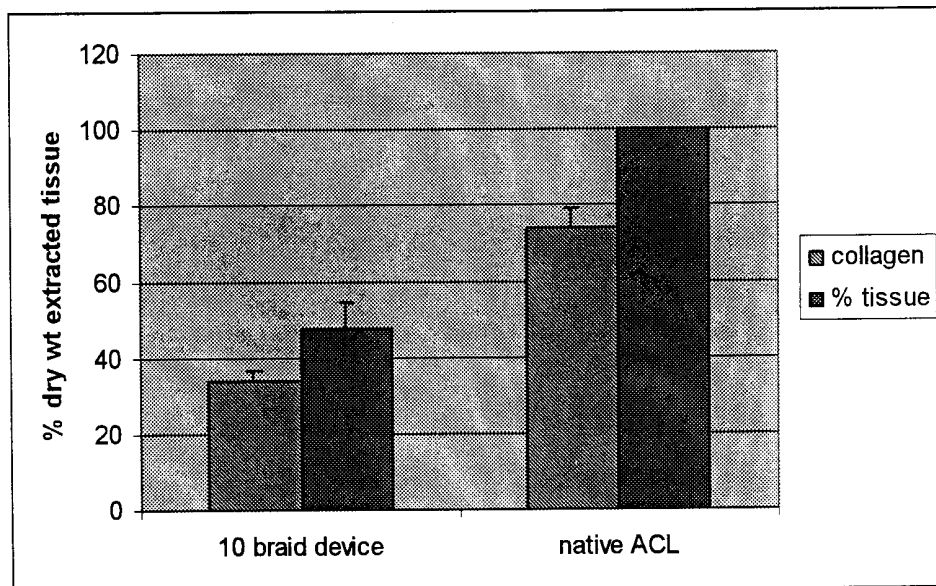


Fig.8

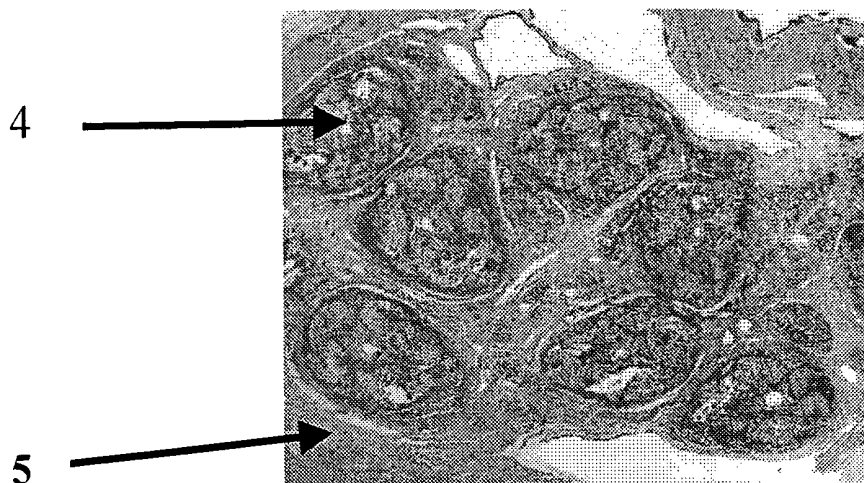
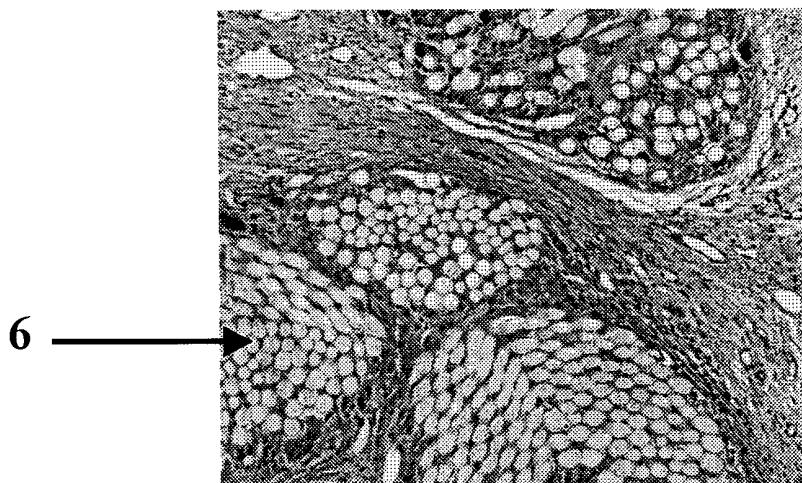
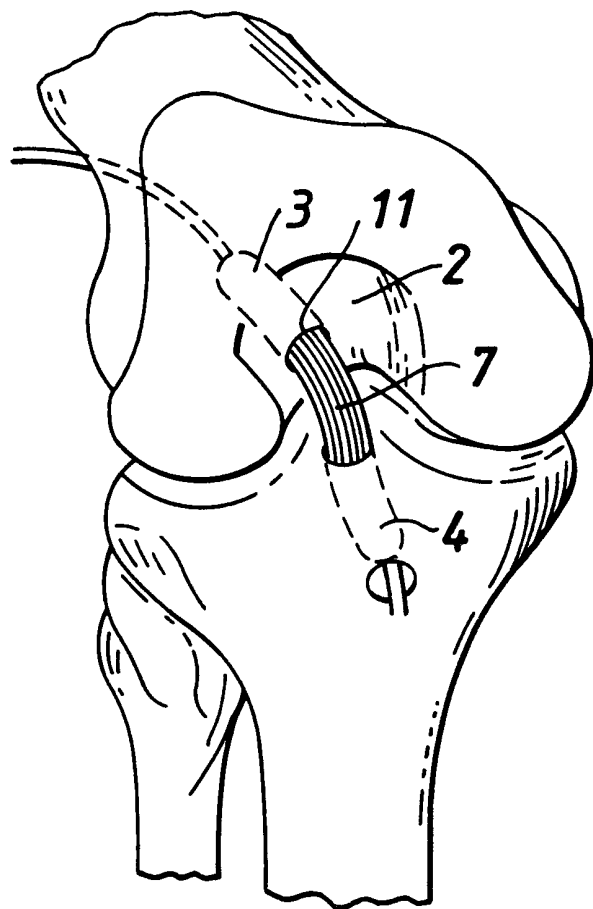


