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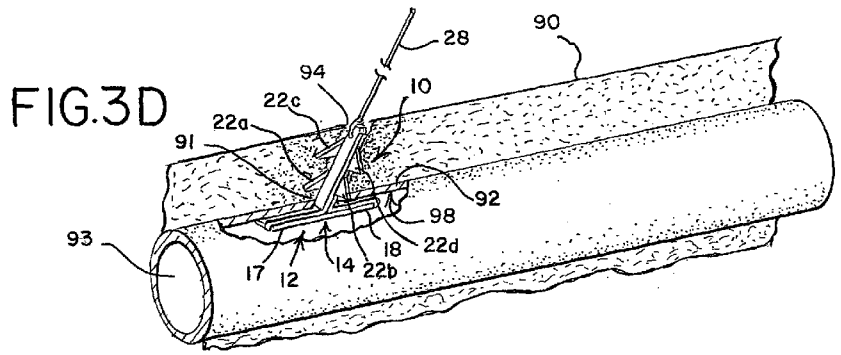
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(57) Abstract: A vessel puncture closure device and assembly for sealing a vessel puncture in a patient includes a unitary T-shaped puncture sealant, including a planar base hingedly connected to a planar post prior to delivery in the patient, including at least one puncture tract retainment member. The puncture sealant is formed from a planar elongate sheet of foldably bonded bio-compatible material, such as ECM sheet material. A bioabsorbable suture attachably extends from the post. The base includes two legs projecting in opposite directions from a proximal end of the post. Each of the base and post comprises a planar elongate structure having a rectangular or obround shape. The base is configured to seal the vessel puncture, while allowing fluid flow through a blood vessel following deployment. The puncture tract retainment member is configured to prevent re¬ entry of the post into a blood vessel lumen and facilitate the seating of the base against the inside wall of the vessel following deployment.

# VESSEL PUNCTURE CLOSURE DEVICE

[0001] This application claims the benefit of priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 61/146,863, filed January 23, 2009, which is hereby incorporated by reference in its entirety.

## TECHNICAL FIELD

[0002] This invention relates generally to a medical device for sealing a puncture in the wall of a blood vessel, such as a puncture in a femoral artery accompanying an intravascular access procedure.

## BACKGROUND

[0003] Percutaneous access of the vascular system for vascular device delivery is a common medical procedure. Typically this involves using a hollow needle to puncture a vessel, then introducing an introducer sheath to open the puncture site for the introduction of catheters and wire guides for navigation through the vascular system to facilitate delivery of suitable interventional devices. In many cases, vascular access requires introduction of catheters and wire guides through the femoral artery. Once the appropriate interventional procedure is completed, the introducer sheath is removed and pressure is applied to the puncture site to stop the bleeding. However, vascular complications, including prolonged bleeding originating from the vessel puncture site, are a relatively common occurrence, especially where femoral access is initiated. Accordingly, the market for vascular closure devices (VCDs) currently exceeds a half billion dollars worldwide.

**[0004]** The development of the VCD market has been accompanied by a varied collection of devices categorized, for example, as being placed in the tissue track or artery versus those applied on the skin; devices actively approximating the edges of the arteriotomy versus those that do not; devices inducing clotting versus those that do not; and devices that leave behind a foreign body versus those that resorb into the tissues quickly or slowly (reviewed in Turi, Endovascular Today, July/August 2008, pp. 24-32). Many of the existing VCDs have complicated structural configurations and/or less than optimal manufacturing processes. In addition, some VCDs are relatively difficult to deploy or may render the access site more vulnerable to complications if accessed again. Accordingly, it is an object of the present invention to provide a simple, easily manufactured device that can be easily deployed without leaving behind any foreign bodies or otherwise rendering an access site vulnerable to later complications.

## SUMMARY

**[0005]** In one aspect, a vessel puncture closure device for sealing a vessel puncture in a patient includes a unitary T-shaped puncture sealant comprising a planar base hingedly connected to a planar post prior to delivery in the patient comprising at least one puncture tract retainment member. The base and post are formed from a planar elongate sheet of foldably bonded biocompatible material. A bioabsorbable suture attachably extends from the post. The base includes two legs horizontally projecting in opposite directions from a proximal end of the post. Each of the base and post comprises a planar elongate structure having a rectangular or obround shape. The base is configured to seal the

vessel puncture, while allowing fluid flow through a blood vessel, such as an artery or vein, following deployment. The puncture tract retainment member is configured to prevent re-entry of the post into a blood vessel lumen and facilitate the seating of the base against the inside wall of the vessel following deployment.

**[0006]** The puncture sealant may be formed from a planar elongate sheet of folded biocompatible material, whereby terminal sheet portions foldably bonded to one another to form the post, and central sheet portions are foldably bonded to one another to form the two legs. Puncture tract retainment member(s) may be configured as a pair of barbs extending substantially perpendicularly from opposite faces of the post when deployed in a patient, each of the barbs including two edges joined to form a pointed end extending downward to a position adjacent to the outer surface of the vessel upon deployment over the puncture. Alternatively, or in addition, the puncture tract retainment member may be configured to form a plug of expandable biocompatible material. In desired embodiments, ECM sheet materials are used to form the puncture sealant. A stiffening material in the form of polymeric substance, chemical crosslinker, or wire may be used to increase the rigidity of ECM sheet material and the component parts derived therefrom.

**[0007]** In another aspect, a vessel puncture closure device assembly includes a vessel puncture closure device connectively linked by a bioabsorbable suture to a deployment shaft. The bioabsorbable suture extends through the deployment shaft lumen from the distal shaft end past the proximal shaft end. In a particular assembly, the device is preloaded into a transfer tube that is coupled to the deployment shaft. In particular, the deployment shaft may be configured to

coaxially extend through the transfer tube and through the introducer when the transfer tube is connectively linked to the introducer. In this embodiment, the transfer tube is configured to allow coupling and entry of the device through a check flow seal in an adaptor linked to an introducer in an introducer set.

**[0008]** In a further aspect, a method for sealing a percutaneous puncture in a blood vessel of a patient includes connectively linking (or loading) a vessel puncture closure device and a deployment shaft to an introducer. The device is pushed through the introducer by extending the deployment shaft though the introducer in a proximal to distal direction, whereby the puncture sealant is extended through an epidermal puncture site and an adjoining puncture tract extending into the vessel lumen of a patient. Then, the deployment shaft is retracted, and the bioabsorbable suture is pulled in a distal to proximal direction to translocate the post and the puncture retainment member from the vessel lumen, through the puncture, and into the puncture tract, wherein translocation of at least one puncture tract retainment member into the puncture creates a puncture sealant configuration preventing re-entry of the post and facilitating seating of the base against the inner surface of the vessel wall to seal the puncture, while allowing fluid flow through the vessel. The step of connectively linking the device and the deployment shaft to the introducer may be mediated by linking a transfer tube preloaded with the device to an introducer through a check flow seal in an adaptor linked to the proximal end of the introducer. The deployment shaft may be connected to the transfer tube by coaxially inserting a distal portion of the shaft into a proximal portion of the transfer tube.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0009]** FIG. 1A illustrates a plan view of an exemplary closure device according to an embodiment of the present invention.

**[0010]** FIG. 1B illustrates a side view of the embodiment depicted in FIG. 1A.

**[0011]** FIG. 2 illustrates a planar elongate sheet of biocompatible material for forming the puncture sealant depicted in FIGs. 1A and 1B.

**[0012]** FIG. 3A illustrates a closure device assembly and method for delivering the closure device depicted in FIGs. 1A and 1B in a patient according to an embodiment of the present invention.

**[0013]** FIG. 3B illustrates a portion of the closure device assembly depicted in FIG. 3B.

**[0014]** FIG. 3C illustrates a closure device assembly and method for delivering the closure device depicted in FIGs. 3A and 3B.

**[0015]** FIG. 3D illustrates the closure device depicted in FIGs. 1A and 1B sealing a vessel puncture in a patient.

**[0016]** FIG. 4A illustrates a closure device assembly and method for linking a closure device to the introducer depicted in FIG. 3A.

**[0017]** FIG. 4B illustrates a closure device assembly depicting a closure device disposed in a transfer tube connectively linked to a deployment shaft.

**[0018]** FIG. 4C illustrates the closure device assembly of FIG. 4B connectively linked to an introducer.

## DETAILED DESCRIPTION

**[0019]** In order to provide a clear and consistent understanding of the specification and claims, the following definitions are provided.

**[0020]** As used herein, the term "proximal" is used in its conventional sense to refer to the end of the member (or component) that is closest to the operator during use.

**[0021]** The term "distal" is used in its conventional sense to refer to the end of the member (or component) that is initially inserted into the patient, or that is closest to the patient.

**[0022]** The term "biocompatible" refers to a material that is substantially non-toxic in the *in vivo* environment of its intended use, and that is not substantially rejected by the patient's physiological system or is non-antigenic. This can be gauged by the ability of a material to pass the biocompatibility tests set forth in International Standards Organization (ISO) Standard No. 10993; the U.S. Pharmacopeia (USP) 23; or the U.S. Food and Drug Administration (FDA) blue book memorandum No. G95-1, entitled "Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing." Typically, these tests measure a material's toxicity, infectivity, pyrogenicity, irritation potential, reactivity, hemolytic activity, carcinogenicity, immunogenicity, and combinations thereof. A biocompatible structure or material, when introduced into a majority of patients, will not cause a significantly adverse, long-lived or escalating biological reaction or response, and is distinguished from a mild, transient inflammation which typically accompanies surgery or implantation of foreign objects into a living organism.

**[0023]** The term "foldably bonded" refers to folded sheet portions bonded to one another to form a 3-dimensional structure whereby a bonding agent or adhesive is applied to the folded sheet portions or wherein the folded sheet

portions are subjected to a bonding process, such as dehydration bonding or the like.

**[0024]** The term "sheet of foldably bonded biocompatible material" refers to a substantially flat unitary sheet of foldably bonded material. The sheet of foldably bonded material may be derived from a single sheet layer of material or it may contain a plurality of sheet layers or tissue layers bonded or laminated to one another with or without an additional coating layer.

**[0025]** The terms "expanded ECM material" and "expandable ECM material" are used interchangeably to refer to a porous ECM material composition processed from a natural ECM tissue source material treated under alkaline conditions and subjected to sufficient cross-linking to form a material capable of expanding from a dried compressed state by at least two times its original bulk volume when placed in a fluid medium.

**[0026]** FIGs. 1A and 1B depict a vessel puncture closure device 10 for sealing a blood vessel puncture according to one embodiment of the present invention. FIGs. 3A-3C depict an exemplary vascular closure device assembly 66 for delivering an exemplary puncture closure device 10 (FIG. 3D) of the present invention to a puncture 91 in a blood vessel 92, such as an artery or vein, following an intravascular access procedure through, for example, the femoral or brachial arteries.

**[0027]** The vessel puncture closure device 10 includes a unitary T-shaped puncture sealant 12 and a bioabsorbable suture 28 attachably extending from the sealant 12. The sealant 12 includes a planar base 14 hingedly connected to a planar post 20, the sealant 12 being formed from a planar elongate sheet of

foldably bonded biocompatible material. Thus, the base 14 and post 20 are connected to form a flexible hinge 27, which can allow the post 20 to lay flat against the base 14 in a deployed state. The base 14 includes two legs 17, 18 projecting in opposite directions from a distal post end 30. The base 14 is configured to seal the vessel puncture 91, while allowing fluid flow through the vessel following deployment. The post 20 includes at least one puncture tract retainment member 22 configured to prevent re-entry of the post 20 into the vessel lumen 93 and facilitate the seating of the base 14 against the inner surface 98 of the vessel 92 following deployment. In FIGs. 1A and 1B, the sealant 12 includes four puncture retainment members 22 configured as downwardly directed barbs, 22a-22d.

