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(71) Applicant: **EDWARDS LIFESCIENCES CORPORATION** [US/US]; One Edwards Way, Irvine, CA 92614 (US).

(72) Inventors: **AFSAR KAZEROONI, Nazanin**; Edwards Lifesciences, One Edwards Way, Legal Department, Irvine, CA 92614 (US). **TKATCHOUK, Ekaterina**; 16921 Lakefront Circle, #42, Huntington Beach, CA 92647 (US).

(74) Agent: **HO, Pui, Tong**; Edwards Lifesciences, One Edwards Way, Irvine, CA 92614 (US).

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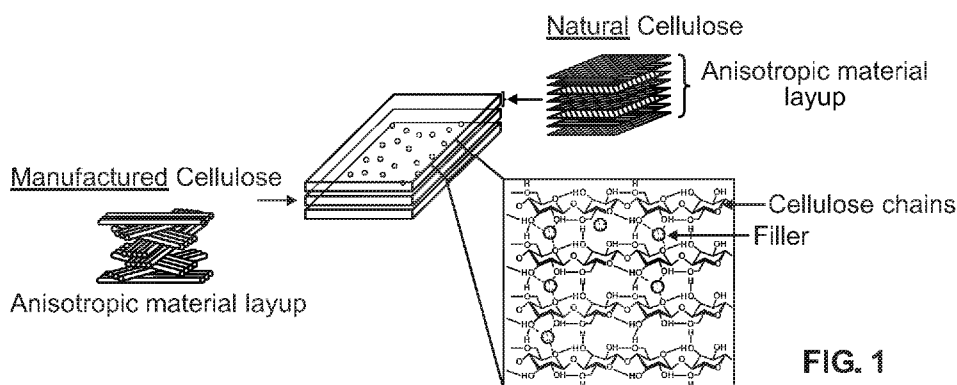


FIG. 1

(57) Abstract: Disclosed herein is a biocompatible material including a plurality of nanolayers, wherein each nanolayer within the plurality of nanolayers includes a plurality of cellulose nanofibers, the plurality of cellulose nanofibers within each nanolayer being substantially disposed along a direction that is substantially unparallel to a direction of a plurality of cellulose nanofibers within a nanolayer below or above. Biocomposites including the biocompatible material are also disclosed, as well as implantable medical devices including the biocompatible material or biocomposite. Methods of making the biocompatible materials and implantable medical devices are further disclosed.

ANISOTROPIC CELLULOSIC MATERIAL

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Patent Application No. 63/618,229 filed January 5, 2024, the entire disclosure which is incorporated by reference for all purposes.

TECHNICAL FIELD

[0002] This disclosure relates to materials that can be used in implantable medical devices and, more particularly, to anisotropic cellulosic materials that can be used in implantable medical devices such as prosthetic valves.

BACKGROUND

[0003] The heart can suffer from various valvular diseases or malformations that result in significant malfunctioning of the heart and ultimately require the replacement of the native heart valve with an artificial valve. Human heart valves, which include the aortic, pulmonary, mitral, and tricuspid valves, function essentially as one-way valves operating in synchronization with the pumping heart. The valves allow blood to flow downstream but block blood from flowing upstream. Diseased heart valves exhibit impairments such as narrowing of the valve or regurgitation, which inhibits the valves' ability to control blood flow. Such impairments reduce the heart's blood-pumping efficiency and can be a debilitating and life-threatening condition. For example, valve insufficiency can lead to conditions such as heart hypertrophy and dilation of the ventricle. Thus, extensive efforts have been made to develop methods and apparatuses to repair or replace impaired heart valves.

[0004] Prostheses exist to correct problems associated with impaired heart valves. For example, mechanical and tissue-based heart valve prostheses can be used to replace impaired native heart valves. More recently, substantial effort has been dedicated to developing replacement heart valves, particularly tissue-based replacement heart valves that can be delivered with less trauma to the patient than through open-heart surgery. Replacement valves are being designed to be delivered through minimally invasive procedures and even percutaneous procedures. Such replacement valves often include a tissue-based valve body that is connected to an expandable frame that is then delivered to the native valve's annulus.

[0005] Because of the drawbacks associated with conventional open-heart surgery, percutaneous and minimally-invasive surgical approaches are garnering intense attention. In one technique, a prosthetic valve is configured to be implanted in a much less invasive procedure by way of catheterization. For instance, U.S. Pat. Nos. 5,411,522 and 6,730,118,

7,393,360, 7,510,575, and 7,993,394, which are incorporated herein by reference, describe collapsible transcatheter heart valves (THVs) that can be percutaneously introduced in a compressed state on a catheter and expanded in the desired position by balloon inflation or by utilization of a self-expanding frame or stent. In yet another example, U.S. U.S. Publication Nos. 2014/0277390, 2014/0277422, 2014/0277427, 2015/0328000, and 2019/0328515, which are incorporated herein by reference in their entireties, describe heart valve prostheses for replacing a native mitral valve, including a self-expanding frame with a plurality of anchoring members that are designed be deployed within a body cavity and prevent axial flow of fluid around an exterior of the prosthesis.

[0006] Bioprosthetic heart valves that use glutaraldehyde-fixed bovine pericardium as leaflet material are widely used for surgical and transcatheter valve interventions but suffer from limited durability due to structural valve degeneration (SVD). Structural valve degeneration is a common, unpreventable, and untreatable consequence of bioprosthetic valve implantation and frequently presents as leaflet calcification resulting in stenosis. Additionally, the development of new eco-friendly and biocompatible materials using ‘green’ technologies represents a significant challenge for the biomedical fields to minimize potential damaging effects on the human body and the environment.

[0007] There is a clear need for the development of alternative biocompatible materials for use in prosthetic heart valves. This disclosure addresses this as well as other needs.

SUMMARY

[0008] Some aspects of the present disclosure provide biocompatible materials. Some nonlimiting aspects of the biocompatible material described herein may include a plurality of nanolayers.

[0009] In some nonlimiting and exemplary aspects, each nanolayer within the plurality of nanolayers includes a plurality of cellulose nanofibers.

[0010] In some nonlimiting and exemplary aspects, the plurality of cellulose fibers within each nanolayer can be substantially disposed along a direction that is substantially unparallel to a direction of a plurality of cellulose nanofibers within a nanolayer below or above.

[0011] In some nonlimiting and exemplary aspects, the cellulose nanofibers can include natural cellulose nanofibers. In some nonlimiting and exemplary aspects, the natural cellulose nanofibers can include bacterial cellulose. In some nonlimiting and exemplary aspects, the bacterial cellulose can be derived from a bacterium selected from *Acetobacter*, *Agrobacterium*, *Alcaligenes*, *Azotobacter*, *Komagataeibacter*, *Pseudomonas*, *Rhizobium*, *Salmonella*, and *Sarcina*.

[0012] In some nonlimiting and exemplary aspects, the cellulose nanofibers may be crosslinked. In some nonlimiting and exemplary aspects, the cellulose nanofibers can be enzymatically crosslinked or chemically crosslinked.

[0013] In some nonlimiting and exemplary aspects, the cellulose nanofibers can include cellulose having a number average molecular weight from about 1 kDa to about 100 kDa. In some nonlimiting and exemplary aspects, the cellulose nanofibers can have an average diameter from about 10 nm to about 100 nm. In some nonlimiting and exemplary aspects, the biocompatible material can be porous. In some nonlimiting and exemplary aspects, the biocompatible material can have a density from about 0.05 to about 0.5 g/nm³ and a porosity from about 70% to about 99.9%. In some nonlimiting and exemplary aspects, the biocompatible material can have anisotropic mechanical properties. In some nonlimiting and exemplary aspects, the biocompatible material can be configured to be implanted into a patient body. In some nonlimiting and exemplary aspects, the biocompatible material can include a backing material or a coating.

[0014] Some aspects of the present disclosure provide biocomposites. In some nonlimiting and exemplary aspects, the biocomposite may include a first layer including a biocompatible material described herein. In some nonlimiting and exemplary aspects, the biocomposite can include a second layer including a plurality of manufactured cellulose nanofibers. In some nonlimiting and exemplary aspects, the biocomposite can include a filler dispersed within the first layer and/or the second layer. In some aspects, the biocomposite can be formed into a leaflet structure.

[0015] Some aspects of the present disclosure provide implantable medical devices. In some nonlimiting aspects, the implantable devices may include a biocompatible material or biocomposite described herein. In some nonlimiting and exemplary aspects, the implantable medical devices can be selected from a surgical aortic valve replacement, a transcatheter mitral valve replacement, a cardiovascular patch, and a vascular graft.

[0016] Some aspects of the present disclosure provide an implantable prosthetic valve. In some nonlimiting and exemplary aspects, the implantable prosthetic valve may include an annular frame having an inner surface and an outer surface. In some nonlimiting and exemplary aspects, the frame has an inflow end and an outflow end, and a central longitudinal axis extending from the inflow end to the outflow end. In some nonlimiting and exemplary aspects, the implantable prosthetic valve includes a leaflet structure having an inner surface and an outer surface and positioned at the inner surface of the annular frame. In some nonlimiting and exemplary aspects, at least a portion of the leaflet structure includes a biocompatible material or a biocomposite described herein.

[0017] Some aspects of the present disclosure provide methods of manufacturing biocompatible materials described herein. In some nonlimiting and exemplary aspects, the method includes depositing a first plurality of cellulose nanofibers to be substantially arranged along a first direction to form a first nanolayer. In some nonlimiting and exemplary aspects, the method includes depositing a second plurality of cellulose nanofibers to be substantially arranged along a second direction to form a second nanolayer disposed upon the first nanolayer. In some nonlimiting and exemplary aspects, the second direction is substantially unparallel to the first direction.

[0018] Some aspects of the present disclosure provide methods of making an implantable prosthetic valve described herein. In some nonlimiting and exemplary aspects, the method includes providing a leaflet structure as described herein. In some nonlimiting and exemplary aspects, the method includes coupling the leaflet structure within an annular frame. In some nonlimiting and exemplary aspects, the annular frame is configured to expand and contract.

[0019] The details of one or more aspects of the disclosure are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the disclosure will be apparent from the description, drawings, and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] FIG. 1 depicts an exemplary biocomposite material according to the disclosure.