Fig.9



6/6

FIG.10.



INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 00/04166

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61L27/18 A61L27/38 A61F2/08

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)
 IPC 7 A61L A61F

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 practical, search terms used)
 EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 595 621 A (HARVEY WILSON ET AL) 21 January 1997 (1997-01-21) column 6, line 35 - line 46; claims; examples ---	1-4,12, 14,19, 21-23
A	EP 0 303 496 A (ETHICON INC) 15 February 1989 (1989-02-15) claims ---	1-42
A	US 4 942 875 A (HLAVACEK ROBERT A ET AL) 24 July 1990 (1990-07-24) claims; examples ---	1-42
A	US 5 197 983 A (BERMAN ANDREW B ET AL) 30 March 1993 (1993-03-30) claims; examples 1-5 ---	1-42
	-/--	

Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

<p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*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)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p>	<p>*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</p> <p>*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</p> <p>*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.</p> <p>* & * document member of the same patent family</p>
--	--

Date of the actual completion of the international search 2 February 2001	Date of mailing of the international search report 09/02/2001
---	---

Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer ESPINOSA, M
--	--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/04166

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 458 636 A (BRANCATO DONALD H) 17 October 1995 (1995-10-17) claims -----	1-42
A	US 5 376 118 A (MUTH ROSS R ET AL) 27 December 1994 (1994-12-27) claims -----	1-42

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/04166

Patent document cited in search report	A	Publication date	Patent family member(s)	Publication date
US 5595621	A	21-01-1997	GB 2282328 A AT 180977 T AU 673769 B AU 7430694 A CA 2133028 A EP 0645149 A ES 2134907 T HK 1002251 A JP 2963015 B JP 7250889 A US 5514181 A ZA 9407263 A	05-04-1995 15-06-1999 21-11-1996 13-04-1995 30-03-1995 29-03-1995 16-10-1999 07-08-1998 12-10-1999 03-10-1995 07-05-1996 19-03-1996
EP 0303496	A	15-02-1989	JP 1131668 A JP 2637782 B	24-05-1989 06-08-1997
US 4942875	A	24-07-1990	US 4792336 A AU 594435 B AU 6959887 A CA 1282205 A DK 106687 A EP 0239775 A FI 870898 A, B, JP 62270152 A KR 9501375 B NO 870858 A, B, US 4987665 A ZA 8701489 A	20-12-1988 08-03-1990 10-09-1987 02-04-1991 04-09-1987 07-10-1987 04-09-1987 24-11-1987 18-02-1995 04-09-1987 29-01-1991 21-08-1987
US 5197983	A	30-03-1993	NONE	
US 5458636	A	17-10-1995	NONE	
US 5376118	A	27-12-1994	US 5217495 A US 5147400 A US 4990158 A EP 0485986 A CA 2016493 A, C DE 69021261 D DE 69021261 T EP 0397500 A	08-06-1993 15-09-1992 05-02-1991 20-05-1992 10-11-1990 07-09-1995 01-02-1996 14-11-1990