**[0028]** The base 14 and post 20 are generally configured as planar elongate structures having a rectangular or obround shape. These structures are generally flat by nature, but may contain portions that may expand in volume when placed in an aqueous environment or when exposed to bodily fluids, such as blood. The dimensions of the base 14 and post 20 can vary depending on the size of the puncture 91, the puncture tract 96 and the size of the vessel 92. In exemplary embodiments, the length of the post 20 may vary between about 0.05 inches to about 0.5 inches, or more. In desired embodiments, the length of the post 20 may range between about 0.15 to about 0.3 inches. In exemplary embodiments, the length of the base 14 may vary between about 0.08 inches to about 0.8 inches, or more. In desired embodiments, the length of the base 14 may range between about 0.2 to about 0.5 inches. Although, the dimensions can be varied, the proximal end 30 of the post 20 generally will be joined to the base

14 at the midpoint of the longitudinal axis of the base 14 as depicted in FIGs. 1A and 1B. Accordingly, the length of each leg 17, 18 typically will be about half the length of the base 14. Further, the length of the post 20 generally will exceed the length of at least one leg 17, 18, although this is not an essential requirement.

**[0029]** In FIGs. 1A, 1B, the post 20 includes four puncture tract retainment members, which are depicted as downwardly directed barbs 22a-22d. The puncture retainment member(s) 22 may be integral to the post 20 or may be connectively linked to the post 20. In a desired embodiment, the puncture tract retainment member 22 is a folded appendage integral to the post 20. A puncture retainment member 22 includes one or more structural features that are designed to prevent re-entry of the post 20 into the vessel lumen 93, provide anchoring of the post 20 to a puncture tract 96, or both.

**[0030]** In one embodiment depicted in FIGs. 1A and 1B, a first barb 22a extends substantially perpendicularly from a left plane face 39 of the post 20 when deployed in a patient, and a second barb 22b extends substantially perpendicularly from a right plane face 40 of the post 20 when deployed in a patient. Each of the first and second barbs 20a, 20b includes two barb edges 36, 37 joined to form a pointed end 38 extending downward toward the outer surface of the vessel 92 upon deployment over the puncture 91. As shown in FIG. 1B, the pointed ends 38 in the first and second barbs 20a, 20b may extend from opposite post faces 39, 40 when deployed. Further, each of the first and second barbs 20a, 20b may foldably extend from an edge 41, 42, respectively, along the longitudinal axis of the post 20. An additional pair of barbs 20c, 20d may be included to aid in anchoring the post 20 to the puncture tract 96.

**[0031]** In another embodiment, the puncture retainment member 22 may comprise an expandable plug portion in the post 20. The expandable plug portion may be integral to the post 20 and may be incorporated into a sheet of biocompatible material prior to folding. Further, in addition to the expandable plug portion, the post 20 may additionally include other puncture retainment members, including, for example, two barbs 22a, 22b or four barbs 22a-22d as depicted in FIGs. 1A-1B. For example, in one embodiment, a distal end portion 31 of the post 20 may include an integrally associated expandable plug portion surrounding the flexible hinge 27 and two barbs positioned between the plug portion and the proximal post end 32. Alternatively, the post 20 may be configured as a planar sheet of biocompatible material or expandable ECM material prior to delivery, whereby all or part of post 20 expands in the puncture tract 96 to a sufficient degree so as to prevent re-entry of the post 20 into the vessel lumen 93 following delivery of the device 10. In either case, the sealant 12 may be formed from a planar elongate sheet of foldably bonded biocompatible or ECM material, including portions in the post 20 that are configured to expand in the puncture tract 96, and non-expanding portions in the base 14 and legs 17, 18.

**[0032]** The puncture sealant 12 is formed into a unitary T-shaped structure using a sheet of biocompatible material. Exemplary biocompatible materials include synthetic polymeric substance materials, ECM materials, and combinations thereof. In a desired embodiment, the sealant 12 is formed from a planar elongate sheet 44 of foldably bonded biocompatible material. In a desired

embodiment, the sealant 12 is formed from a planar elongate sheet 44 of foldably bonded ECM material.

**[0033]** The sheet 44 of biocompatible material may have a substantially flat, elongated rectangular or obround shape, which may be foldably bonded in a number of different ways to create a unitary T-shaped puncture sealant 12 having a planar base 14 hingedly connected to a planar post 20. For example, FIG. 2 depicts an exemplary sheet 44 of biocompatible material that can be foldably bonded to form the sealant 12 depicted in FIGs. 1A and 1B. Adhesives or bonding agents may be applied to sheet portions folded up against one another when forming (by foldable bonding), for example, the post 20, legs 17, 18, and/or base 14. Folded sheet portions may be bonded to one another using any suitable adhesive, bonding agent, or bonding methodology known to those of skill in the art as further described below.

**[0034]** In FIG. 2, the sheet 44 is defined by left and right terminal sheet portions 46, 48 flanking a central sheet portion 54. The left terminal sheet portion 46 is defined by a left sheet end 50 and left sheet fold 51; the right terminal sheet portion 48 is defined by a right sheet end 52 and a right sheet fold 53. The left and right terminal sheet portions 46, 48 can be foldably bonded to one another to form the post 20.

**[0035]** The central sheet portion 54 is defined by central sheet left terminal and right terminal portions 56, 58 flanking a central sheet inner portion 60. The central sheet left terminal portion 56 is defined by a left sheet fold 51 and a central sheet left fold 62; the central sheet right terminal portion 58 is defined by a central sheet right fold 64 and a right sheet fold 53. When folded to form the T

shaped sealant 12, the central sheet left terminal portion 56 may be foldably bonded over the left half of the central sheet inner portion 60, such that the central sheet left terminal portion 56 forms the left leg top face 19. Likewise, the central sheet right terminal portion 58 may be foldably bonded over the right half of the central sheet inner portion 60, such that the central sheet right terminal portion 58 forms the right leg top face 21. Consequently, the central sheet inner portion 60 can be configured to form the bottom base face 25.

**[0036]** In another embodiment, the sheet of foldably bonded biocompatible material is defined by terminal sheet portions 46, 48 flanking a central sheet portion 54, wherein a proximal portion of the central sheet is foldably bonded to a distal portion of the central sheet portion to form the post 20. A sheet of biocompatible material may be foldably bonded to form a post 20 hingedly coupled to a base 14 by a number of different folding schemes known to those of skill in the art.

**[0037]** As shown in FIG. 2, the left and right terminal sheet portions 46, 48 may be further defined by oppositely facing left terminal sheet barbs 20a, 20b and right terminal sheet barbs 20b, 20d, respectively, which are configured to form puncture retainment members. The barbs 20a-20d may be further folded substantially perpendicularly to the plane of the sheet 44. In addition to facilitating retainment of the post 20 in the puncture tract 96 following deployment as described above, the folded barbs 20a-20d can further reduce the width of the post 20 to allow loading of the puncture sealant 12 into an introducer sheath 75 of a device assembly 66 as further described below.

**[0038]** In FIG. 2, the central sheet inner portion 60 or bottom base face 25 is depicted as having a wider width than the portions forming the leg faces 19, 21 or the post 20. However, it should be noted that the sheet portions depicted in the drawings are merely representational and are not to reflect the actual scale of the puncture sealant 12 materials. For example, the lengths and widths of the various sheet portions in FIGs. 1 and 2 may be increased in some instances or decreased in others, depending on the size or site of the puncture and/or the need for structural rigidity, etc. The drawings are intended to illustrate various implementations of the invention, which can be understood and appropriately carried out by those of ordinary skill in the art.

**[0039]** Sheet(s) 40 of biocompatible materials may include a variety of materials as further described below. In one embodiment, the sheet of biocompatible material includes a synthetic polymeric sheet material. In a desired embodiment, the sheet of biocompatible material 44 includes or is made from ECM sheet material. Alternatively, or in addition, portions of the ECM sheet material may be coated with a synthetic polymeric material or treated with a synthetic polymeric adhesive, for example, to provide increased rigidity. The use of puncture sealants 12 made from remodelable ECM sheet materials may allow for stable integration of the sealant 12 into the vessel tissue surrounding the puncture so as to permanently close the puncture 91 without leaving behind any trace of the device 10 following integration and resorption of the biocompatible materials therein.

**[0040]** Desirably, the sheet 44 of biocompatible material will be configured so that the base 14 is sufficiently rigid or stiff to enhance the sealing of the puncture

91 and/or the seating of the legs 17, 18 against an inner vessel wall 98. In one embodiment, the sheet material may be configuring as a multilayer sheet composed of multiple polymeric or tissue layers of laminated or otherwise linked layers (or laminated sheets) of biocompatible material.

**[0041]** In another embodiment, the sheet 44 of biocompatible material may further incorporate a stiffening material suitable for increasing the rigidity of the biocompatible sheet material 44. Applicant has discovered that a puncture sealant 12 made from one type of ECM sheet material softens when exposed to blood, thereby limiting the ability of the base 14 or legs 17, 18 to properly seat against the vessel surface 98 so as to effectively seal its corresponding vessel puncture 91. Thus, when using biocompatible material that soften in bodily fluids, a stiffening material may be included in at least a portion of the base 14 or legs 17, 18 to confer rigidity sufficient to allow seating (or sealing) of the legs and base against the inner surface of the vessel at the vessel puncture. Exemplary stiffening materials include coating layers or adhesive layers containing a stiffening polymer, chemical crosslinking agents, wires, and combinations thereof.

**[0042]** The stiffening material may be coated on one or more surfaces of the puncture sealant 12. In one embodiment, the stiffening material comprises a synthetic polymeric coating applied onto one or more surface(s) of an ECM sheet material prior to foldably bonding one or more puncture sealant 12 portions to one another as described above. For increased stiffness, the ECM sheet materials may include multilayer sheets of crosslinked ECM materials.

**[0043]** Alternatively, or in addition, a stiffening material, such an adhesive may be incorporated into the puncture sealant 12 between sheet portions during the

process of adhesive bonding. The adhesive may be incorporated between one or more sheets of ECM material and/or between one or more ECM tissue layers in any one of the ECM sheet materials. For example, ECM tissue layers may be laminated to one another to form a unitary ECM sheet construct, whereby a stiffening material is incorporated between the ECM tissue layers during the lamination step. Lamination may be achieved, for example, by crosslinking, including for example dehydrothermal crosslinking or chemical crosslinking, and/or by the use of a bonding agent or adhesive as further described herein.

**[0044]** Selection of a stiffening material or adhesive, and the manner of applying the same to portions of the puncture sealant 12 may be chosen to perform a desired function upon implantation. Depending on the objective, a stiffening material or adhesive may be applied to, or included within, any suitable part of the puncture sealant 12.