[0021] FIG. 2 depicts exemplary incorporation of silver ions or nanoparticles into the biocompatible materials according to the disclosure.

[0022] FIG. 3 depicts an exemplary scheme regarding crosslinking of cellulose with cyclodextrins according to the disclosure.

[0023] FIG. 4 depicts an exemplary frame according to the disclosure.

[0024] FIG. 5 depicts an exemplary valve according to the disclosure.

[0025] FIG. 6A depicts an exemplary valve according to the disclosure.

[0026] FIG. 6B depicts an exemplary valve according to the disclosure.

[0027] FIG. 7 depicts cell proliferation into a bacterial cellulose material after implantation as shown by Mason's Trichome staining as described in Example 2.

[0028] FIG. 8 depicts no calcification of a bacterial cellulose material after implantation as shown by Van Kossa staining as described in Example 2.

DETAILED DESCRIPTION

[0029] The following description of the disclosure is provided as an enabling teaching of the disclosure in its best, currently known aspects. Many modifications and other aspects disclosed herein will come to mind to one skilled in the art to which the disclosed compositions and methods pertain, benefiting from the teachings presented in the descriptions herein and the associated drawings. Therefore, it is understood that the disclosures are not limited to the specific aspects disclosed and that modifications and other aspects are intended to be included within the scope of the appended claims. The skilled artisan will recognize many variants and adaptations of the aspects described herein. These variants and adaptations are intended to be included in the teachings of this disclosure and to be encompassed by the claims herein.

[0030] Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation.

[0031] As apparent to those of skill in the art upon reading this disclosure, each of the individual aspects described and illustrated herein has discrete components and features that may be readily separated from or combined with the features of any of the other several aspects without departing from the scope or spirit of the present disclosure.

[0032] Any recited method can be carried out in the order of events recited or any other order that is logically possible. Unless otherwise expressly stated, it is in no way intended that any method or aspect set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not explicitly state in the claims or descriptions that the steps are to be limited to a particular order, it is in no way intended that an order be inferred in any respect. This holds for any possible non-express basis for interpretation, including logic concerning arrangement of steps or operational flow, meaning derived from grammatical organization or punctuation, or the number or type of aspects described in the specification.

[0033] All publications mentioned herein are incorporated by reference to disclose and describe the methods or materials in connection with which the publications are cited. The publications discussed herein are provided solely for their disclosure before the filing date of the present application. Nothing herein is to be construed as an admission that the present disclosure is not entitled to antedate such publication. Further, the dates of publication provided herein can be different from the actual publication dates, which can require independent confirmation.

[0034] It is also to be understood that the terminology herein describes particular aspects only and is not intended to be limiting. Unless defined otherwise, all technical and

scientific terms herein have the same meaning as commonly understood by one of ordinary skill in the art to which the disclosed compositions and methods belong. It can be further understood that terms, such as those defined in commonly used dictionaries, should be interpreted as having a meaning that is consistent with their meaning in the context of the specification and relevant art and should not be interpreted in an idealized or overly formal sense unless expressly defined herein.

[0035] Before describing the various aspects of the present disclosure, the following definitions are provided and should be used unless otherwise indicated. Additional terms may be defined elsewhere in the present disclosure.

Definitions

[0036] As used herein, “comprising” is interpreted as specifying the presence of the stated features, integers, steps, or components but does not preclude the presence or addition of one or more features, integers, steps, components, or groups thereof. Moreover, each of the terms “by,” “comprising,” “comprises,” “comprised of,” “including,” “includes,” “included,” “involving,” “involves,” “involved,” and “such as” are used in their open, non-limiting sense and may be used interchangeably. Further, the term “comprising” is intended to include examples and aspects encompassed by the terms “consisting essentially of” and “consisting of.” Similarly, “consisting essentially of” is intended to include examples encompassed by the term “consisting of.”

[0037] As used in the specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context dictates otherwise.

[0038] Ratios, concentrations, amounts, and other numerical data can be expressed herein in a range format. Further, the endpoints of each of the ranges are significant both in relation to the other endpoint and independently of the other endpoint. There are many values disclosed herein, and each value is also disclosed as “about” that particular value in addition to the value itself. For example, if the value “10” is disclosed, then “about 10” is also disclosed. Ranges can be expressed herein as from “about” one particular value and to “about” another particular value. Similarly, when values are expressed as approximations, using the antecedent “about,” the particular value forms a further aspect. For example, if the value “about 10” is disclosed, then “10” is also disclosed.

[0039] When a range is expressed, a further aspect includes from the one particular value and to the other particular value. For example, where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the disclosure, for example, the phrase “x to y” includes the range from ‘x’ to ‘y’ as well as the range greater than ‘x’ and less than ‘y’. The range can also be expressed as an upper limit, for

example, 'about x, y, z, or less' and should be interpreted to include the specific ranges of 'about x,' 'about y,' and 'about z' as well as the ranges of 'less than x,' 'less than y,' and 'less than z.' Likewise, the phrase 'about x, y, z, or greater' should be interpreted to include the specific ranges of 'about x,' 'about y,' and 'about z' as well as the ranges of 'greater than x,' 'greater than y,' and 'greater than z.' In addition, the phrase "about 'x' to 'y'," where 'x' and 'y' are numerical values, includes "about 'x' to about 'y'."

[0040] Such a range format is used for convenience and brevity and, thus, should be interpreted flexibly to include not only the numerical values explicitly recited as the limits of the range but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited. To illustrate, a numerical range of "about 0.1% to 5%" should be interpreted to include not only the explicitly recited values of about 0.1% to about 5%, but also include individual values (for example, about 1%, about 2%, about 3%, and about 4%) and the sub-ranges (for example, about 0.5% to about 1.1%; about 5% to about 2.4%; about 0.5% to about 3.2%, and about 0.5% to about 4.4%, and other possible sub-ranges) within the indicated range.

[0041] As used herein, the terms "about," "approximate," "at or about," and "substantially" mean that the amount or value in question can be the exact value or a value that provides equivalent results or effects as recited in the claims or taught herein. That is, amounts, sizes, formulations, parameters, and other quantities and characteristics are not and need not be exact but may be approximate, larger or smaller, as desired, reflecting tolerances, conversion factors, rounding, measurement error, and the like, and other factors known to those of skill in the art such that equivalent results or effects are obtained. In some circumstances, the value that provides equivalent results or effects cannot be reasonably determined. In such cases, as used herein, "about" and "at or about" mean the nominal value indicated $\pm 10\%$ variation unless otherwise indicated or inferred. In general, an amount, size, formulation, parameter, or other quantity or characteristic is "about," "approximate," or "at or about," whether or not expressly stated to be such. Where "about," "approximate," or "at or about" is used before a quantitative value, the parameter also includes the specific quantitative value itself unless expressly stated otherwise.

[0042] As used herein, "optional" or "optionally" means that the subsequently described event or circumstance can or cannot occur. The description includes instances where said event or circumstance occurs and those where it does not.

[0043] As used interchangeably herein, "subject," "individual," or "patient" can refer to a vertebrate organism, such as a mammal (for example, a human).

[0044] The terms “coupled” and “associated” generally mean electrically, electromagnetically, and/or physically (for example, mechanically or chemically) coupled or linked and do not exclude the presence of intermediate elements between the coupled or associated items.

[0045] It will be understood that when an element is referred to as being “connected” or “coupled” to another element, it can be directly connected or coupled to the other element, or intervening elements can be present. In contrast, when an element is referred to as being “directly connected” or “directly coupled” to another element, there are no intervening elements present. Other words used to describe the relationship between elements or layers should be interpreted in a like fashion (for example, “between” versus “directly between,” “adjacent” versus “directly adjacent,” “on” versus “directly on”).

[0046] It will be understood that although the terms “first,” “second,” etc., can be used herein to describe various elements, components, regions, layers and/or sections. These elements, components, regions, layers, and/or sections should not be limited by these terms. These terms are only used to distinguish one element, component, region, layer, or section from another element, component, region, layer, or a section. Thus, a first element, component, region, layer, or section discussed below could be termed a second element, component, region, layer, or section without departing from the teachings of example aspects.

[0047] Spatially relative terms, such as, “beneath,” “below,” “lower,” “above,” “upper,” “upward,” “downward,” “top,” “bottom,” and the like, can be used herein for ease of description to describe one element or feature’s relationship to another element(s) or feature(s) as illustrated in the figures. It will be understood that the spatially relative terms are intended to encompass different orientations of the device in use or operation in addition to the orientation depicted in the figures. For example, if the device in the figures is turned over, elements described as “below” or “beneath” other elements or features would then be oriented “above” the other elements or features. Thus, the term “below” can encompass both an orientation of above and below. The device can be otherwise oriented (rotated 90 degrees or at other orientations), and the spatially relative descriptors used herein are interpreted accordingly.

[0048] Terms such as “proximal,” “distal,” “radially outward,” “radially inward,” “outer,” “inner,” and “side” describe the orientation and/or location of portions of the components or elements within a consistent but arbitrary frame of reference which is made clear by reference to the text and the associated drawings describing the components or elements under discussion. Such terminology can include the words specifically mentioned above, derivatives thereof, and words of similar import. Similarly, the terms “first,” “second,” and

other such numerical terms referring to structures neither imply a sequence nor order unless clearly indicated by the context.

[0049] As used herein, the term “substantially” means that the subsequently described event or circumstance completely occurs or that the subsequently described event or circumstance generally, typically, or approximately occurs.

[0050] Still further, the term “substantially” can, in some aspects, refer to at least about 90 %, at least about 91 %, at least about 92 %, at least about 93 %, at least about 94 %, at least about 95 %, at least about 96 %, at least about 97 %, at least about 98 %, at least about 99 %, or about 100 % of the stated property, component, composition, or other condition for which substantially is used to characterize or otherwise quantify an amount.

[0051] As used herein, the term “substantially,” in, for example, the context “substantially identical” or “substantially similar,” refers to a method or a system, or a component that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% by similar to the method, system, or the component it is compared to.

[0052] “Cellulose” as used herein refers to a polysaccharide consisting of a linear chain of $\beta(1\rightarrow4)$ -linked D-glucose units.

[0053] Moreover, for the sake of simplicity, the attached figures cannot show the various ways (readily discernable, based on this disclosure, by one of ordinary skill in the art) in which the disclosed system, method, and apparatus can be used in combination with other systems, methods, and apparatuses. Additionally, the description sometimes uses terms such as “produce” and “provide” to describe the disclosed method. These terms are high-level abstractions of the actual operations that can be performed. The actual operations that correspond to these terms can vary depending on the particular implementation and are, based on this disclosure, readily discernible by one of ordinary skill in the art.

Biocompatible Materials

[0054] The present disclosure provides biocompatible materials which can be used in the construction of implantable medical devices. The disclosed materials show substantially no calcification over the time period of implantation with a patient body as compared to tissue-based materials used in implantable medical devices.

[0055] Cellulose is one of the most versatile polymers in the world, and due to its biocompatibility, non-toxicity, and tunable biodegradation is widely used in pharmaceutical and medical industries. Cellulose is a linear homopolymer composed of cellobiose, with two units of anhydro-D-glucopyranose (AGUs) linked by β -1,4-glycosidic bonds. D-Glucose units

have a chair conformation, with the hydroxyl groups in the equatorial positions. Cellulose is biosynthesized by the cellulose synthase enzyme, undergoing condensation reaction, from glucose in the form of the substrate uridine diphosphate (UDP)-glucose. Depending on the origin, the degree of polymerization can range from a few hundred to a few thousand AGU units. The regular arrangement of the chain and the presence of three hydroxyl groups, in the AGU unit of this polymer, is responsible for forming strong hydrogen bonds, which impart unique characteristics such as high crystallinity, low solubility in conventional solvents, an inertness. Without wishing to be bound by any theory, the mentioned hydrogen bonding will be widely used in this disclosure to form hydrogen bonding interactions within biocomposite materials described herein.

[0056] In one aspect, the biocompatible material includes a plurality of nanolayers. In some aspects, the plurality of nanolayers may include a plurality of cellulose nanofibers. In some aspects, the plurality of cellulose nanofibers within each nanolayer is substantially disposed along a direction that is substantially unparallel to a direction of a plurality of cellulose nanofibers within a nanolayer below or above.

[0057] In some aspects, the cellulose nanofibers may include natural cellulose nanofibers. “Natural cellulose nanofibers” as used herein are considered as still recognizable as being from a part of an original organism (such as a plant or microorganism) due to only being processed as much as needed to clean the associated fibers for use. This contrasts with “manufactured cellulose nanofibers,” as used herein, which are derived from cellulose processed into a pulp and then extruded.

[0058] In some aspects, the cellulose nanofibers may be derived from a plant. Cellulose nanofibers may be derived from a bast fiber (obtained from bark), a core fiber (obtained from wood), or a leaf fiber (obtained from leaves). Representative examples of fibers from which the cellulose nanofibers may be derived include, but are not limited to, bast fibers such as fiber flax, seed flax, kenaf, jute, hemp, and ramie, core fibers such as kenaf and jute, and leaf fibers such as abaca, sisal, and henequen. In some particular aspects, the cellulose nanofibers are derived from *Spurtium junceum*.

[0059] Natural cellulose nanofibers may be isolated from plant-based fibers using mechanical methods that expose the pulp to high shear forces, ripping the larger fibers apart into nanofibers. Typically, high-pressure homogenizers, grinders, or microfluidizers can be used, which delaminate the cell walls of the fibers and liberate the nanofibers. Enzymatic and mechanical pretreatments may also be used.

[0060] In other aspects, the cellulose nanofibers may be derived from a bacterium. In some aspects, the bacterium may include a Gram-negative bacterium or a Gram-positive

bacterium. Representative examples of bacteria capable of producing cellulose that may be used include those found in the genera *Acetobacter*, *Agrobacterium*, *Alcaligenes*, *Azotobacter*, *Komagataeibacter*, *Pseudomonas*, *Rhizobium*, *Salmonella*, and *Sarcina*. In particular aspects, the bacterium may be selected from *Komagataeibacter xylinus*, *Komagataeibacter hansenii*, and *Acetobacter pasteurianus*.

[0061] In some aspects, the cellulose nanofibers may be chemically modified. In some aspects, the cellulose nanofibers may include a cellulose ester or a cellulose ether. Representative examples of cellulose esters that may be used include, but are not limited to, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, cellulose acetate propionate (CAP), cellulose acetate butyrate (CAB), or cellulose acetate phthalate (CAP). Representative examples of cellulose ethers that may be used include, but are not limited to, methylcellulose, ethylcellulose, ethyl methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose (HPC), hydroxyethyl methyl cellulose, hydroxypropyl methyl cellulose (HPMC), ethyl hydroxyethyl cellulose, or carboxymethyl cellulose (CMC). Further examples of chemically modified cellulose which can be used include, but are not limited to, cellulose propionate, α -cellulose, (hydroxypropyl)methyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose triacetate, cyanoethylated cellulose, sodium carboxymethyl cellulose, cellulose acetate butyrate, and cellulose acetate propionate.

[0062] In some aspects, the cellulose nanofibers may be crosslinked. The cellulose nanofibers may be enzymatically or chemically crosslinked. Representative examples of chemical crosslinkers which may be used include, but are not limited to, glutaraldehyde, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), citric acid, 1,2,3,4-butanetetracarboxylic acid (BTCA), epichlorohydrin, genipin, divinylsulfone (DVS), cellodextrin phosphorylase, cellodextrin or cellodextrin nano- or microparticles (from about 10 to about 100 microns), epichlorohydrin triethanolamine-cellulose, cyclodextrins, epichlorohydrin, chitosan, sodium hypophosphite, or combinations thereof. In some aspects, the cellulose nanofibers are enzymatically crosslinked. FIG. 3 depicts an exemplary scheme regarding crosslinking of cellulose with cyclodextrins as described herein.

[0063] In some aspects, the cellulose nanofibers may include one or more additional polymers. Representative examples of such polymers include, but are not limited to, collagen, chitosan, gelatin, or combinations thereof. In some aspects, the cellulose nanofibers include collagen. In some aspects, the cellulose nanofibers include chitosan. In some aspects, the cellulose nanofibers include gelatin.

[0064] In some aspects, the cellulose nanofibers have a number average molecular weight from about 1 kDa to about 100 kDa, including exemplary values of about 1 kPa, about 2 kPa, about 3 kPa, about 4 kPa, about 5 kPa, about 6 kPa, about 7 kPa, about 8 kPa, about 9

kPa, about 10 kPa, about 11 kPa, about 12 kPa, about 13 kPa, about 14 kPa, about 15 kPa, about 16 kPa, about 17 kPa, about 18 kPa, about 19 kPa, about 20 kPa, about 21 kPa, about 22 kPa, about 23 kPa, about 24 kPa, about 25 kPa, about 26 kPa, about 27 kPa, about 28 kPa, about 29 kPa, about 30 kPa, about 31 kPa, about 32 kPa, about 33 kPa, about 34 kPa, about 35 kPa, about 36 kPa, about 37 kPa, about 38 kPa, about 39 kPa, about 40 kPa, about 41 kPa, about 42 kPa, about 43 kPa, about 44 kPa, about 45 kPa, about 46 kPa, about 47 kPa, about 48 kPa, about 49 kPa, about 50 kPa, about 51 kPa, about 52 kPa, about 53 kPa, about 54 kPa, about 55 kPa, about 56 kPa, about 57 kPa, about 58 kPa, about 59 kPa, about 60 kPa, about 61 kPa, about 62 kPa, about 63 kPa, about 64 kPa, about 65 kPa, about 66 kPa, about 67 kPa, about 68 kPa, about 69 kPa, about 70 kPa, about 71 kPa, about 72 kPa, about 73 kPa, about 74 kPa, about 75 kPa, about 76 kPa, about 77 kPa, about 78 kPa, about 79 kPa, about 80 kPa, about 81 kPa, about 82 kPa, about 83 kPa, about 84 kPa, about 85 kPa, about 86 kPa, about 87 kPa, about 88 kPa, about 89 kPa, about 90 kPa, about 91 kPa, about 92 kPa, about 93 kPa, about 94 kPa, about 95 kPa, about 96 kPa, about 97 kPa, about 98 kPa, about 99 kPa, about 100 kPa, any number average molecular weight between any two foregoing values, or any subrange formed by any two foregoing values.

[0065] In some aspects, the cellulose nanofibers have an average diameter from about 10 nm to about 100 nm, including exemplary values of about 10 nm, about 15 nm, about 20 nm, about 25 nm, about 30 nm, about 35 nm, about 40 nm, about 45 nm, about 50 nm, about 55 nm, about 60 nm, about 65 nm, about 70 nm, about 75 nm, about 80 nm, about 85 nm, about 90 nm, about 95 nm, about 100 nm, any average diameter between any two foregoing values, or any subrange formed by any two foregoing values.

[0066] In some aspects, the biocompatible material is porous. In some aspects, the biocompatible material has a density from about 0.05 to about 0.5 g/nm³, including the exemplary values of about 0.05 g/nm³, about 0.1 g/nm³, about 0.15 g/nm³, about 0.2 g/nm³, about 0.25 g/nm³, about 0.3 g/nm³, about 0.35 g/nm³, about 0.4 g/nm³, about 0.45 g/nm³, and about 0.5 g/nm³, any density between any two foregoing values, or any subrange formed by any two foregoing values. In such aspects, the biocompatible material may have a porosity from about 70% to about 99%, including the exemplary values of about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, any porosity between any two foregoing values, or any subrange formed by any two foregoing values.

[0067] In some aspects, the biocompatible material has a density from about 0.55 to about 0.95 g/nm³, including the exemplary values of about 0.55 g/nm³, about 0.6 g/nm³,

about 0.65 g/nm³, about 0.7 g/nm³, about 0.75 g/nm³, about 0.8 g/nm³, about 0.85 g/nm³, about 0.9 g/nm³, any density between any two foregoing values, or any subrange formed by any two foregoing values. In such aspects, the biocompatible material may have a porosity from about 20% to about 65%, including exemplary values of about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, any porosity between any two foregoing values, or any subrange formed by any two foregoing values.