**[0045]** Exemplary polymers or polymer-forming substances for use as stiffening materials in coatings, for example, include polymeric substances selected from the group consisting of: poly(ethylene glycols) (PEGs); low molecular weight diols having a molecular weight from about 62-700, with or without aliphatic, alicyclic or aromatic groups, including ethylene glycol, diethylene glycol, propane 1,2-diol, propane 1,3-diol, butane 1,4-diol, butylene 1,3-glycol, neopentyl glycol, butyl ethyl propane diol, cyclohexane diol, 1,4-cyclohexane dimethanol, hexane 1,6-diol, bisphenol A (2,2-bis(4-hydroxyphenyl)propane), hydrogenated bisphenol A (2,2-bis(4-hydroxycyclohexyl)propane); polyurethanes, including THORALON™ (THORATEC, Pleasanton, Calif.), as described in U.S. Pat. Nos. 4,675,361,

6,939,377, and U.S. Patent Application Publication No. 2006/0052816, the disclosures of which are incorporated by reference herein; polyether ether ketone (PEEK), polyether block amide (PEBA), polytetrafluoroethylene (PTFE), low density polyethylene, linear low density polyethylene, high density polyethylene (HDPE), poly(lactic acid), poly(glycolide) and poly(lactide-co-glycolide) copolymers; polypropylene homopolymer, polypropylene random copolymer, polyolefins, polyimides, polystyrenes, styrene acrylate, styrene-acrylonitrile, styrene-acrylonitrile-butadiene, styrene butadiene, carboxylated styrene-butadiene, ethylene-vinyl acetate, ethylene-vinyl chloride, cyclic-olefin copolymer, vinyl chloride, polyvinyl chloride, polyvinyl acetate, alkyl acrylates, such as methyl methacrylate, polyvinylidene chloride, including copolymers, terpolymer, and blends thereof. In desired embodiments, the synthetic polymeric materials or polymer-forming substances are biocompatible and bioresorbable.

**[0046]** In one embodiment, the stiffening material is integral to the sheet of folded biocompatible material. In another embodiment, the stiffening material is applied as a coating over all, or a portion, of the puncture sealant 12. In a desired embodiment, the coating is formed from one or more of the above described polymeric substances configured to form a stiff bioresorbable coating prior to delivery in a patient, whereby the coating breaks down or dissolves with exposure to bodily fluids, thereby facilitating remodeling and integration of adjoining ECM sheet materials into the vessel 92 at the site of the vessel puncture 91. Coatings may be applied by any method known to those of skill in the art, including but not limited to spraying, dip coating, over-extrusion of the

polymeric coating onto a biocompatible sheet, or heat shrinking the coating as a laminate onto the sheet.

**[0047]** In some embodiments of the invention, sheet or tissue portions may be bonded or coated with one- or two component adhesive agents or glues, including for example, fibrin glue (e.g., having thrombin and fibrinogen as separate bonding components). For example, one component of a glue may be added to a sheet of material or layer of tissue after coating a previously-applied sheet or layer with one bonding component (e.g., thrombin) and coating a second sheet or layer with a second component of the bonding agent (e.g., fibrinogen). Thereafter, the sheet(s) or layer(s) are positioned over one another so as to bring the two bonding components into contact, thus causing the curing process to begin. This process can be repeated for any and all additional layers to be applied to the resulting construct.

**[0048]** In addition, the adhesive may be curable by light. For example, light curable adhesives suitable for medical devices are disclosed in U.S. Publication No. 2008/0004686 to James Hunt et al. and in U.S. Publication No. 2008/0306453 to James Elsesser et al., the disclosures of which are incorporated by reference herein.

**[0049]** Exemplary adhesives include, but are not limited to, the following: (1) cyanoacrylates such as ethyl cyanoacrylate, butyl cyanoacrylate, octyl cyanoacrylate, and hexyl cyanoacrylate; (2) fibrinogen, with or without thrombin, fibrin, fibropectin, elastin, and laminin; (3) mussel adhesive protein, chitosan, prolamine gel and transforming growth factor beta(TGF-B); (4) polysaccharides such as acacia, carboxymethyl-cellulose, dextran, hyaluronic acid, hydroxypropyl-

cellulose, hydroxypropyl-methylcellulose, karaya gum, pectin, starch, alginates, and tragacanth; (5) polymeric adhesives or glues made from polyacrylic acid, polycarbophil, modified hydromellose, gelatin, polyvinyl-pyrilidone, polyvinylalcohol, polyethylene glycol, polyethylene oxide, aldehyde reactive multifunctional chemicals, maleic anhydride co-polymers, and polypeptides; (6) bioactive ceramic-based sealants; and (7) any bioabsorbable and biostable polymers derivatized with sticky molecules such as arginine, glycine, and aspartic acid, and copolymers.

**[0050]** Alternatively, or in addition to the use of stiffening agents for increased rigidity, tissue adhesives may be applied to the top faces 19, 21 of the left and right legs 17, 18 to promote increased affinity or adherence of the leg faces 19, 21 to the inner blood vessel surface 98 against which they are urged.

**[0051]** Commercially available tissue adhesives that may be used include, but are not limited to: FOCALSEAL® (biodegradable eosin-PEG-lactide hydrogel requiring photopolymerization with Xenon light wand) produced by Focal; BERIPLAST® produced by Adventis-Bering; VIVOSTAT® produced by ConvaTec (Bristol-Meyers-Squibb); SEALAGEN™ produced by Baxter; FIBRX® (containing virally inactivated human fibrinogen and inhibited-human thrombin) produced by CryoLife; TISSEEL® (fibrin glue composed of plasma derivatives from the last stages in the natural coagulation pathway where soluble fibrinogen is converted into a solid fibrin) and TISSUCOL® produced by Baxter; QUIXIL® (Biological Active Component and Thrombin) produced by Omrix Biopharm; HEMASEEL APR™ (fibrin-based sealant) produced by Haemacure; BIOGLUE® (two component BSA:glutaraldehyde surgical adhesive produced by CryoLife; a

PEG-collagen conjugate produced by Cohesion (Collagen); Platelet Plasma Concentrate (PPC; fibrin-based sealant produced by PlasmaSeal; HYSTOACRYL® BLUE (ENBUCRILATE) (cyanoacrylate) produced by Davis & Geck; NEXACRYL™ (N-butyl cyanoacrylate), NEXABOND™, NEXABOND™ S/C, and TRAUMASEAL™ (product based on cyanoacrylate) produced by Closure Medical (TriPoint Medical); DERMABOND® which consists of 2-octyl cyanoacrylate produced as DERMABOND® by Ethicon; TISSUEGLU® produced by Medi-West Pharma; and VETBOND® which consists of n-butyl cyanoacrylate produced by 3M.

**[0052]** Bonding materials and methods adapted for use with ECM materials are further described in U.S. Pat. Appl. Publ. Nos. 2006/0147433, 2008/0183280, the disclosure of which is incorporated by reference herein.

**[0053]** Although preferred embodiments of the puncture sealant 12 are described as being made from foldably bonded biocompatible materials, a puncture sealant 12 may be alternatively prepared from ECM materials, including suitably cross-linked expandable ECM materials, or synthetic polymeric materials (as further described below), which are molded to form a unitary T-shaped device with a base 14 and post 20, whereby the sealant is linked to a suture 28 as described above,

**[0054]** Vascular Closure Device Assembly and Method of Use

**[0055]** FIGs. 3A-3C depict an exemplary vascular closure device assembly 66 for delivering an exemplary closure device 10 (FIG. 3D) of the present invention to a puncture 91 in a blood vessel 92. In one embodiment, as shown in FIGs. 3A-3C, the assembly 66 includes a closure device 10 (as described above),

including a puncture sealant 12 connectively linked to a deployment shaft 68 by a bioabsorbable suture 28. The deployment shaft 68 is configured to coaxially extend though an introducer 74, functioning as an elongate pushing device for axial movement though the introducer lumen 76 relative to the introducer sheath 75. The introducer 74 is defined by a distal introducer end 77 and a proximal introducer end 78. The deployment shaft 68 includes a sheath 69 and a lumen 70, the shaft 68 being defined by a distal shaft end 71 and a proximal shaft end 72. The puncture sealant 12 is connected to the distal end 29 of the suture 28, the suture containing a proximal suture end 31 extending though the proximal deployment shaft end 72..

**[0056]** In FIG. 3, the deployment shaft 68 is used as an elongate pusher suitable for expelling the closure device 10 from the distal end 77 of the introducer sheath 75. The puncture closure device 10 may be pushed distally by, or removably coupled to, the distal end of the deployment shaft 68 and deployable through the distal introducer end 77 by means of the relative axial movement of the deployment shaft 68. The shaft 68 may be configured as a catheter, stylet, or rod. Although the shaft 68 is depicted in FIG. 3B as having a relatively thin wall sheath 69 surrounding a lumen 70 having a substantially larger cross-sectional diameter than the width of the sheath 69, the lumen 70 need be only large enough to allow axial movement of the suture 28 therethrough.

**[0057]** The suture 28 includes a distal suture end 29 and a proximal suture end 31, the suture 28 extending through the shaft lumen 70 from the distal shaft end 71 past the proximal shaft end 72. In FIGs. 3A-3D, the suture 28 is connected though a hole in the post 20 at a suture connection site 34. The

suture 28 may be further centered and secured to the post 20 via a top post indent 33. The suture 28 may be connected to the puncture sealant in any suitable manner apparent to those of skill in the art. For example, the suture 28 may extend through or along the post 20, the distal suture 29 being connected to the legs 17, 18 or base 14 near the hinge 27.

**[0058]** Prior to deployment of the closure device 10, a closure device 10 according to the present invention may be loaded onto the distal end 71 of the deployment shaft 68 such that the suture extends through the entire length of the deployment shaft lumen 70. Alternatively, the closure device 10 may be preloaded into a transfer tube 79 (FIGs. 4A-4C) connectively linked to an introducer 74 and deployment shaft 68 as further described below. Following completion of a suitable percutaneous procedure, delivery catheter(s) and/or other delivery components are removed from the body 90 by way of the introducer 74. A deployment shaft 68 or transfer tube 79 loaded with a closure device 10 of the present invention is then inserted through a proximal portion of the introducer 74. The loaded deployment shaft 68 is extended through the introducer sheath lumen 76 (FIGs. 3A, 3B) until the puncture sealant 12 and the distal deployment shaft end 71 traverses through the puncture tract 96 into the blood vessel lumen 93 distal to the puncture 91 (FIG. 3C). Upon deployment of the closure device 10 into the vessel lumen 93, the introducer sheath 75 may be withdrawn from the body through the epidermal puncture site 94. Then, while holding the deployment shaft 68 and the suture 28, the deployment shaft 68 may be completely or partially withdrawn from the body 90 through the epidermal puncture site 94, leaving the suture 28 connected to the puncture sealant 12, the

suture 28 extending through the puncture tract 96 proximal to the body 90. Following retraction of the distal deployment shaft end 71 proximal to the vessel puncture 91, the suture 28 is retracted until there is resistance to further movement, whereby the legs 17, 18 of the base 14 become seated against the inner vessel surface 98, such that the legs 17, 18 and base 14 seal the puncture 91 and the puncture tract retainment member(s) 22a-22d on the post 20 become embedded or structurally engaged to the walls of the puncture tract 96. Following deployment of the puncture sealant 12, the proximal portion of the suture 28 extending outside the body 90 may be trimmed.

**[0059]** As one of skill in the art can appreciate, the length of the deployment shaft 68 in the assembly 66 may exceed the length of the introducer 74 to a sufficient degree so as to allow securement by the operator of a proximal portion of the deployment shaft 68 outside of the body 90 proximal to the epidermal puncture site 94 following withdrawal of the introducer 74. Similarly, the length of the suture 28 may exceed the length of the deployment shaft 68 to a sufficient degree so as to allow securement by the operator of a proximal portion of the suture 68 outside of the body 90 proximal to the epidermal puncture site 94 following withdrawal of the deployment shaft 68.

**[0060]** In another embodiment, a closure device assembly 66 may be configured for loading a closure device 10 onto an introducer set 73 though a check flow seal 89 in an adaptor 86 connectively linked to the proximal end 78 of an introducer 74 (FIGs. 4A-4C). In this assembly 66, the puncture sealant 12 is preloaded in a transfer tube 79. The transfer tube 79 is connectively linked to a deployment shaft 68. The transfer tube 79 is defined by distal 80 and proximal

81 ends and includes a transfer tube sheath 82 and a transfer tube lumen 83. A puncture sealant 12 is coaxially disposed in the transfer tube lumen 83. A suture 28, connectively linked to the puncture sealant 12, extends from the proximal end 81 of the transfer tube 79.

**[0061]** In one assembly 66, as shown in FIGs. 4A-4C, the transfer tube 79 is connectively linked to the deployment shaft 68 in a pre-assembled form. Specifically, the distal end 71 of the deployment shaft 68 may be coaxially disposed within a proximal portion of the transfer tube 79 in the assembly 66, such that the suture 28 extends through the transfer tube lumen 83 and through the deployment shaft lumen 70, the suture 28 extending beyond the proximal end 72 the deployment shaft 68. Alternatively, a transfer tube 79 containing the puncture sealant 12 may be subsequently linked to a deployment shaft 68, wherein the suture 28 is connectively threaded through the deployment shaft lumen 70 prior to connecting the assembly 66 to a suitable introducer 74.

**[0062]** Following completion of a suitable percutaneous procedure and withdrawal of accompanying delivery components from the introducer 74, the device 10 in FIGs. 4A-4C may be delivered by connecting the assembly 66 to an introducer set 73 as illustrated in FIG. 4A. In Fig. 4A, the introducer set 74 is depicted as an introducer 74 connected to tubing 85 by an adaptor 86. A stopcock 84 at the proximal end of the tubing 85 may be used to flush the introducer 73 with fluids, such as saline, to remove any air bubbles in the introducer 73. The adaptor 86 includes a lumen 88 and a check flow seal 89 adjacent to an adaptor insertion site 87. An assembly 66 containing a closure device 10 preloaded in a transfer tube 79 connectively linked to the distal end 71

of the deployment shaft 68 (FIG. 4B), is inserted though the adaptor insertion site 87, past the check flow seal 89 until the distal end 82 of the transfer tube sheath 82 is abutted against the proximal end 78 of the introducer sheath 75 as shown in FIG. 4C. Then, the deployment shaft 68 may be used to push the puncture sealant 12 through the introducer sheath lumen 76 to deliver the device 10 as described above.

**[0063]** In one embodiment, the assembly 66 may include an introducer sheath 75 structurally modified with apertures and/or modified lumenal portions to allow exchange (and insertion) of the deployment shaft 68 through a distal portion of the introducer sheath 75 (not shown). By way of example, such a modified introducer sheath may be exchanged with the pre-existing introducer sheath used for delivery of a percutaneous interventional device as described above. Moreover, such an embodiment can accommodate a shorter deployment shaft 68, inasmuch as withdrawal of the deployment shaft 68 does not require extension through the proximal introducer end 78, but rather an aperture through a distal portion of the modified introducer sheath 75 proximal to the epidermal puncture site 91 when deploying the device 10.

**[0064]** ECM Sheet Materials

**[0065]** As noted above, the puncture sealant 12 may be formed form one or more sheets of bioremodelable ECM sheet material, suitably configured to close a blood vessel puncture and become permanently integrated into the vessel tissue. In particular, bioremodelable ECM sheet material is capable of remodeling the surrounding vessel tissues, such that upon implantation in a patient, the sheet of bioremodelable material is degraded and replaced by the

patient's endogenous tissues. As the sheet of bioremodelable material is remodeled by host tissues, the vessel puncture becomes stably closed, obviating concerns about migration of the device or re-entry of percutaneous devices into the vessel region at a later date.

**[0066]** The sheet of bioremodelable material may include one or more bioremodelable tissue layers formed into a sheet. The sheet may include, for example, a single tissue layer containing ECM material, or it may include additionally adjacent tissue layers or additional tissue layers laminated together in a multilaminate structure. The sheet may include or be made from reconstituted or naturally-derived collagenous materials. Desired bioremodelable materials include naturally derived tissues with ECMs possessing biotropic properties, including in certain forms angiogenic collagenous ECMs. Desired ECMs include naturally-derived collagenous tissue materials retaining native matrix configurations and bioactive agents, such as growth factors, which serve to facilitate tissue remodeling, as opposed to collagen-based materials formed by separately purifying natural collagen and other associated components away from their native three dimensional matrix configurations or bioactive agents, including growth factors. Suitable collagenous ECMs include those derived from a variety of native tissues, including but not limited to, intestine, stomach, bladder, liver, fascia, skin, artery, vein, pericardium, pleura, heart valve, dura mater, ligament, tendon, bone, cartilage, bladder, liver, including submucosal tissues therefrom, renal capsule membrane, dermal collagen, serosa, mesenterium, peritoneum, mesothelium, various tissue membranes and basement membrane layers, including liver basement membrane, and the like.

Suitable submucosa tissue materials for these purposes include, for instance, intestinal submucosa, including small intestinal submucosa, stomach submucosa, urinary bladder submucosa, and uterine submucosa. A particularly preferred ECM material is porcine small intestinal submucosal (SIS) material. Commercially available ECM materials capable of remodeling to the qualities of its host when implanted in human soft tissues include porcine SIS material (Surgisis® and Oasis® lines of SIS materials, Cook Biotech Inc., West Lafayette, IN) and bovine pericardium (Peri-Strips®, Synovis Surgical Innovations, St. Paul, MN).

**[0067]** ECM sheet materials for use in the present invention may have a thickness in the range of about 0.2 mm to about 2 mm, more preferably about 0.4 mm to about 1.5 mm, and most preferably about 0.5 mm to about 1 mm. In desired embodiments, a multilaminate ECM sheet material may be employed. For example, a plurality of (i.e. two or more) layers of a remodelable collagenous ECM material can be bonded or otherwise coupled together to form a multilaminate sheet. Illustratively, two, three, four, five, six, seven, or eight or more layers of an remodelable collagenous material can be bonded together to provide a multilaminate material. In certain embodiments, two to six expanded, submucosa-containing layers isolated from intestinal tissue of a warm-blooded vertebrate, particularly small intestinal tissue, are bonded together to provide a medical material. Porcine-derived small intestinal tissue is preferred for this purpose. In alternative embodiments, one or more sheets of ECM material (e.g., submucosa) can be bonded or otherwise coupled to one or more sheets of an expanded remodelable collagenous material. Any number of layers can be used

for this purpose and can be arranged in any suitable fashion with any number of layers of a non-expanded remodelable collagenous material bonded to any number of layers of an expanded remodelable collagenous material. The layers of collagenous tissue can be bonded together in any suitable fashion, including dehydrothermal bonding under heated, non-heated or lyophilization conditions, using adhesives as described herein, glues or other bonding agents, crosslinking with chemical agents or radiation (including UV radiation), or any combination of these with each other or other suitable methods.

**[0068]** A variety of dehydration-induced bonding methods can be used to fuse portions of multi-layered medical materials together. In one preferred embodiment, the multiple layers of material are compressed under dehydrating conditions. The term "dehydrating conditions" can include any mechanical or environmental condition which promotes or induces the removal of water from the multi-layered medical material. To promote dehydration of the compressed material, at least one of the two surfaces compressing the matrix structure can be water permeable. Dehydration of the material can optionally be further enhanced by applying blotting material, heating the matrix structure or blowing air, or other inert gas, across the exterior of the compressing surfaces. One particularly useful method of dehydration bonding multi-layered medical materials is lyophilization, e.g. freeze-drying or evaporative cooling conditions.

**[0069]** Another method of dehydration bonding comprises pulling a vacuum on the assembly while simultaneously pressing the assembly together. This method is known as vacuum pressing. During vacuum pressing, dehydration of the multi-layered medical materials in forced contact with one another effectively bonds the

materials to one another, even in the absence of other agents for achieving a bond, although such agents can be used while also taking advantage at least in part of the dehydration-induced bonding. With sufficient compression and dehydration, the multi-layered medical materials can be caused to form a generally unitary laminate structure.

**[0070]** It is advantageous in some aspects of the invention to perform drying operations under relatively mild temperature exposure conditions that minimize deleterious effects upon the multi-layered medical materials of the invention, for example native collagen structures and potentially bioactive substances present. Thus, drying operations conducted with no or substantially no duration of exposure to temperatures above human body temperature or slightly higher, say, no higher than about 38°C, will preferably be used in some forms of the present invention. These include, for example, vacuum pressing operations at less than about 38°C, forced air drying at less than about 38°C, or either of these processes with no active heating at about room temperature (about 25°C) or with cooling. Relatively low temperature conditions also, of course, include lyophilization conditions. It will be understood that the above-described means for coupling two or more multi-layered medical materials together to form a laminate can also apply for coupling together one or more layers of peritoneum and fascia when these layers are isolated independent from one another.

**[0071]** When a multi-layered laminate material is contemplated, the layers of the laminate can be additionally crosslinked to bond multiple layers of a multi-layered medical material to one another. Crosslinking of multi-layered medical materials can also be catalyzed by exposing the matrix to UV radiation, by

treating the collagen-based matrix with enzymes such as transglutaminase and lysyl oxidase, and by photocrosslinking. Thus, additional crosslinking may be added to individual layers prior to coupling to one another, during coupling to one another; and/or after coupling to one another.

**[0072]** Bioremodelable ECM sheet materials may be isolated and used in the form of intact natural sheets, tissue layers, or strips, which may be optimally configured from native, wet, fluidized, or dry formulations or states into sheets, or knitted meshes using one or more of the following, including stretching, chemical crosslinking, lamination under dehydrating conditions, and/or compression under dehydrating conditions, in accordance with teachings set forth in U.S. Pat. Nos. 6,206,931 and 6,358,284; U.S. Patent Application Publication Nos. 2006/0201996, 2006/0052816, 2005/0249772, and 2004/0166169, and U.S. Pat. Appl. No. 61/074,441, entitled "Physically Modified Extracellular Matrix Materials and Uses Thereof," filed June 20, 2008, the teachings of which are expressly incorporated by reference herein, the disclosures of which are expressly incorporated by reference herein.

**[0073]** Synthetic Polymeric Sheet Materials

**[0074]** Bioremodelable ECM sheet materials provide a desired source of biocompatible materials for making the sealant 12. Alternative biocompatible sheet materials may include a variety of synthetic polymeric substances which can be formed into flexible sheet materials. Exemplary synthetic polymeric sheet materials may be formed from a variety of synthetic polymeric substances, including fibrous and/or thrombogenic materials, and other synthetic polymeric

materials known to those of skill in the art. In desired embodiments, the synthetic polymeric materials are biocompatible and bioresorbable.

**[0075]** Biocompatible sheet materials may be formed from fibers, or any suitable material (natural, synthetic, or combination thereof) that is pliable, strong, resilient, elastic, and flexible. These materials may be biocompatible or capable of being rendered biocompatible by coating, chemical treatment, and the like. Thus, in general, the material may comprise a synthetic biocompatible material that may include, for example, polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL), polydioxanone (PDO), trimethylene carbonate (TMC), polyvinyl alcohol (PVA), and copolymers or blends thereof; polyurethanes, including THORALON™ as described above; cellulose acetate, cellulose nitrate, silicone, polyethylene teraphthalate, polyamide, polyester, polyorthoester, polyanhydride, polyether sulfone, polycarbonate, polypropylene, high molecular weight polyethylene, polytetrafluoroethylene, or mixtures or copolymers thereof, a polyanhydride, polycaprolactone, polyhydroxy-butyrate valerate, polyhydroxyalkanoate, or another polymer able to be made biocompatible.