[0068] In some aspects, the biocompatible material exhibits anisotropic material properties. In some aspects, the anisotropic material properties may be with respect to strength, elastic modulus, permanent deformation, or combinations thereof.

[0069] In some aspects, the biocompatible material exhibits a Young's modulus from about 0.5 MPa to about 100 MPa, including exemplary values of about 1 MPa, about 2 MPa, about 3 MPa, about 4 MPa, about 5 MPa, about 6 MPa, about 7 MPa, about 8 MPa, about 9 MPa, about 10 MPa, about 11 MPa, about 12 MPa, about 13 MPa, about 14 MPa, about 15 MPa, about 16 MPa, about 17 MPa, about 18 MPa, about 19 MPa, about 20 MPa, about 21 MPa, about 22 MPa, about 23 MPa, about 24 MPa, about 25 MPa, about 26 MPa, about 27 MPa, about 28 MPa, about 29 MPa, about 30 MPa, about 31 MPa, about 32 MPa, about 33 MPa, about 34 MPa, about 35 MPa, about 36 MPa, about 37 MPa, about 38 MPa, about 39 MPa, about 40 MPa, about 41 MPa, about 42 MPa, about 43 MPa, about 44 MPa, about 45 MPa, about 46 MPa, about 47 MPa, about 48 MPa, about 49 MPa, about 50 MPa, about 51 MPa, about 52 MPa, about 53 MPa, about 54 MPa, about 55 MPa, about 56 MPa, about 57 MPa, about 58 MPa, about 59 MPa, about 60 MPa, about 61 MPa, about 62 MPa, about 63 MPa, about 64 MPa, about 65 MPa, about 66 MPa, about 67 MPa, about 68 MPa, about 69 MPa, about 70 MPa, about 71 MPa, about 72 MPa, about 73 MPa, about 74 MPa, about 75 MPa, about 76 MPa, about 77 MPa, about 78 MPa, about 79 MPa, about 80 MPa, about 81 MPa, about 82 MPa, about 83 MPa, about 84 MPa, about 85 MPa, about 86 MPa, about 87 MPa, about 88 MPa, about 89 MPa, about 90 MPa, about 91 MPa, about 92 MPa, about 93 MPa, about 94 MPa, about 95 MPa, about 96 MPa, about 97 MPa, about 98 MPa, about 99 MPa, about 100 MPa, any Young's modulus between any two foregoing values, or any subrange formed by any two foregoing values.

[0070] In some aspects, the biocompatible material exhibits a tenacity from about 3 to about 5 g/denier, including exemplary values of about 3 denier, about 3.5 denier, about 4

denier, about 4.5 denier, about 5 denier, any tenacity between any two foregoing values, or any subrange formed by any two foregoing values.

[0071] In some aspects, the biocompatible material exhibits an ultimate tensile strength from about 25 MPa to about 50 MPa, including exemplary values of about 5MPa, about 26MPa, about 27MPa, about 28MPa, about 29MPa, about 30MPa, about 31MPa, about 32MPa, about 33MPa, about 34MPa, about 35MPa, about 36MPa, about 37MPa, about 38MPa, about 39MPa, about 40MPa, about 41MPa, about 42MPa, about 43MPa, about 44MPa, about 45MPa, about 46MPa, about 47MPa, about 48MPa, about 49MPa, about 50MPa, any ultimate tensile strength between any two foregoing values, or any subrange formed by any two foregoing values.

[0072] In some aspects, the biocompatible material exhibits an elongation at break from about 20% to about 500%, including exemplary values of about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 100%, about 105%, about 110%, about 115%, about 120%, about 125%, about 130%, about 135%, about 140%, about 145%, about 150%, about 155%, about 160%, about 165%, about 170%, about 175%, about 180%, about 185%, about 190%, about 195%, about 200%, about 205%, about 210%, about 215%, about 220%, about 225%, about 230%, about 235%, about 240%, about 245%, about 250%, about 255%, about 260%, about 265%, about 270%, about 275%, about 280%, about 285%, about 290%, about 295%, about 300%, about 305%, about 310%, about 315%, about 320%, about 325%, about 330%, about 335%, about 340%, about 345%, about 350%, about 355%, about 360%, about 365%, about 370%, about 375%, about 380%, about 385%, about 390%, about 395%, about 400%, about 405%, about 410%, about 415%, about 420%, about 425%, about 430%, about 435%, about 440%, about 445%, about 450%, about 455%, about 460%, about 465%, about 470%, about 475%, about 480%, about 485%, about 490%, about 495%, about 500%, any elongation at break between two foregoing values, or any subrange formed by any two foregoing values.

[0073] In some aspects, the biocompatible material is configured to be implanted into a patient body. In some aspects, the biocompatible material exhibits substantially no calcification over a time of implantation within a patient body. In some aspects, the biocompatible material exhibits substantially no calcification over 3 months, 6, months, 9 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, 12 years, 13 years, 14 years, or 15 years within a patient body.

[0074] In some aspects, the biocompatible material may include a backing material. In some aspects, the biocompatible material may include a coating. Suitable examples of

backing materials and coatings that may be used will be readily understood by those of skill in the art.

[0075] In some aspects, the biocompatible materials described herein may be formed into a leaflet structure.

Biocomposites

[0076] The present disclosure provides in some aspects biocomposites including the biocompatible materials described herein that can be used in the construction of implantable medical devices. In some aspects, the biocomposite may include a first layer including a biocompatible material described herein. In some aspects, the biocomposite further includes a second layer including a plurality of manufactured cellulose nanofibers. In some aspects, the biocomposite even further includes a filler dispersed within the first layer and/or the second layer. FIG. 1 depicts an exemplary biocomposite material as described herein.

[0077] In some aspects, the first layer and the second layer may be chemically linked, for example via covalent or ionic bonding between the first layer and the second layer.

[0078] The manufactured cellulose nanofibers as found in the second layer may be formed by any suitable method known in the art. In general, manufactured cellulose nanofibers are derived from plant materials that are first processed into a pulp. The manufactured cellulose nanofibers may then be extruded in the same way that other synthetic fibers are made. In some aspects, the manufactured cellulose nanofibers may be formed from cellulose dissolved in cuprammonium solution, which is then regenerated into the desired fibers. In such processes, cellulose, which is otherwise insoluble in water, is rendered aqueous solubility in the presence of Schweizer's reagent ($[\text{Cu}(\text{NH}_3)_4(\text{H}_2\text{O})_2](\text{OH})_2$). The resulting solution is then passed through a spinneret, and the cellulose is regenerated in hardening baths that remove the copper and ammonia and neutralize any remaining hydroxide ions. The hardening baths typically include acid solutions (such as sulfuric acid) which precipitate the cellulose and wash out any copper salts from the formed fibers.

[0079] In some aspects, the second layer may include a binding material. Representative examples of binding materials epoxy resins, natural rubber, nitrile rubber, phenol-formaldehyde, polyethylene, polypropylene, polystyrene, polyurethane, polyvinyl chloride, polyester, and styrene-butadiene.

[0080] In some aspects, the biocomposite may include a third layer including a biocompatible material described herein. In some aspects, the second layer is disposed between the first layer and the third layer. In some aspects, the filler is dispersed within the third layer.

[0081] Suitable fillers which may be used within the biocomposites described herein may be readily identified by those skilled in the art. In some aspects, the filler is chemically bound to the biocomposite, for example by covalent or ionic bonding. In some aspects, the filler may include a single component filler. Representative examples of single component fillers which may be used include, but are not limited to, glycerol, propylene carbonate, ethylene carbonate, hydroxyethyl cellulose (HEC), tetradecyltrimethylammonium bromide (TTAB), silicone oil, (Z)-(2*R*,3*R*,4*S*)-2-((*R*)-1-hydroxy-2-(oleoyloxy)ethyl)tetrahydrofuran-3,4-diylidioleate (LP), and 2-((3-dodecanamidopropyl)dimethylammonio)acetate (LS). In other aspects, the filler may include a two component filler, such as a deep eutectic solvent. Representative examples of two component fillers include, but are not limited to: choline in combination with glycerol, glucose, urea, or citric acid; and tetrabutylammonium bromide in combination with propylene carbonate or ethylene carbonate. In some aspects, the filler may include an inorganic filler, for example silver, zinc oxide, or titanium oxide. FIG. 2 depicts exemplary incorporation of silver ions or nanoparticles into the biocompatible materials as described herein.

[0082] In some aspects, the biocomposite may include a plurality of nanoparticles. Representative examples of nanoparticles that can be incorporated into the biocomposites described herein include, but are not limited to, silver nanoparticles, PEG hydrogel nanoparticles, graphene nanoparticles, polylactic acid (PLA) nanoparticles, polycaprolactone (PCL) nanoparticles, polyvinyl alcohol (PVA) nanoparticles, and nanoparticles formed from other biodegradable hydrogel or non-hydrogel polymers.

[0083] In some aspects, the biocomposite, as described herein, may be formed into a leaflet structure.

Methods of Manufacture

[0084] Methods of manufacturing biocompatible materials of the present disclosure are also provided. In some aspects, the method includes depositing a first plurality of cellulose nanofibers to be substantially arranged along a first direction to form a first nanolayer. The method may include depositing a second plurality of cellulose nanofibers to be substantially arranged along a second direction to form a second nanolayer disposed upon the first nanolayer, wherein the second direction is substantially unparallel to the first direction. The method may include depositing a third plurality of cellulose nanofibers to be substantially arranged along a third direction to form a third nanolayers disposed upon the second layer, wherein the third direction is substantially unparallel to the second direction.

[0085] In some aspects, the cellulose nanofibers as used in the disclosed methods include natural cellulose nanofibers. "Natural cellulose nanofibers" as used herein are considered as still recognizable as being from a part of an original organism (such as a plant or

microorganism) due to only being processed as much as needed to clean the associated fibers for use. This contrasts with “manufactured cellulose nanofibers,” as used herein, which are derived from cellulose processed into a pulp and then extruded.