**[0076]** Thrombogenic fibrous materials include synthetic or natural fibrous material having thrombogenic properties. Exemplary thrombogenic fibrous materials include, but are not limited to, DACRON, cotton, silk, wool, polyester thread and the like.

**[0077]** The polymeric materials may include a textile material. The textile includes fibers and may take many forms, including woven (including knitted) and non-woven. Preferably, the fibers of the textile comprise a synthetic polymer. Preferred textiles include those formed from polyethylene terephthalate,

polytetrafluoroethylene (PTFE), expanded polytetrafluoroethylene (ePTFE), and PTFE. These materials are inexpensive, easy to handle, have good physical characteristics and are suitable for clinical application.

**[0078]** Expandable ECM Post Materials

**[0079]** As noted above, the puncture retainment member 22 may be configured to form an expandable plug portion in the post 20 when deployed. When deployed as a puncture retainment member 22, the expandable ECM material may be suitably configured to occlude a puncture tract 96, based on the size of the puncture tract and the expandability of the ECM material.

**[0080]** The expandable plug portion may be integral to the post 20 and may be incorporated into a sheet 44 of biocompatible material prior folding. For example, sheet portions of expandable ECM material may be bonded to left and right terminal ECM sheet portions 46, 48 adjacent to the left and right sheet folds 51, 53 near the flexible hinge 27 or the distal post portion 31. An expandable ECM material may be bonded by a variety of dehydration-induced bonding methods, as described below.

**[0081]** 1. Alkaline treatment

**[0082]** The expandable plug material may include an expandable ECM material formed by controlled contact with an alkaline substance. Application of alkaline substances to a source of native ECM material, as for example, a collagenous animal tissue layer, alters its structural morphology. ECM materials are composed of collagen fibrils comprising a quarter-staggered array of tropocollagen molecules formed as a triple helix of comprising three polypeptide chains linked together by covalent intramolecular bonds and hydrogen bonds.

Additionally, covalent intermolecular bonds are formed between different tropocollagen molecules within the collagen fibril. Frequently, multiple collagen fibrils assemble with one another to form collagen fibers. It is believed that the addition of an alkaline substance to the material as described herein will not significantly disrupt the intramolecular and intermolecular bonds, but will denature the material so as to provide a processed thickness to an intact collagenous sheet material that is substantially greater (i.e. at least about 20% greater) than, and preferably at least twice the naturally-occurring thickness of, the collagenous animal tissue layer. Microscopic analysis (at 100x magnification) has established that non-expanded ECM materials exhibit a tightly bound collagenous network whereas the same views of an expanded material exhibit a denatured, but still intact, collagenous network reflecting expansion of the material.

**[0083]** In addition, chemical crosslinks may be introduced in the ECM material in an amount sufficient to produce a desired level of resiliency. The introduction of collagen crosslinks, for example with chemical crosslinkers such as glutaraldehyde, carbodimides, or other chemical crosslinkers identified herein, can enhance the resiliency of the foam plugs, and produce ECM materials sufficiently compressed for delivery through a catheter or sheath. Increased resiliency in turn provides additional compression upon adjacent tissues when the compressed ECM materials are delivered to a blood vessel and then allowed to expand in the puncture tract of a patient wherein retainment or anchorage of the post 20 is desired.

**[0084]** Notably, such treatments can be used to provide an expandable ECM material expandable an aqueous fluid environment by at least about 2, at least

about 3, at least about 4, at least about 5, or even at least about 6 times its original bulk volume. The expandable material may be further characterized by a tensile strength of less than 50% of that of its corresponding non-expanded ECM material. The magnitude of expansion can be regulated by varying the concentration of the alkaline substance, the exposure time of the alkaline substance to the material, and temperature, among others. These factors can be varied to achieve a material having the desired level of expansion, given the disclosures set forth below.

**[0085]** In addition to allowing for expansion of an ECM material, the application of an alkaline substance alters the collagen packing characteristics of the material as well. Altering such characteristics of the material can be caused, at least in part, by the disruption of the tightly bound collagenous network. A non-expanded ECM material having a tightly bound collagenous network typically has a continuous surface that is substantially uniform even when viewed under magnification (e.g. 100x magnification). Conversely, an expanded ECM material typically has a surface-that is quite different in that the surface is typically not continuous but rather presents collagen strands or bundles in many regions that are separated by substantial gaps in material between the strands or bundles. Consequently, an expanded ECM material typically appears more porous than a non-expanded ECM material. Moreover, the expanded ECM material can be demonstrated as having increased porosity, e.g. by measuring its permeability to water or other fluid passage.

**[0086]** With respect to the alkaline substance used to prepare an expanded ECM material, any suitable alkaline substance generally known in the art can be

used. Suitable alkaline substances can include, for example, salts or other compounds that that provide hydroxide ions in an aqueous medium. Preferably, the alkaline substance comprises sodium hydroxide (NaOH). The concentration of the alkaline substance that is added to the material can be in the range of about 0.5 to about 4 M. Preferably, the concentration of the alkaline substance is in the range of about 1 to about 3 M. Additionally, the pH of the alkaline substance will typically range from about 8 to about 14. In preferred embodiments, the alkaline substance will have a pH of from about 10 to about 14, and most preferably of from about 12 to about 14.

**[0087]** In addition to concentration and pH, other factors such as temperature and exposure time will contribute to the extent of expansion. In this respect, it is preferred that the exposure of the ECM material to the alkaline substance is performed at a temperature of about 4 to about 45 °C. In preferred embodiments, the exposure is performed at a temperature of about 25 to about 37 °C, with 37°C being most preferred. Moreover, the exposure time can range from about several minutes to about 5 hours or more. In preferred embodiments, the exposure time is about 1 to about 2 hours. In a particularly preferred embodiment, the ECM material is exposed to a 3 M solution of NaOH having a pH of 14 at a temperature of about 37°C for about 1.5 to 2 hours. Such treatment results in the expansion of an ECM material to at least about twice its original volume. As indicated above, these processing steps can be modified to achieve the desired level of expansion.

**[0088]** Expandable ECM materials may be comminuted by shearing the material with a rotating blade, e.g. in a blender. When utilizing an ECM material

harvested as a decellurized sheet, the sheet can be contacted with the alkaline medium under conditions sufficient to substantially reduce the tensile strength of the sheet, so that the sheet material is disrupted by the rotating blade. Without sufficient reduction of tensile strength by the alkaline medium, the sheet material can tend to wrap around the rotating blade, thus frustrating the process of comminution. Therefore, prior to comminution by the blade or otherwise, the sheet may be desirably treated with the alkaline medium for a time and under conditions sufficient to reduce the tensile strength of the sheet to less than about 50% of its original tensile strength, more preferably to less than about 30% of its original tensile strength. Such methods can be practiced, for example, with harvested sheet-form ECM materials such as submucosa-containing sheets, e.g. obtained from small intestinal, stomach or bladder tissue, pericardial tissue, peritoneal tissue, fascia, dermal tissue, and other sheet-form ECM materials.

**[0089]** 2. Crosslinking treatment

**[0090]** With regard to compressible/expandable plug materials described herein, cross-linking and/or expansion additives can be used to impart desirable compression/re-expansion properties. For example, crosslinking of compressed ECM materials can promote re-expansion of the construct after implantation into a patient.

**[0091]** An expanded ECM material can be crosslinked either before or after it is formed into a medical device, or both. Increasing the amount (or number) of crosslinkages within the material or between two or more layers of the material can be used to enhance its strength. However, when a remodelable material is used, the introduction of crosslinkages within the material may also affect its

resorbability or remodelability. Consequently, in certain embodiments, an ECM material will substantially retain its native level of crosslinking, or the amount of added crosslinkages within the medical device will be judiciously selected depending upon the desired treatment regime. In many cases, the material will exhibit remodelable properties such that the remodeling process occurs over the course of several days or several weeks. In certain preferred embodiments, the remodeling process occurs within a matter of about 5 days to about 12 weeks.

**[0092]** Crosslinking of the expanded ECM material may be achieved by photo-crosslinking techniques, or by the application of a crosslinking agent, such as by chemical crosslinkers, or by protein crosslinking induced by dehydration or other means. Chemical crosslinkers that may be used include for example aldehydes such as glutaraldehydes, diimides such as carbodiimides, e.g., 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC), diisocyanates such as hexamethylene-diisocyanate, ribose or other sugars, acylazide, sulfo-N-hydroxysuccinamide, or polyepoxide compounds, including for example polyglycidyl ethers such as ethylene glycol diglycidyl ether, available under the trade name DENACOL EX810 from Nagese Chemical Co., Osaka, Japan, and glycerol polyglycerol ether available under the trade name DENACOL EX 313 also from Nagese Chemical Co. Typically, when used, polyglycerol ethers or other polyepoxide compounds will have from 2 to about 10 epoxide groups per molecule.

**[0093]** 3. Lyophilization

**[0094]** The expandable ECM materials for use in the present invention may be freeze-dried by lyophilization. Freezing can be done at a temperature of about -

80°C for about 1 to about 4 hours; and lyophilization can be performed for about 8 to about 48 hours. In addition, the expandable ECM materials may be comminuted prior to lyophilization.

**[0095]** In preferred forms, the expandable ECM materials are capable of volumetric compression when dry at a ratio of at least 10:1 (i.e. the compressed form occupies no more than 10% of its original, relaxed and unexpanded volume), more preferably at a ratio of at least 20:1. At the same time, in preferred forms, the compressed constructs are capable of re-expansion to substantially their original volume (e.g. at least about 80% of their original volume, more preferably at least 90%, and most preferably at least 95%) within about 30 seconds when delivered in their dry, compressed form into a volume of water.

**[0096]** Typically, a dried and compressed expanded ECM material may have a density of at least about 0.05 g/cm$^3$, preferably in the range of about 0.05 g/cm$^3$ to about 0.2 g/cm$^3$, and more preferably about 0.075 g/cm$^3$ to about 0.2 g/cm$^3$. The expanded ECM material will be configured to be resiliently compacted for passage through a needle during delivery. Expanded ECM densities (dry) will generally be less than the corresponding compacted densities. Typical expanded densities (dry) may range from about 0.01 g/cm$^3$ to about 0.1 g/cm$^3$, more preferably about 0.02 g/cm$^3$ to about 0.07 g/cm$^3$.

**[0097]** 4. ECM source materials

**[0098]** The expandable ECM materials of the present invention may be derived from native ECM tissue source materials and/or tissue extracts therefrom as described below. Suitable ECM tissue source materials may be isolated from

warm-blooded vertebrate, especially mammals, and may be processed so as to have remodelable properties promoting cellular invasion and ingrowth, as well as biotropic properties promoting angiogenesis, for example. Exemplary ECM tissue source materials include submucosa, renal capsule membrane, dermal collagen, dura mater, pericardium, fascia lata, serosa, and peritoneum or basement membrane layers, including liver basement membrane. These and other similar animal-derived tissue layers can be expanded and processed as described herein. Suitable submucosa materials for these purposes include, for instance, intestinal submucosa, including small intestinal submucosa, stomach submucosa, urinary bladder submucosa, and uterine submucosa.

**[0099]** Submucosa or other ECM tissue used in the invention is preferably highly purified, for example, as described in U.S. Patent No. 6,206,931 to Cook et al. Thus, preferred ECM material will exhibit an endotoxin level of less than about 12 endotoxin units (EU) per gram, more preferably less than about 5 EU per gram, and most preferably less than about 1 EU per gram. As additional preferences, the submucosa or other ECM material may have a bioburden of less than about 1 colony forming units (CFU) per gram, more preferably less than about 0.5 CFU per gram. Fungus levels are desirably similarly low, for example less than about 1 CFU per gram, more preferably less than about 0.5 CFU per gram. Nucleic acid levels are preferably less than about 5 µg/mg, more preferably less than about 2 µg/mg, and virus levels are preferably less than about 50 plaque forming units (PFU) per gram, more preferably less than about 5 PFU per gram. These and additional properties of submucosa or other ECM

tissue taught in U.S. Patent No. 6,206,931 may be characteristic of the submucosa tissue used in the present invention.