[0086] In some aspects, the cellulose nanofibers, as used in the disclosed methods, may be derived from a plant. Cellulose nanofibers may be derived from a bast fiber (obtained from bark), a core fiber (obtained from wood), or a leaf fiber (obtained from leaves). Representative examples of fibers from which the cellulose nanofibers may be derived include, but are not limited to, bast fibers such as fiber flax, seed flax, kenaf, jute, hemp, and ramie, core fibers such as kenaf and jute, and leaf fibers such as abaca, sisal, and henequen. In some particular aspects, the cellulose nanofibers are derived from *Spurtium junceum*.

[0087] Natural cellulose nanofibers, as used in the disclosed methods, may be isolated from plant-based fibers using mechanical methods which expose the pulp to high shear forces, ripping the larger fibers apart into nanofibers. Typically, high-pressure homogenizers, grinders, or microfluidizers can be used, which delaminate the cell walls of the fibers and liberate the nanofibers. Enzymatic and mechanical pretreatments may also be used.

[0088] In other aspects, the cellulose nanofibers, as used in the disclosed methods, may be derived from a bacterium. In some aspects, the bacterium may include a Gram-negative bacterium or a Gram-positive bacterium. Representative examples of bacteria capable of producing cellulose that may be used include those found in the genera *Acetobacter*, *Agrobacterium*, *Alcaligenes*, *Azotobacter*, *Komagataeibacter*, *Pseudomonas*, *Rhizobium*, *Salmonella*, and *Sarcina*. In particular aspects, the bacterium may be selected from *Komagataeibacter xylinus*, *Komagataeibacter hansenii*, and *Acetobacter pasteurianus*.

[0089] In some aspects, the cellulose nanofibers, as used in the disclosed methods, may be chemically modified. In some aspects, the cellulose nanofibers may include a cellulose ester or a cellulose ether. Representative examples of cellulose esters that may be used include, but are not limited to, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, cellulose acetate propionate (CAP), cellulose acetate butyrate (CAB), or cellulose acetate phthalate (CAP). Representative examples cellulose ethers that may be used include, but are not limited to, methylcellulose, ethylcellulose, ethyl methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose (HPC), hydroxyethyl methyl cellulose, hydroxypropyl methyl cellulose (HPMC), ethyl hydroxyethyl cellulose, or carboxymethyl cellulose (CMC).

[0090] In some aspects, the cellulose nanofibers, as used in the disclosed methods, may be crosslinked. The cellulose nanofibers may be enzymatically or chemically crosslinked. Representative examples of chemical crosslinkers that may be used include, but are not

limited to, glutaraldehyde, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), citric acid, epichlorohydrin, genipin, divinylsulfone (DVS), or combinations thereof. In some aspects, the cellulose nanofibers are enzymatically crosslinked.

[0091] In some aspects, the cellulose nanofibers, as used in the disclosed methods, may include one or more additional polymers. Representative examples of such polymers include, but are not limited to, collagen, chitosan, gelatin, or combinations thereof. In some aspects, the cellulose nanofibers include collagen. In some aspects, the cellulose nanofibers include chitosan. In some aspects, the cellulose nanofibers include gelatin.

[0092] In some aspects, the cellulose nanofibers as used in the disclosed methods have a number average molecular weight from about 1 kDa to about 100 kDa, including exemplary values of about 1 kPa, about 2 kPa, about 3 kPa, about 4 kPa, about 5 kPa, about 6 kPa, about 7 kPa, about 8 kPa, about 9 kPa, about 10 kPa, about 11 kPa, about 12 kPa, about 13 kPa, about 14 kPa, about 15 kPa, about 16 kPa, about 17 kPa, about 18 kPa, about 19 kPa, about 20 kPa, about 21 kPa, about 22 kPa, about 23 kPa, about 24 kPa, about 25 kPa, about 26 kPa, about 27 kPa, about 28 kPa, about 29 kPa, about 30 kPa, about 31 kPa, about 32 kPa, about 33 kPa, about 34 kPa, about 35 kPa, about 36 kPa, about 37 kPa, about 38 kPa, about 39 kPa, about 40 kPa, about 41 kPa, about 42 kPa, about 43 kPa, about 44 kPa, about 45 kPa, about 46 kPa, about 47 kPa, about 48 kPa, about 49 kPa, about 50 kPa, about 51 kPa, about 52 kPa, about 53 kPa, about 54 kPa, about 55 kPa, about 56 kPa, about 57 kPa, about 58 kPa, about 59 kPa, about 60 kPa, about 61 kPa, about 62 kPa, about 63 kPa, about 64 kPa, about 65 kPa, about 66 kPa, about 67 kPa, about 68 kPa, about 69 kPa, about 70 kPa, about 71 kPa, about 72 kPa, about 73 kPa, about 74 kPa, about 75 kPa, about 76 kPa, about 77 kPa, about 78 kPa, about 79 kPa, about 80 kPa, about 81 kPa, about 82 kPa, about 83 kPa, about 84 kPa, about 85 kPa, about 86 kPa, about 87 kPa, about 88 kPa, about 89 kPa, about 90 kPa, about 91 kPa, about 92 kPa, about 93 kPa, about 94 kPa, about 95 kPa, about 96 kPa, about 97 kPa, about 98 kPa, about 99 kPa, about 100 kPa, any number average molecular weight between any two foregoing values, or any subrange formed by any two foregoing values.

[0093] In some aspects, the cellulose nanofibers as used in the disclosed methods have an average diameter from about 10 nm to about 100 nm, including exemplary values of about 10 nm, about 15 nm, about 20 nm, about 25 nm, about 30 nm, about 35 nm, about 40 nm, about 45 nm, about 50 nm, about 55 nm, about 60 nm, about 65 nm, about 70 nm, about 75 nm, about 80 nm, about 85 nm, about 90 nm, about 95 nm, about 100 nm, any average diameter between any two foregoing values, or any subrange formed by any two foregoing values.

[0094] In another aspect, a biocompatible material is provided prepared according to the methods described herein.

[0095] In some aspects, the biocompatible material as prepared according to the disclosed methods is porous. In some aspects, the biocompatible material has a density from about 0.05 to about 0.5 g/nm³, including the exemplary values of about 0.05 g/nm³, about 0.1 g/nm³, about 0.15 g/nm³, about 0.2 g/nm³, about 0.25 g/nm³, about 0.3 g/nm³, about 0.35 g/nm³, about 0.4 g/nm³, about 0.45 g/nm³, and about 0.5 g/nm³, any density between any two foregoing values, or any subrange formed by any two foregoing values. In such aspects, the biocompatible material may have a porosity from about 70% to about 99%, including the exemplary values of about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, any porosity between any two foregoing values, or any subrange formed by any two foregoing values.

[0096] In some aspects, the biocompatible material as prepared according to the disclosed methods has a density from about 0.55 to about 0.95 g/nm³, including the exemplary values of about 0.55 g/nm³, about 0.6 g/nm³, about 0.65 g/nm³, about 0.7 g/nm³, about 0.75 g/nm³, about 0.8 g/nm³, about 0.85 g/nm³, about 0.9 g/nm³, any density between any two foregoing values, or any subrange formed by any two foregoing values. In such aspects, the biocompatible material may have a porosity from about 20% to about 65%, including exemplary values of about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, any porosity between any two foregoing values, or any subrange formed by any two foregoing values.

[0097] In some aspects, the biocompatible material, as prepared according to the disclosed methods, exhibits anisotropic material properties. In some aspects, the anisotropic material properties may be with respect to strength, elastic modulus, permanent deformation, or combinations thereof.

[0098] In some aspects, the biocompatible material as prepared according to the disclosed methods exhibits a Young's modulus from about 0.5 MPa to about 100 MPa, including exemplary values of about 1 MPa, about 2 MPa, about 3 MPa, about 4 MPa, about 5 MPa, about 6 MPa, about 7 MPa, about 8 MPa, about 9 MPa, about 10 MPa, about 11 MPa, about 12 MPa, about 13 MPa, about 14 MPa, about 15 MPa, about 16 MPa, about 17 MPa,

about 18 MPa, about 19 MPa, about 20 MPa, about 21 MPa, about 22 MPa, about 23 MPa, about 24 MPa, about 25 MPa, about 26 MPa, about 27 MPa, about 28 MPa, about 29 MPa, about 30 MPa, about 31 MPa, about 32 MPa, about 33 MPa, about 34 MPa, about 35 MPa, about 36 MPa, about 37 MPa, about 38 MPa, about 39 MPa, about 40 MPa, about 41 MPa, about 42 MPa, about 43 MPa, about 44 MPa, about 45 MPa, about 46 MPa, about 47 MPa, about 48 MPa, about 49 MPa, about 50 MPa, about 51 MPa, about 52 MPa, about 53 MPa, about 54 MPa, about 55 MPa, about 56 MPa, about 57 MPa, about 58 MPa, about 59 MPa, about 60 MPa, about 61 MPa, about 62 MPa, about 63 MPa, about 64 MPa, about 65 MPa, about 66 MPa, about 67 MPa, about 68 MPa, about 69 MPa, about 70 MPa, about 71 MPa, about 72 MPa, about 73 MPa, about 74 MPa, about 75 MPa, about 76 MPa, about 77 MPa, about 78 MPa, about 79 MPa, about 80 MPa, about 81 MPa, about 82 MPa, about 83 MPa, about 84 MPa, about 85 MPa, about 86 MPa, about 87 MPa, about 88 MPa, about 89 MPa, about 90 MPa, about 91 MPa, about 92 MPa, about 93 MPa, about 94 MPa, about 95 MPa, about 96 MPa, about 97 MPa, about 98 MPa, about 99 MPa, about 100 MPa, any Young's modulus between any two foregoing values, or any subrange formed by any two foregoing values.

[0099] In some aspects, the biocompatible material, as prepared according to the disclosed methods, exhibits a tenacity from about 3 to about 5 g/denier, including exemplary values of about 3 denier, about 3.5 denier, about 4 denier, about 4.5 denier, about 5 denier, any tenacity between any two foregoing values, or any subrange formed by any two foregoing values.

[0100] In some aspects, the biocompatible material as prepared according to the disclosed methods exhibits an ultimate tensile strength from about 25 MPa to about 50 MPa, including exemplary values of about 5MPa, about 26MPa, about 27MPa, about 28MPa, about 29MPa, about 30MPa, about 31MPa, about 32MPa, about 33MPa, about 34MPa, about 35MPa, about 36MPa, about 37MPa, about 38MPa, about 39MPa, about 40MPa, about 41MPa, about 42MPa, about 43MPa, about 44MPa, about 45MPa, about 46MPa, about 47MPa, about 48MPa, about 49MPa, about 50MPa, any ultimate tensile strength between any two foregoing values, or any subrange formed by any two foregoing values.

[0101] In some aspects, the biocompatible material as prepared according to the disclosed methods exhibits an elongation at break from about 20% to about 500%, including exemplary values of about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 100%, about 105%, about 110%, about 115%, about 120%, about 125%, about 130%, about 135%, about 140%, about 145%, about 150%, about 155%, about 160%, about 165%, about 170%, about 175%, about 180%, about 185%, about 190%,

about 195%, about 200%, about 205%, about 210%, about 215%, about 220%, about 225%, about 230%, about 235%, about 240%, about 245%, about 250%, about 255%, about 260%, about 265%, about 270%, about 275%, about 280%, about 285%, about 290%, about 295%, about 300%, about 305%, about 310%, about 315%, about 320%, about 325%, about 330%, about 335%, about 340%, about 345%, about 350%, about 355%, about 360%, about 365%, about 370%, about 375%, about 380%, about 385%, about 390%, about 395%, about 400%, about 405%, about 410%, about 415%, about 420%, about 425%, about 430%, about 435%, about 440%, about 445%, about 450%, about 455%, about 460%, about 465%, about 470%, about 475%, about 480%, about 485%, about 490%, about 495%, about 500%, any elongation at break between two foregoing values, or any subrange formed by any two foregoing values.

[0102] In some aspects, the biocompatible material as prepared according to the disclosed methods is configured to be implanted into a patient body. In some aspects, the biocompatible material exhibits substantially no calcification over a time of implantation within a patient body. In some aspects, the biocompatible material exhibits substantially no calcification over 3 months, 6 months, 9 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, 12 years, 13 years, 14 years, or 15 years within a patient body.

[0103] In some aspects, the methods described herein may include adhering or attaching the biocompatible material to a backing material. In other aspects, the methods described herein may include applying a coating to the biocompatible material. Suitable examples of backing materials and coatings that may be used will be readily understood by those of skill in the art.

Implantable Medical Devices

[0104] The present disclosure also provides implantable medical devices, such as but not limited to prosthetic valves, patches, clasps, sleeves, conduits, bands, and the like. In some aspects, the implantable medical device may include a surgical aortic valve replacement, a transcatheter mitral valve replacement, a cardiovascular patch, and a vascular graft.

[0105] In some aspects, the device includes a cardiovascular patch. In some aspects, at least a portion of the cardiovascular patch includes a biocompatible material or biocomposite described herein.

[0106] In some aspects, the device includes an annuloplasty device. In some aspects, the annuloplasty device includes a sleeve and one or more anchors. In some aspects, at least a portion of the sleeve includes a biocompatible material or biocomposite described herein. In

some aspects, at least a portion of the one or more anchors include a biocompatible material or biocomposite described herein.

[0107] In some aspects, the device includes a vascular graft. In some aspects, at least a portion of the cardiovascular patch includes a biocompatible material or biocomposite described herein.

[0108] In some aspects, the device includes an implantable prosthetic valve. In some aspects, the implantable prosthetic valve includes an annular frame having an inner surface and an outer surface. In some aspects, the frame has an inflow end and an outflow end, and a central longitudinal axis extending from the inflow end to the outflow end. In some aspects, the device may include a leaflet structure having an inner surface and an outer surface. In some aspects, the leaflet structure may be positioned at the inner surface of the annular frame. In some aspects, at least a portion of the leaflet structure includes a biocompatible material or biocomposite described herein. In some aspects, the annular frame is configured to expand and contract.

[0109] In some aspects, the implantable prosthetic valve includes an inner skirt having an inner surface and an outer surface and positioned along the inner surface of the frame. In some aspects, at least a portion of the inner skirt includes a biocompatible material or biocomposite described herein.

[0110] In some aspects, the implantable prosthetic valve includes an outer skirt having an inner surface and an outer surface and positioned at the outer surface of the annular frame. In some aspects, at least a portion of the outer skirt includes a biocompatible material or biocomposite described herein.

[0111] In certain aspects, the exemplary implantable medical device can include a frame **1000**, as shown in **FIG. 4**. In such an aspect, the frame **1000** is shown in an expanded configuration. The frame **1000** can include a frame portion **1002**. In certain aspects, at least a portion of frame portion **1002** may include a biocompatible material or biocomposite described herein. Frame portion **1002** can have an upper region **1004**, an intermediate region **1006**, and a lower region **1008** (and corresponding upper region, inner side, upper region, outer side; intermediate region, inner side, intermediate region, outer side, lower region, inner side, and lower region outside side (not shown)).

[0112] A longitudinal axis (not shown) of the frame **1000** can be defined as the central axis that extends through the center of the frame **1000** between the upper and lower ends of the frame **1000**. In some aspects, the frame **1000** can be oriented such that the upper region **1004** is a proximal portion, and the lower region **1008** is a distal portion. The frame **1000** can include a plurality of anchoring members **1010**. In some aspects, the frame **1000**

can be oriented such that the plurality of anchoring members **1010** are distal anchoring members. In certain aspects, at least a portion of the anchors may include a biocompatible material or biocomposite described herein.

[0113] In some aspects, the implantable device is a prosthetic valve configured to be deployed to a native valve of the heart. Exemplary prosthetic valves are shown in **FIGs. 4, 5, 6A, and 6B**, and described below in more detail.

[0114] Referring to **FIG. 5**, in this aspect, the prosthetic valve **2000**, includes a frame **2002**, as described in **FIG. 4**. The valve includes a plurality of prosthetic leaves **2020**, an inner skirt **2016**, and an outer skirt **2018**. The outer skirt or a sealing element can be used for a paravalvular leak seal. The implantable medical device has an inflow end **2040** and an outflow end **2030**. In certain aspects, at least a portion of the prosthetic leaves **2020** may include a biocompatible material or biocomposite described herein. In certain aspects, at least a portion of the inner skirt **2016** may include a biocompatible material or biocomposite described herein. In certain aspects, at least a portion of the outer skirt **2018** may include a biocompatible material or biocomposite described herein.

[0115] In some aspects, the implantable medical device is configured to be deployed to a native valve of a heart, wherein the prosthetic valve includes the plurality of prosthetic valve leaflets as shown herein, wherein the one or more anchors are coupled to the plurality of prosthetic valve leaflets, and each is configured to anchor to a portion of the heart.

[0116] Some exemplary prosthetic devices are shown in **FIG. 6A and 6B**. In one aspect is an implantable prosthetic valve **3100**, including: an annular frame **3040**, wherein the frame has an inflow end **3020** and an outflow end **3030**. An exemplary prosthetic heart valve **3100** is also described in U.S. Patent No. 10,463,484, titled “Prosthetic Heart Valve Having Leaflet Inflow Below Frame,” which is incorporated herein by reference. The illustrated prosthetic valve **3100** is adapted to be implanted in the native aortic annulus, although in other aspects, it can be adapted to be implanted in the other native annuluses of the heart (the mitral valve, pulmonary valve, and tricuspid valve).

[0117] In some aspects, the implantable prosthetic valve also includes an inner skirt **3005** that is positioned along the inner surface of the frame. In some aspects, the valve includes a leaflet structure **3060** including one or more leaflets, having an inner surface and an outer surface and positioned at the inner surface of the annular frame. In some aspects, at least a portion of the leaflets may include a biocompatible material or biocomposite described herein. In some aspects, the valve can optionally include an outer skirt. The outer skirt **3009** is positioned at the outer surface of the annular frame **3040**. The outer skirt can also be attached to the frame with one or more sutures **3007**. The valve can also include

additional sutures, for example, **3006** and **3014**, that run along various portions of the device. In some aspects, the sutures can be used to attach at least a portion of the inner skirt and/or at least a portion of the leaflet structure and/or at least a portion of the outer skirt, if present, to at least a frame of an implantable prosthetic valve. In some aspects, the sutures can be used to attach various components of the valve together.

[0118] In certain aspects, the prosthetic valve **3100** can include a leaflet structure **3060**. In certain aspects, the leaflet structure can include one or more leaflets, each of which can be arranged to collapse in a tricuspid arrangement. In certain aspects, an edge of the leaflet structure **3060** can have an undulating, curved, scalloped shape. Moreover, by virtue of the scalloped shape, folds, and ripples at the belly of each leaflet, which can cause early calcification in those areas, can be eliminated or at least minimized. Leaflets can have various other shapes and/or configurations in other aspects. It is understood, however, that the leaflets of the leaflet structure need not have a V-shaped or scalloped inflow edge, and instead, each leaflet can have a square or rectangular shape defining a straight inflow edge. As described earlier, at least a portion of the leaflets may include a biocompatible material or biocomposite as described herein.

[0119] As shown in FIGs. **6A** and **6B**, the leaflet structure **3060** can be secured with the one or more sutures **3014** to the frame **3040**. The frame **3040** can be made of any of various suitable plastically-expandable materials (for example, stainless steel, cobalt chromium, etc.) or self-expanding materials (for example, nitinol) as is known in the art. When constructed of a plastically-expandable material, the frame **3040** can be crimped to a radially compressed state on a delivery catheter and then expanded inside a patient by an inflatable balloon or equivalent expansion mechanism. When constructed of a self-expandable material, the frame **3040** can be crimped to a radially compressed state and restrained in the compressed state by insertion into a sheath or equivalent mechanism of a delivery catheter. Once inside the body, the valve can be advanced from the delivery sheath, which allows the valve to expand to its functional size. Suitable plastically-expandable materials that can be used to form the frame **3040** include, without limitation, stainless steel, a nickel-based alloy (for example, a cobalt-chromium or a nickel-cobalt-chromium alloy), polymers, or combinations thereof. In particular aspects, frame **3040** can be made of a nickel-cobalt-chromium-molybdenum alloy, such as MP35N™ alloy (tradename of SPS Technologies), which is equivalent to UNS R30035 alloy (covered by ASTM F562-02). MP35N™/UNS R30035 alloy includes 35% nickel, 35% cobalt, 20% chromium, and 10% molybdenum by weight. In aspects when MP35N alloy is used as the frame material, less material is needed to achieve the same or better performance in radial and crush force resistance, fatigue resistance, and corrosion resistance. Moreover, since less material is

required, the crimped profile of the frame can be reduced, thereby providing a lower profile valve assembly for percutaneous delivery to the treatment location in the body.