**[00100]** When preparing an expanded ECM material, the material is preferably treated with a disinfecting agent so as to produce a disinfected, expanded ECM material. Treatment with a disinfecting agent can be done either prior to or after isolation of the ECM material from the tissue source or can be done either prior to or after expansion. In one preferred embodiment, the tissue source material is rinsed with a solvent, such as water, and is subsequently treated with a disinfecting agent prior to delamination. It has been found that by following this post-disinfection-stripping procedure, it is easier to separate the ECM material from the attached tissues as compared to stripping the ECM material prior to disinfection. Additionally, it has been discovered that the resultant ECM material in its most preferred form exhibits superior histology, in that there is less attached tissue and debris on the surface compared to an ECM material obtained by first delaminating the submucosa layer from its source and then disinfecting the material. Moreover, a more uniform ECM material can be obtained from this process, and an ECM material having the same or similar physical and biochemical properties can be obtained more consistently from each separate processing run. Importantly, a highly purified, substantially disinfected ECM material is obtained by this process. In this regard, one embodiment of the invention provides a method for preparing an expanded ECM material. The method comprises providing a tissue source including an ECM material, disinfecting the tissue source, isolating the ECM material from the tissue source, and contacting the disinfected ECM material with an alkaline substance under

conditions effective to expand the ECM material to at least about two times its original volume, thereby forming the expanded ECM material. Upon formation of the expanded ECM material, the material can be further processed into medical materials and/or devices, or can be stored, e.g. in high purity water at 4 °C, for later use.

**[00101]** Preferred disinfecting agents are desirably oxidizing agents such as peroxy compounds, preferably organic peroxy compounds, and more preferably peracids. As to peracid compounds that can be used, these include peracetic acid, perpropioic acid, or perbenzoic acid. Peracetic acid is the most preferred disinfecting agent for purposes of the present invention. Such disinfecting agents are desirably used in a liquid medium, preferably a solution, having a pH of about 1.5 to about 10, more preferably a pH of about 2 to about 6, and most preferably a pH of about 2 to about 4. In methods of the present invention, the disinfecting agent will generally be used under conditions and for a period of time which provide the recovery of characteristic, purified submucosa materials as described herein, preferably exhibiting a bioburden of essentially zero and/or essential freedom from pyrogens. In this regard, desirable processes of the invention involve immersing the tissue source or isolated ECM material (e.g. by submersing or showering) in a liquid medium containing the disinfecting agent for a period of at least about 5 minutes, typically in the range of about 5 minutes to about 40 hours, and more typically in the range of about 0.5 hours to about 5 hours.

**[00102]** When used, peracetic acid is desirably diluted into about a 2% to about 50% by volume of alcohol solution, preferably ethanol. The concentration

of the peracetic acid may range, for instance, from about 0.05% by volume to about 1.0% by volume. Most preferably, the concentration of the peracetic acid is from about 0.1% to about 0.3% by volume. When hydrogen peroxide is used, the concentration can range from about 0.05% to about 30% by volume. More desirably the hydrogen peroxide concentration is from about 1 % to about 10% by volume, and most preferably from about 2% to about 5% by volume. The solution may or may not be buffered to a pH from about 5 to about 9, with more preferred pH's being from about 6 to about 7.5. These concentrations of hydrogen peroxide can be diluted in water or in an aqueous solution of about 2% to about 50% by volume of alcohol, most preferably ethanol.

**[00103]** 5. ECM sheet material processing

**[00104]** Expandable ECM materials for use in the present invention may be processed from expanded ECM sheet materials or from non-expanded ECM sheet materials treated as described above to form expanded ECM sheet materials. Generally, the ECM sheet materials will have a thickness in the range of about 0.2 mm to about 2 mm, more preferably about 0.4 mm to about 1.5 mm, and most preferably about 0.5 mm to about 1 mm. If necessary or desired, a multilaminate material can be used. For example, a plurality of (i.e. two or more) layers of an expanded ECM material can be bonded or otherwise coupled together to form a multilaminate structure. Illustratively, two, three, four, five, six, seven, or eight or more layers of an expanded ECM material can be bonded together to provide a multilaminate material. In certain embodiments, two to six expanded, submucosa-containing layers isolated from intestinal tissue of a warm-blooded vertebrate, particularly small intestinal tissue, are bonded together to

provide a medical material. Porcine-derived small intestinal tissue is preferred for this purpose. In alternative embodiments, one or more sheets of a non-expanded collagenous material (e.g., submucosa) can be bonded or otherwise coupled to one or more sheets of an expanded ECM material. Any number of layers can be used for this purpose and can be arranged in any suitable fashion with any number of layers of a non-expanded ECM material bonded to any number of layers of an expanded ECM material. The layers of collagenous tissue can be bonded together in any suitable fashion, including dehydrothermal bonding under heated, non-heated or lyophilization conditions, using adhesives as described herein, glues or other bonding agents, crosslinking with chemical agents or radiation (including UV radiation), or any combination of these with each other or other suitable methods.

**[00105]** A variety of dehydration-induced bonding methods can be used to fuse portions of multi-layered medical materials together. In one preferred embodiment, the multiple layers of material are compressed under dehydrating conditions. The term "dehydrating conditions" can include any mechanical or environmental condition which promotes or induces the removal of water from the multi-layered medical material. To promote dehydration of the compressed material, at least one of the two surfaces compressing the matrix structure can be water permeable. Dehydration of the material can optionally be further enhanced by applying blotting material, heating the matrix structure or blowing air, or other inert gas, across the exterior of the compressing surfaces. One particularly useful method of dehydration bonding multi-layered medical materials is lyophilization, e.g. freeze-drying or evaporative cooling conditions.

**[00106]** Another method of dehydration bonding comprises pulling a vacuum on the assembly while simultaneously pressing the assembly together. This method is known as vacuum pressing. During vacuum pressing, dehydration of the multi-layered medical materials in forced contact with one another effectively bonds the materials to one another, even in the absence of other agents for achieving a bond, although such agents can be used while also taking advantage at least in part of the dehydration-induced bonding. With sufficient compression and dehydration, the multi-layered medical materials can be caused to form a generally unitary laminate structure.

**[00107]** It is advantageous in some aspects of the invention to perform drying operations under relatively mild temperature exposure conditions that minimize deleterious effects upon the multi-layered medical materials of the invention, for example native collagen structures and potentially bioactive substances present. Thus, drying operations conducted with no or substantially no duration of exposure to temperatures above human body temperature or slightly higher, say, no higher than about 38°C, will preferably be used in some forms of the present invention. These include, for example, vacuum pressing operations at less than about 38°C, forced air drying at less than about 38°C, or either of these processes with no active heating at about room temperature (about 25°C) or with cooling. Relatively low temperature conditions also, of course, include lyophilization conditions. It will be understood that the above-described means for coupling two or more multi-layered medical materials together to form a laminate can also apply for coupling together one or more

layers of peritoneum and fascia when these layers are isolated independent from one another.

**[00108]** When a multi-layered laminate material is contemplated, the layers of the laminate can be additionally crosslinked to bond multiple layers of a multi-layered medical material to one another. Crosslinking of multi-layered medical materials can also be catalyzed by exposing the matrix to UV radiation, by treating the collagen-based matrix with enzymes such as transglutaminase and lysyl oxidase, and by photocrosslinking. Thus, additional crosslinking may be added to individual layers prior to coupling to one another, during coupling to one another; and/or after coupling to one another.

**[00109]** Additional materials, compositions, and methods adapted for forming and using expandable ECM materials are disclosed in U.S. Pat. Appl. No. 61/074,441, entitled "Physically Modified Extracellular Matrix Materials and Uses Thereof," filed June 20, 2008, the disclosures of which are expressly incorporated by reference herein.

**[00110]** Other Expandable Post Materials

**[00111]** Other expandable post materials for use in the present invention include virtually any natural or synthetic porous, hydrophilic hydrogel materials known to those of skill in the art which can be formed into a compressed cylinder or tube capable of expanding in a fluid environment so as to occlude a blood vessel 66. Expandable plugs that can be formed into a suitably compressed hydrogel material, sponge body, or foam body, include a variety of natural or synthetic polymeric materials, fibrous materials; and combinations thereof.

**[00112]** Examples of natural polymers that expand in the presence of aqueous fluids such as biological fluids to form hydrogels, include a variety of natural polymers, including but are not limited to collagens, hydrolyzed collagens (gelatin), collagen sponges and plugs, COLLASTAT® Hemostatic Sponge (Vitaphore Corp.), VITACOL™ (Vitaphore Corp.), fibronectin, fibrin, albumin, crosslinked derivatives therefrom, and the like. Other examples of water-swelling polymers include polysaccharides, mucopolysaccharides, cyclodextrins, hyaluronates, pectins, agarose, alginate, chitosan, chitosan derivatives, including chitosan modified with fructose or galactose; and the like.

**[00113]** Hydrogels, foams, or sponges may also be formed from a variety of synthetic polymers, copolymers, and block copolymers, including non-biodegradable, biodegradable polymers, and cross-linked derivatives therefrom. These polymeric materials may be configured to expand in the presence of aqueous fluids such as biological fluids, and may be cross-linked with agents, such as ethylene glycol dimethacrylate or methylene-bis-acrylamide.

**[00114]** Exemplary synthetic polymers include polyurethanes, including THORALON™ (THORATEC, Pleasanton, Calif.), as described in U.S. Pat. Nos. 4,675,361, 6,939,377, and U.S. Patent Application Publication No. 2006/0052816, the disclosures of which are incorporated by reference herein; acrylates, including but not limited to poly(hydroxyalkyl methylacrylates), such as poly(hydroxyethyl methacrylate), poly(glyceryl methacrylate)poly(acrylamide), and poly(vinyl alcohol)poly(ethylene glycol) diacrylate; and various silicones.

**[00115]** Exemplary non-biodegradable polymers include but are not limited to poly(hydroxyalkyl methylacrylates), including poly(glyceryl

methacrylate)poly(acrylamide), poly(methacrylamide) and derivatives; fluoropolymers, including but not limited to homopolymers of polytetrafluoroethylene and copolymers of polytetrafluoroethylene in which the co-monomer is ethylene, chlorotrifluoroethylene, perfluoroalkoxytetrafluoroethylene, and fluorinated propylene; polyolefins, including but not limited to polypropylene, polyethylene, polyethylene terephthalate, expanded polytetrafluoroethylene (ePTFE), DACRON®, polystyrene, and ultra high molecular weight polyethylene; polyethers, including but not limited to poly(ethylene oxide); water-soluble polymers, including but not limited to poly(vinyl alcohol), polyvinylpyrrolidone, and poly(hydroxyethyl methacrylate; carboxy alkyl celluloses, including but not limited to carboxymethyl cellulose; partially oxidized cellulose, cross-linked derivatives therefrom; and other synthetic polymers known to those of skill in the art.

**[00116]** Exemplary biodegradable polymers include polyphosphazenes, polyphosphoesters, polyanhydrides, polyethylene oxides, polyethylene oxide-co-polypropyleneoxide block copolymers, polylactides, polyglycolide, polycaprolactone, poly(3-hydroxy-butyric acid), polyvinyl alcohols, PEG, dextran, alginic acid and sodium alginate.