[0120] The leaflets can be sutured together to form the leaflet structure **3060**, which can then be secured to the frame **3040**. It is understood that when the leaflets are sutured together, each of the leaflets can include any of the disclosed herein sutures if desired. However, also disclosed herein are the aspects, when different from the disclosed one or more sutures are used to secure the leaflet structure within the valve. In some exemplary and nonlimiting aspects, the leaflets of the leaflet structure **3060** can be secured to one another at their adjacent sides to form commissures **3011** of the leaflet structure. It is understood that sutures, as disclosed herein, can also be used to form such commissures. Yet, in other aspects, sutures different from those disclosed herein can also be used.

[0121] In some exemplary aspects, the one or more leaflets of the leaflet structure **3060** can be attached to the inner skirt **3005**, with sutures **3014**. The suture **3014** can track the curvature of the bottom edge of the leaflet structure **3060** and are collectively referred to as the scallop line.

[0122] The inner skirt **3005** can have a plurality of functions, which can include assisting in securing the leaflet structure **3060** and/or the outer skirt **3009** to the frame **3040** and in forming a good seal between the valve **3100** and the native annulus by blocking the flow of blood below the lower edges of the leaflets. It is understood that any known in the art configuration/construction of the skirt can be used. For example, and without limitation, the configuration/construction of the skirt can include a textile that is braided, knitted, woven and/or nonwoven. The inner skirt **3005** can include a tough, tear-resistant material such as polyethylene terephthalate (PET), although various other synthetic or natural materials can be used. The thickness of the skirt is desirably less than 6 mils or 0.15 mm, and desirably less than 4 mils or 0.10 mm, and even more desirably about 2 mils or 0.05 mm, and even still more desirably about 1.1 mils or 0.03 mm. In particular aspects, the skirt **3005** can have a variable thickness, for example, the skirt can be thicker at its edges than at its center. In one aspect, the skirt **3005** can include a PET skirt having a thickness of about 0.07 mm at its edges and about 0.06 mm at its center. The thinner skirt can provide for better crimping performances while still providing good perivalvular sealing.

[0123] In some aspects, the implantable medical device is configured to be deployed to a native valve of a heart, wherein the prosthetic valve includes the plurality of prosthetic valve leaflets as shown herein, wherein the one or more anchors are coupled to the plurality of prosthetic valve leaflets, and each is configured to anchor to a portion of the heart.

[0124] Features of an implant that can be utilized are disclosed in U.S. Patent Application No. 16/028,172, the entire content of which is incorporated by reference herein. Additional details and example designs for an implant and prosthesis that can be utilized in examples herein are described in U.S. Patent Nos. 8,403,983, 8,414,644, 8,652,203 and U.S. Patent Publication Nos. 2011/0313515, 2012/0215303, 2014/0277390, 2014/0277422, 2014/0277427, 2018/0021129, and 2018/0055629, the entirety of these patents and publications are hereby incorporated by reference and made a part of this specification. Further details and examples of a replacement heart valve or prosthesis and its method of implantation are described in U.S. Publication Nos. 2015/0328000 and 2016/0317301, the entirety of each of which is hereby incorporated by reference and made a part of this specification.

[0125] The implantable medical devices disclosed herein can include a mitral replacement valve or a tricuspid replacement valve, among other forms of valves (for example, aortic replacement valves, pulmonary replacement valves, or other valves). The implantable medical devices disclosed herein can include prosthetic heart valves or other forms of implants, such as stents, filters, or diagnostic devices, among others. The implantable medical devices can be expandable implants configured to move from a compressed or undeployed state to an expanded or deployed state. The implantable medical devices can be compressible implants configured to be compressed inward to have a reduced outer profile and to move the implant to the compressed or undeployed state.

[0126] Various forms of delivery apparatuses can be utilized with the examples disclosed herein. The delivery apparatuses as disclosed herein can be utilized for aortic, mitral, tricuspid, and pulmonary replacement and repair as well. The delivery apparatuses can include delivery apparatuses for the delivery of other forms of implants, such as stents, filters, or diagnostic devices, among others.

[0127] The implantable medical devices and the systems disclosed herein can be used in transcatheter aortic valve implantation (TAVI) or replacement of other native heart valves (for example, mitral, tricuspid, or pulmonary). The delivery apparatuses and the systems disclosed herein can be utilized for transarterial access, including transfemoral access, to a patient's heart. The delivery apparatuses and systems can be utilized in transcatheter percutaneous procedures, including transarterial procedures, which can be transfemoral or transjugular. Transapical procedures, among others, can also be utilized. Other procedures can be utilized as desired. Features of aspects can be modified, substituted, excluded, or combined across examples as desired.

[0128] In some aspects, disclosed is a method including: deploying a prosthetic valve to a native valve of a patient's heart, the prosthetic valve including: a plurality of prosthetic valve

leaflets, one or more anchors coupled to the plurality of prosthetic valve leaflets, and each configured to anchor to a portion of the patient's heart, wherein each of the one or more anchors is inserted into the disclosed herein woven article. In such aspects, the one or more anchors include ventricular anchors. In some aspects, the method includes hooking each of the one or more anchors around a native valve leaflet. In some aspects, the native valve is a native mitral valve or a native tricuspid valve.

[0129] A number of aspects of the disclosure have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the disclosure. Accordingly, other aspects are within the scope of the following claims.

Examples

[0130] The following examples are put forth to provide those of ordinary skill in the art with a complete disclosure and description of how the compositions, articles, devices, and methods claimed herein are made and evaluated and are intended to be purely exemplary of the disclosure. Efforts have been made to ensure accuracy concerning numbers (for example, amounts, temperature, etc.), but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in degrees Celsius or is at ambient temperature, and pressure is at or near atmospheric pressure.

EXAMPLE 1.

PREPARATION OF EXEMPLARY BIOCOMPOSITE MATERIALS

[0131] Carboxymethylcellulose (CMC) was dissolved in acetone (at 1–10%w/w); then, DI water (in the same amount as acetone) was added to the CMC solution, and the system was heated to 60 °C, obtaining a X% w/w CMC solution in water. Citric Acid (CA) at 1–10 wt% was added to the solution and then kept under stirring for 30 min at 60 °C. Then, the solution was kept in an oven for 24 h at 40 °C, and after more 24 h at 80 °C. Cellulose fibers isolated from a plant were acquired and chemically treated with NaOH and then washed with ethanol water (80%) mixture. Cellulose fibers were randomly deposited in layers and then processed by compression molding to obtain multilayers of randomly oriented fibers. Multilayered cellulose material was submerged into CMC-DI water and CA solution. Biocomposite material was treated in the following proportions, in weight, of CMC-CA solution 99:X (where X = 1–10).

EXAMPLE 2.

ASSESSMENT OF BACTERIAL CELLULOSE CELL PENETRATION AND CALCIFICATION IN VIVO

[0132] Bacterial cellulose supplied by Evonik Industries was implanted in rabbits for 60 days to assess calcification *in vivo*. Ten rabbits demonstrate remarkable cell proliferation

and penetration in the fibrous structure of the cellulose, as shown by Mason's Trichrome staining in FIG. 7. Further, no calcification was observed, as shown by Van Kossa staining in FIG. 8.

Exemplary Aspects

[0133] In view of the described processes and compositions, hereinbelow are described certain more particularly described aspects of the disclosures. These particularly recited aspects should not, however, be interpreted to have any limiting effect on any different claims containing different or more general teachings described herein, or that the "particular" aspects are somehow limited in some way other than the inherent meanings of the language and formulas literally used therein.

[0134] Aspect 1. A biocompatible material comprising a plurality of nanolayers, wherein each nanolayer within the plurality of nanolayers comprises a plurality of cellulose nanofibers, the plurality of cellulose nanofibers within each nanolayer being substantially disposed along a direction that is substantially unparallel to a direction of a plurality of cellulose nanofibers within a nanolayer below or above.

[0135] Aspect 2. The biocompatible material of any one of the aspects herein, particularly aspect 1, wherein the cellulose nanofibers comprise natural cellulose nanofibers.

[0136] Aspect 3. The biocompatible material of any one of the aspects herein, particularly aspect 2, wherein the natural cellulose nanofibers comprise bacterial cellulose.

[0137] Aspect 4. The biocompatible material of any one of the aspects herein, particularly aspect 3, wherein the bacterial cellulose is derived from a bacterium selected from *Acetobacter*, *Agrobacterium*, *Alcaligenes*, *Azotobacter*, *Komagataeibacter*, *Pseudomonas*, *Rhizobium*, *Salmonella*, and *Sarcina*.

[0138] Aspect 5. The biocompatible material of any one of the aspects herein, particularly aspect 3 or aspect 4, wherein the bacterial cellulose is derived from a bacterium selected from *Komagataeibacter xylinus*, *Komagataeibacter hansenii*, and *Acetobacter pasteurianus*.

[0139] Aspect 6. The biocompatible material of any one of the aspects herein, particularly any one of aspects 1–5, wherein the cellulose nanofibers are crosslinked.

[0140] Aspect 7. The biocompatible material of any one of the aspects herein, particularly aspect 6, wherein the cellulose nanofibers are enzymatically crosslinked.

[0141] Aspect 8. The biocompatible material of any one of the aspects herein, particularly aspect 6, wherein the cellulose nanofibers are chemically crosslinked.

[0142] Aspect 9. The biocompatible material of any one of the aspects herein, particularly aspect 8, wherein the cellulose nanofibers are chemically crosslinked with a crosslinker selected from glutaraldehyde, EDC, citric acid, epichlorohydrin, genipin, divinylsulfone (DVS), or combinations thereof.