**[00117]** Expandable biocompatible post materials, including hydrogel, foam, sponge, and associated materials therefrom, as well as methods for molding or machining such materials into a plug or tube are further described in U.S. Patent Application Numbers 2006/0008419, 2005/0085885, and 2003/0109899; and U.S. Pat. Nos. 6,818,018; 6,602,261; 6,238,403; 6,245,090; 5,823,198;

5,570,585; 5,456,693; 5,258,042; and 4,663,358, the disclosure of which are incorporated by reference herein.

**[00118]** The foregoing description of various embodiments of the invention has been presented for purposes of illustration and description. It is not intended to be exhaustive or to limit the invention to the precise embodiments disclosed. Numerous modifications or variations are possible in light of the above teachings. The embodiments discussed were chosen and described to provide the best illustration of the principles of the invention and its practical application to thereby enable one of ordinary skill in the art to utilize the invention in various embodiments and with various modifications as are suited to the particular use contemplated. All such modifications and variations are within the scope of the invention as determined by the appended claims when interpreted in accordance with the breadth to which they are fairly, legally, and equitably entitled.

## CLAIMS

1. A vessel puncture closure device for sealing a vessel puncture in a patient comprising:

a unitary T-shaped puncture sealant comprising a planar base hingedly connected to a planar post prior to delivery in the patient, the planar post comprising at least one puncture tract retainment member, the base comprising two legs projecting in opposite directions from a proximal end of the post, the puncture sealant being formed from a planar elongate sheet of foldably bonded biocompatible material; and

a suture attachably extending from the post,

wherein the base is configured to seal the vessel puncture, while allowing fluid flow through a blood vessel following deployment; and

wherein the puncture tract retainment member is configured to prevent re-entry of the post into a blood vessel lumen and facilitate the seating of the base against the inside wall of the vessel following deployment.

2. The device of claim 1, wherein each of the base and post comprises a planar elongate structure having a rectangular or obround shape.

3. The device of claim 1, wherein the length of the post exceeds the length of at least one leg.

4. The device of claim 1, wherein the puncture tract retainment member comprises a first barb extending substantially perpendicularly from a first plane face of the post when deployed in a patient, and a second barb extending substantially perpendicularly from a second plane face of the post when deployed

in a patient, each of the first and second barbs comprising two edges joined to form a pointed end extending downward toward the outer surface of the vessel upon deployment over the puncture,

wherein the pointed ends in the first and second barbs extend from opposite sides of the post when deployed.

5. The device of claim 4, wherein each of the first and second barbs foldably extends from an edge of the post.

6. The device of claim 1, wherein the sheet of foldably bonded biocompatible material comprises a synthetic polymeric sheet material.

7. The device of claim 1, wherein the sheet of foldably bonded biocompatible material comprises an ECM sheet material.

8. The device of claim 1, comprising a sheet of foldably bonded biocompatible material, the sheet defined by terminal sheet portions flanking a central sheet portion, wherein the terminal sheet portions are foldably bonded to one another to form the post, and central sheet portions are foldably bonded to one another to form the two legs.

9. The device of claim 1, comprising a sheet of foldably bonded biocompatible material, the sheet defined by terminal sheet portions flanking a central sheet portion, wherein a proximal portion of the central sheet is foldably bonded to a distal portion of the central sheet portion to form the post.

10. The device of claim 1, wherein the puncture tract retainment member comprises a first barb extending substantially perpendicular from a first plane

face of the post when deployed in a patient, and a second barb extending substantially perpendicular from a second plane face of the post when deployed in a patient, each of the first and second barbs comprises two edges joined to form a pointed end extending downward toward the outer surface of the vessel upon deployment over the puncture,

wherein the pointed ends in the first and second barbs extend from opposite sides the post when deployed.

11. The device of claim 10, wherein each of the first and second barbs foldably extends from an edge of the post.

12. The device of claim 1, wherein the sheet of foldably bonded biocompatible material comprises ECM sheet material.

13. The device of claim 12, wherein the ECM sheet material comprises a plurality of laminated ECM tissue layers.

14. The device of claim 12, wherein the ECM sheet material further comprises a stiffening material increasing the rigidity of the ECM sheet material.

15. The device of claim 14, wherein the base comprises the stiffening material.

16. The device of claim 14, wherein the stiffening material comprises a chemical crosslinker, a wire, a polymeric substance, an adhesive, or combination thereof.

17. The device of claim 14, wherein the stiffening material comprises a polymeric substance.

18. The device of claim 17, wherein the polymeric substance is applied as a coating onto one or more surfaces of the ECM sheet material.

19. The device of claims 17, wherein the polymeric substance comprises a poly(ethylene glycol) polymer.

20. The device of claim 17, wherein the polymeric substance or adhesive is incorporated between one or more sheets of ECM material or between one or more ECM tissue layers in any one of the one or more sheets ECM material.

21. A device assembly comprising:

the device of claim 1; and

a deployment shaft comprising a lumen, a sheath, a distal shaft end, and a proximal shaft end;

wherein the device is connectively linked to the deployment shaft by the bioabsorbable suture, the bioabsorbable suture extending through the deployment shaft lumen from the distal shaft end past the proximal shaft end

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22. The device assembly of claim 21, further comprising:

a transfer tube comprising a transfer tube lumen and a transfer tube sheath, including a proximal transfer tube end and proximal transfer tube end;

wherein the device of claim 1 is coaxially disposed in the transfer tube lumen; and wherein the deployment shaft is configured to coaxially extend through the transfer tube lumen and through an introducer.

23. A method for sealing a percutaneous puncture in a blood vessel of a patient comprising:

connectively linking each of the device of claim 1 and a deployment shaft to an introducer;

pushing the device by extending the deployment shaft through the introducer in a proximal to distal direction;

extending the puncture sealant through the puncture site and an adjoining puncture tract extending into the vessel lumen;

retracting the deployment shaft from the introducer sheath;

pulling the bioabsorbable suture in a distal to proximal direction to translocate the post and the puncture tract retainment member from the vessel lumen, through the puncture, and into the puncture tract,

wherein translocation of the at least one puncture tract retainment member into the puncture tract creates a puncture sealant configuration preventing re-entry of the post and facilitates seating of the base against the inner surface of the vessel wall to seal the puncture, while allowing fluid flow through the vessel.

24. The method of claim 23, wherein the step of connectively linking each of the device of claim 1 and the deployment shaft to the introducer comprises linking a transfer tube preloaded with the device to an introducer through a check flow seal in an adaptor linked to the proximal end of the introducer.

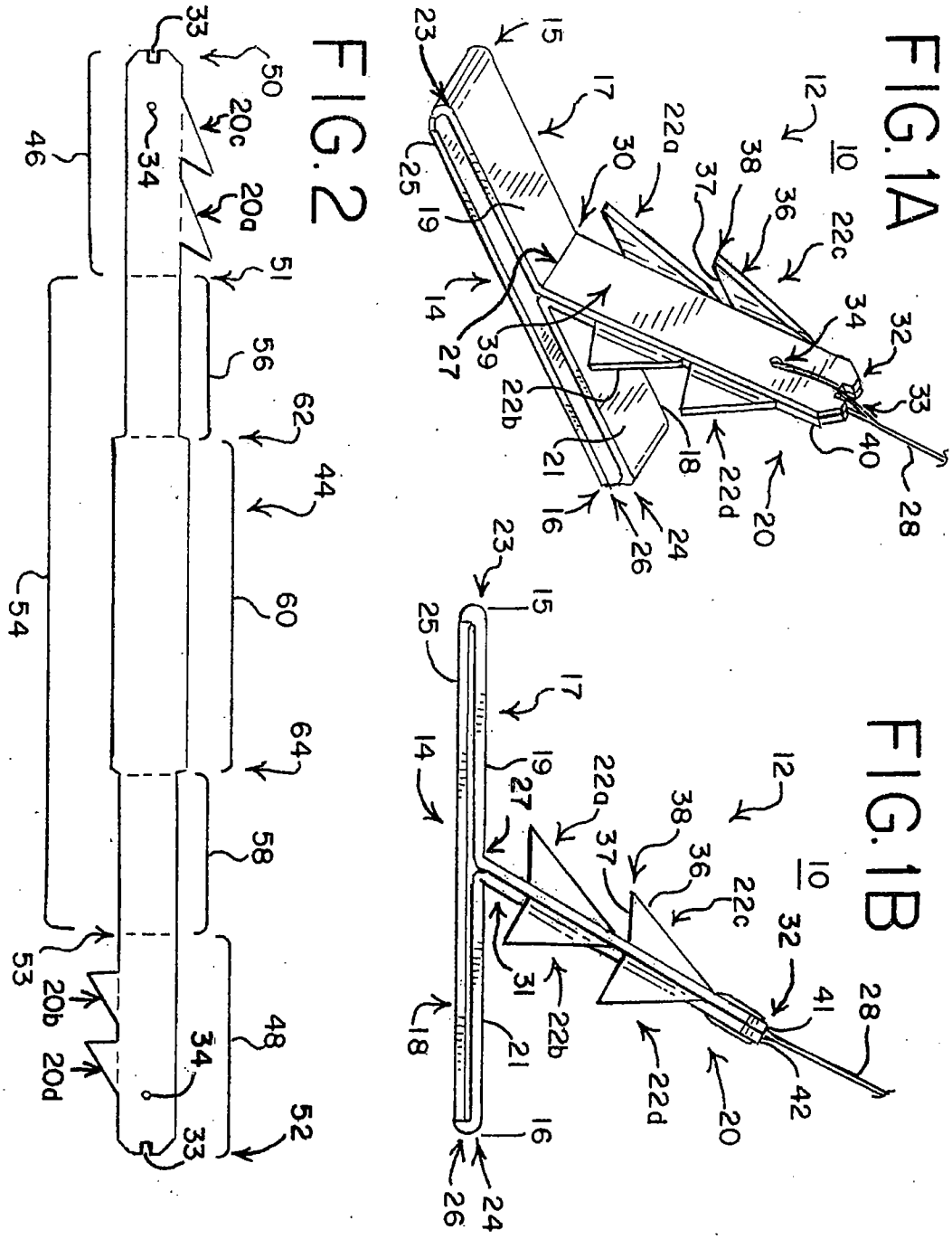



FIG. 1A

FIG. 1B




FIG. 2

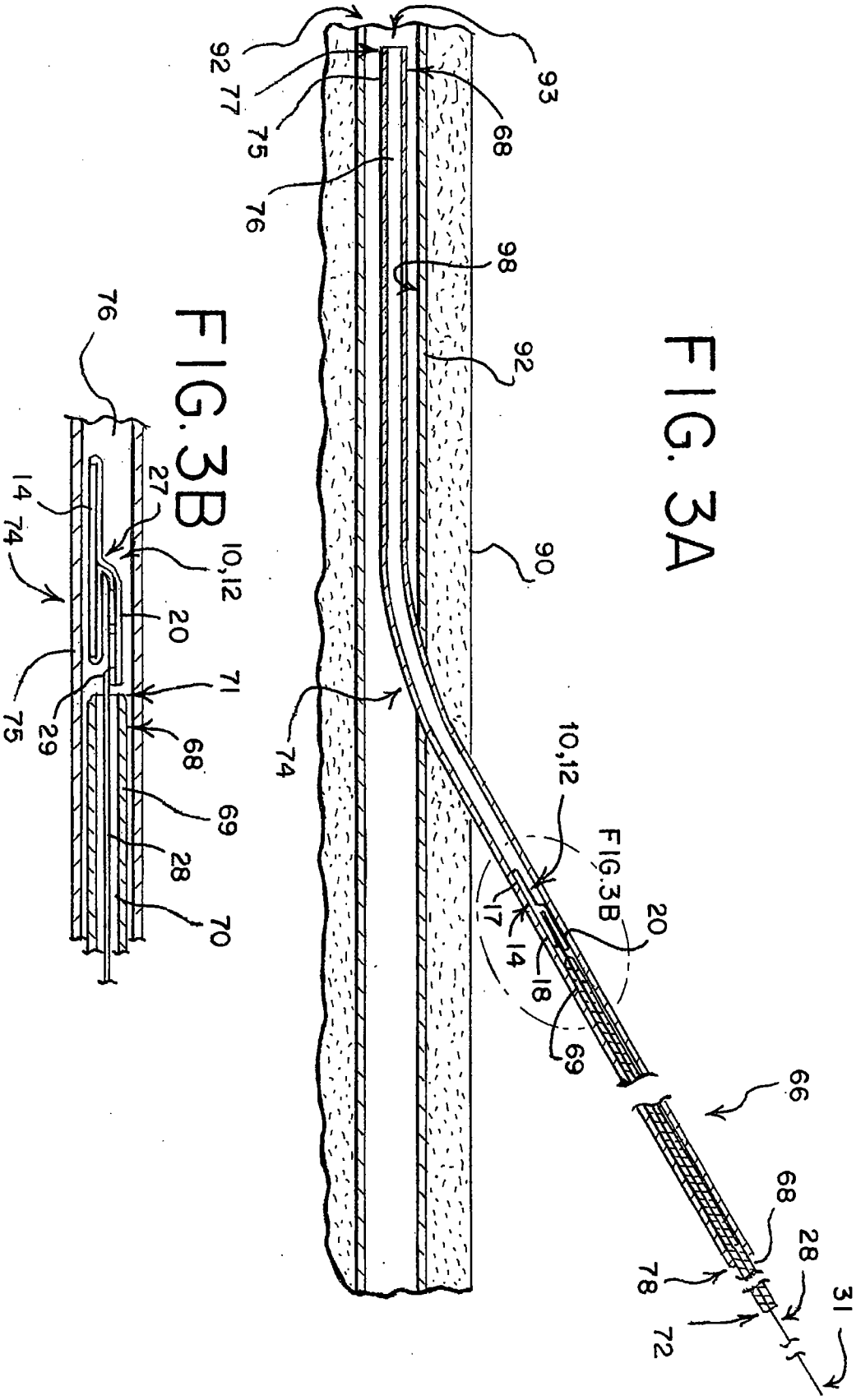

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FIG.3B
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FIG. 3A


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FIG. 3B

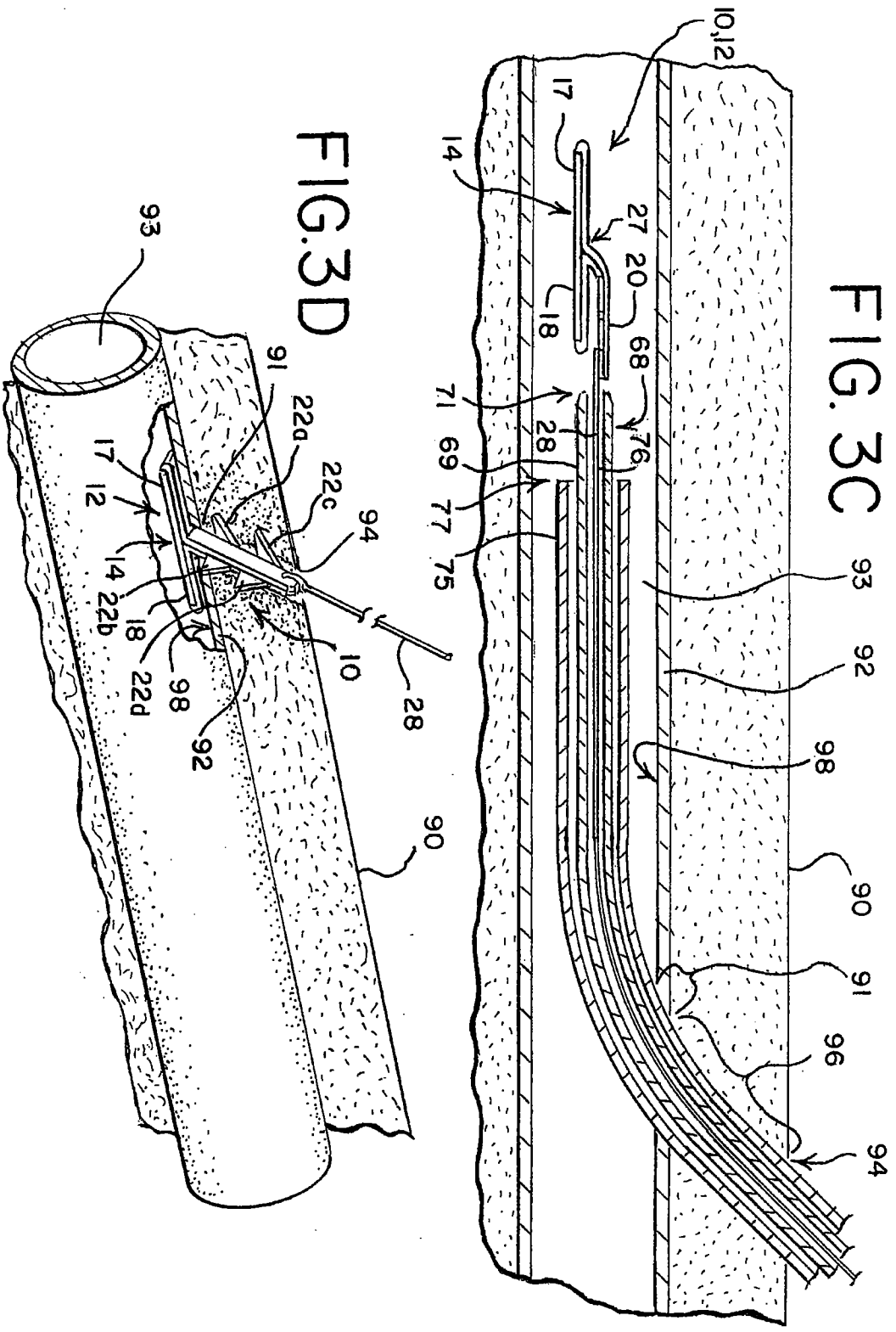
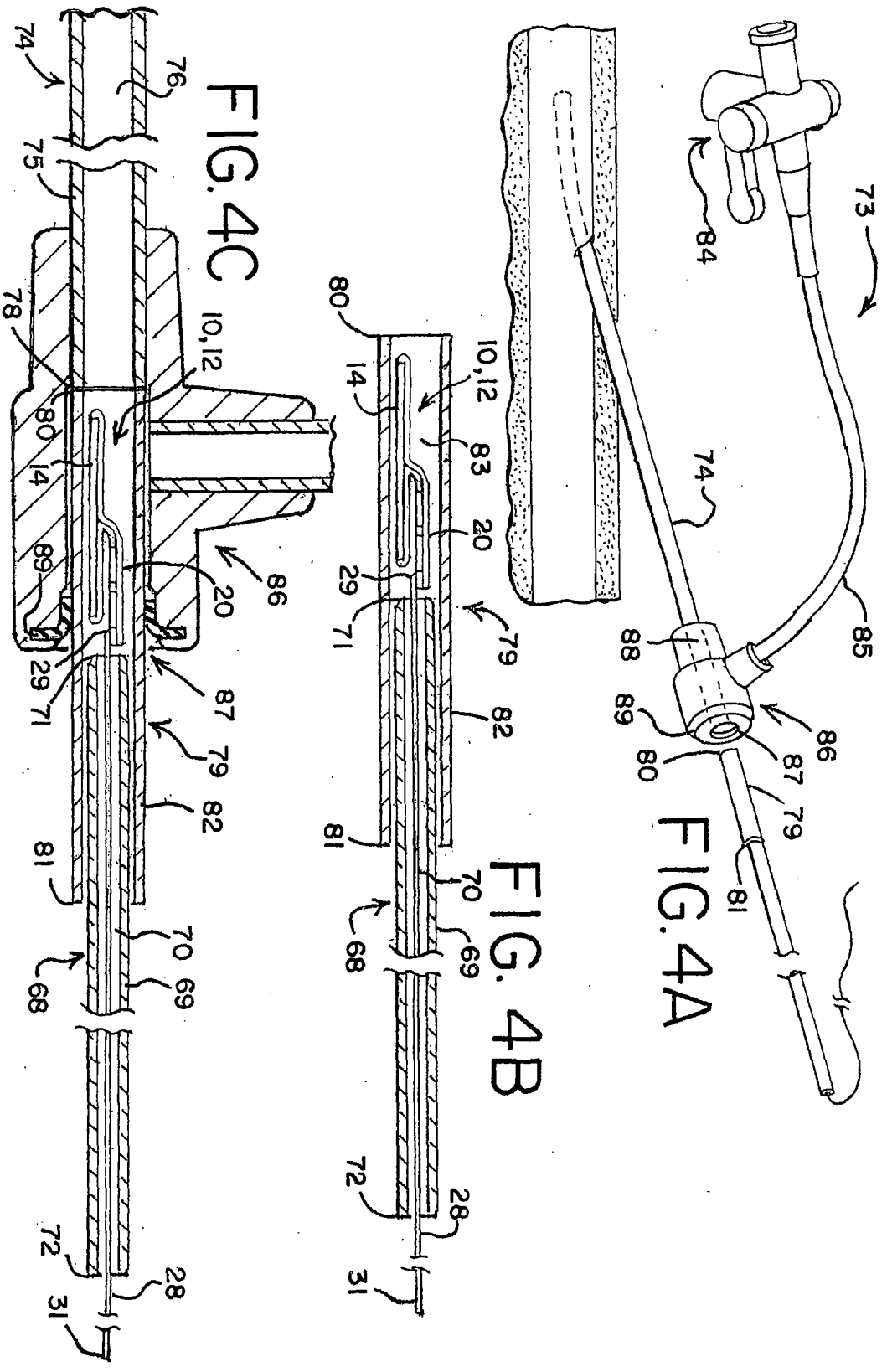

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FIG. 3C


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FIG. 3D


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FIG. 4C
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FIG. 4B
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FIG. 4A

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/021386

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B17/00 A61B17/04

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)
A61B

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 2004/176800 A1 (PARASCHAC ET AL.)<br>9 September 2004 (2004-09-09)<br>abstract; figures 1-8<br>paragraphs [0009] - [0012], [0035] - [0042] | 1-22 |
| Y | WO 2004/012627 A1 (C.R. BARD, INC.)<br>12 February 2004 (2004-02-12)<br>abstract; figures 5-7<br>page 11, lines 5-7<br>page 11, line 29 - page 12, line 28 | 1-22 |
| A | US 2008/004657 A1 (OBERMILLER ET AL.)<br>3 January 2008 (2008-01-03)<br>abstract; claims 92,93; figures<br>paragraphs [0028], [0029], [0099] | 6-7,<br>12-20 |

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 17 March 2010 | 25/03/2010 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040,<br>Fax: (+31–70) 340–3016 | Giménez Burgos, R |

Form PCT/ISA/210 (second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/021386

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 2004/243052 A1 (KAUPHUSMAN ET AL.)<br>2 December 2004 (2004-12-02)<br>abstract; figures 1-5E | 1,21-22 |
| A | CA 2 122 041 A1 (KENSEY NASH CORPORATION)<br>29 April 1993 (1993-04-29)<br>abstract; figures | 1,21-22 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2010/021386

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 23-24
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/021386

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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