[0143] Aspect 10. The biocompatible material of any one of any one of the aspects herein, particularly aspects 1–9, wherein the cellulose nanofibers further comprise collagen, chitosan, gelatin, or combinations thereof.

[0144] Aspect 11. The biocompatible material of any one of the aspects herein, particularly any one of aspects 1–10, wherein the cellulose nanofibers comprise cellulose having a number average molecular weight from about 1 kDa to about 100 kDa.

[0145] Aspect 12. The biocompatible material of any one of the aspects herein, particularly any one of aspects 1–11, wherein the cellulose nanofibers have an average diameter from about 10 nm to about 100 nm.

[0146] Aspect 13. The biocompatible material of any one of the aspects herein, particularly any one of aspects 1–12, wherein the biocompatible material is porous.

[0147] Aspect 14. The biocompatible material of any one of the aspects herein, particularly aspect 13, wherein the biocompatible material has a density from about 0.05 to about 0.5 g/nm³ and a porosity from about 70% to about 99.9%.

[0148] Aspect 15. The biocompatible material of any one of the aspects herein, particularly aspect 13, wherein the biocompatible material has a density from about 0.55 to about 0.95 g/nm³ and a porosity from about 20% to about 65%.

[0149] Aspect 16. The biocompatible material of any one of the aspects herein, particularly any one of aspects 1–15, having anisotropic mechanical properties.

[0150] Aspect 17. The biocompatible material of any one of the aspects herein, particularly aspect 16, having anisotropic properties with respect to strength, elastic modulus, permanent deformation, or combinations thereof.

[0151] Aspect 18. The biocompatible material of any one of the aspects herein, particularly any one of aspects 1–17, wherein the biocompatible material exhibits a Young's modulus from about 0.5 MPa to about 100 MPa.

[0152] Aspect 19. The biocompatible material of any one of the aspects herein, particularly any one of aspects 1–18, wherein the biocompatible material exhibits a tenacity from about 3 to about 5 g/denier.

[0153] Aspect 20. The biocompatible material of any one of the aspects herein, particularly any one of aspects 1–19, wherein the biocompatible material exhibits an ultimate tensile strength from about 25 MPa to about 50 MPa.

[0154] Aspect 21. The biocompatible material of any one of the aspects herein, particularly any one of aspects 1–20, wherein the biocompatible material exhibits an elongation at break from about 20% to about 500%.

[0155] Aspect 22. The biocompatible material of any one of the aspects herein, particularly any one of aspects 1–21, wherein the biocompatible material is configured to be implanted into a patient body.

[0156] Aspect 23. The biocompatible material of any one of the aspects herein, particularly aspect 22, wherein the biocompatible material exhibits substantially no calcification over a time of implantation within a patient body.

[0157] Aspect 24. The biocompatible material of any one of the aspects herein, particularly any one of aspects 1–23, further comprising a backing material.

[0158] Aspect 25. The biocompatible material of any one of the aspects herein, particularly any one of aspects 1–23, further comprising a coating.

[0159] Aspect 26. A biocomposite comprising:
a first layer comprising a biocompatible material of any one of the aspects herein, particularly any one of aspects 1–25;
a second layer comprising a plurality of manufactured cellulose nanofibers; and
a filler dispersed within the first layer and/or the second layer.

[0160] Aspect 27. The biocomposite of any one of the aspects herein, particularly aspect 26, wherein first layer and the second layer are chemically linked.

[0161] Aspect 28. The biocomposite of any one of the aspects herein, particularly aspect 26 or aspect 27, further comprising a third layer comprising a biocompatible material of any one of the aspects herein, particularly any one of aspects 1–25, wherein the second layer is disposed between the first layer and the third layer.

[0162] Aspect 29. The biocomposite of any one of the aspects herein, particularly aspect 28, wherein the filler is dispersed within the third layer.

[0163] Aspect 30. The biocomposite of any one of the aspects herein, particularly aspect 28 or aspect 29, wherein the third layer and the second layer are chemically linked.

[0164] Aspect 31. The biocomposite of any one of the aspects herein, particularly any one of aspects 26–30, wherein the filler is chemically bound to the biocomposite.

[0165] Aspect 32. The biocomposite of any one of the aspects herein, particularly any one of aspects 26–31, wherein the filler comprises a single component filler.

[0166] Aspect 33. The biocomposite of any one of the aspects herein, particularly aspect 32, wherein the single component filler is selected from: glycerol; propylene carbonate; ethylene carbonate; hydroxyethyl cellulose (HEC); tetradecyltrimethylammonium bromide (TTAB); silicone oil; (*Z*)-(2*R*,3*R*,4*S*)-2-((*R*)-1-hydroxy-2-(oleoyloxy)ethyl)tetrahydrofuran-3,4-diyl dioleate (LP); and 2-((3-dodecanamidopropyl)dimethylammonio)acetate (LS).

[0167] Aspect 34. The biocomposite of any one of the aspects herein, particularly any one of aspects 26–31, wherein the filler comprises a two component filler.

[0168] Aspect 35. The biocomposite of any one of the aspects herein, particularly aspect 34, wherein the two component filler comprises a deep eutectic solvent.

[0169] Aspect 36. The biocomposite of any one of the aspects herein, particularly aspect 34, wherein the two component filler is selected from: choline in combination with glycerol, glucose, urea, or citric acid; and tetrabutylammonium bromide in combination with propylene carbonate or ethylene carbonate.

[0170] Aspect 37. The biocomposite of any one of the aspects herein, particularly any one of aspects 26–31, wherein the filler comprises an inorganic filler.

[0171] Aspect 38. The biocomposite of any one of the aspects herein, particularly aspect 37, wherein the inorganic filler is selected from silver, zinc oxide, and titanium dioxide.

[0172] Aspect 39. The biocompatible material of any one of the aspects herein, particularly any one of aspects 1–25 formed into a leaflet structure.

[0173] Aspect 40. The biocomposite of any one of the aspects herein, particularly any one of aspects 26–38 formed into a leaflet structure.

[0174] Aspect 41. An implantable medical device comprising the biocompatible material of any one of the aspects herein, particularly any one of aspects 1–25 or the biocomposite of any one of the aspects herein, particularly any one of aspects 26–38.

[0175] Aspect 42. The implantable medical device of any one of the aspects herein, particularly aspect 41 selected from a surgical aortic valve replacement, a transcatheter mitral valve replacement, a cardiovascular patch, and a vascular graft.

[0176] Aspect 43. An implantable prosthetic valve comprising:

an annular frame having an inner surface and an outer surface wherein the frame has an inflow end and an outflow end, and a central longitudinal axis extending from the inflow end to the outflow end; and

a leaflet structure having an inner surface and an outer surface and positioned at the inner surface of the annular frame;

wherein at least a portion of the leaflet structure comprises the biocompatible material of any one of the aspects herein, particularly any one of aspects 1–25 or the biocomposite of any one of the aspects herein, particularly any one of aspects 26–38;

wherein the annular frame is configured to expand and contract.

[0177] Aspect 44. The implantable prosthetic valve of any one of the aspects herein, particularly aspect 43, further comprising an inner skirt having an inner surface and an outer surface and positioned along the inner surface of the frame.

[0178] Aspect 45. The implantable prosthetic valve of any one of the aspects herein, particularly aspect 44, wherein at least a portion of the inner skirt comprises the biocompatible material of any one of the aspects herein, particularly any one of aspects 1–25 or the biocomposite of any one of the aspects herein, particularly any one of aspects 26–38.

[0179] Aspect 46. The implantable prosthetic valve of any one of the aspects herein, particularly any one of aspects 41–43, further comprising an outer skirt having an inner surface and an outer surface and positioned at the outer surface of the annular frame.

[0180] Aspect 47. The implantable prosthetic valve of any one of the aspects herein, particularly aspect 46, wherein at least a portion of the outer skirt comprises the biocompatible material of any one of the aspects herein, particularly any one of aspects 1–25 or the biocomposite of any one of the aspects herein, particularly any one of aspects 26–38.

[0181] Aspect 48. A method of manufacturing a biocompatible material comprising:
depositing a first plurality of cellulose nanofibers to be substantially arranged along a first direction to form a first nanolayer; and
depositing a second plurality of cellulose nanofibers to be substantially arranged along a second direction to form a second nanolayer disposed upon the first nanolayer, wherein the second direction is substantially unparallel to the first direction.

[0182] Aspect 49. The method of any one of the aspects herein, particularly aspect 48, further comprising:

depositing a third plurality of cellulose nanofibers to be substantially arranged along a third direction to form a third nanolayer disposed upon the second nanolayer, wherein the third direction is substantially unparallel to the second direction.

[0183] Aspect 50. The method of any one of the aspects herein, particularly aspect 48 or aspect 49, wherein the cellulose nanofibers comprise natural cellulose nanofibers.

[0184] Aspect 51. The method of any one of the aspects herein, particularly aspect 50, wherein the natural cellulose nanofibers comprise bacterial cellulose.

[0185] Aspect 52. The method of any one of the aspects herein, particularly aspect 51, wherein the bacterial cellulose is derived from a bacterium selected from *Acetobacter*, *Agrobacterium*, *Alcaligenes*, *Azotobacter*, *Komagataeibacter*, *Pseudomonas*, *Rhizobium*, *Salmonella*, and *Sarcina*.

[0186] Aspect 53. The method of any one of the aspects herein, particularly aspect 51 or aspect 52, wherein the bacterial cellulose is derived from a bacterium selected from *Komagataeibacter xylinus*, *Komagataeibacter hansenii*, and *Acetobacter pasteurianus*.

[0187] Aspect 54. The method of any one of the aspects herein, particularly any one of aspects 48–53, wherein the cellulose nanofibers are crosslinked.

[0188] Aspect 55. The method of any one of the aspects herein, particularly aspect 54, wherein the cellulose nanofibers are enzymatically crosslinked.

[0189] Aspect 56. The method of any one of the aspects herein, particularly aspect 54, wherein the cellulose nanofibers are chemically crosslinked.

[0190] Aspect 57. The method of any one of the aspects herein, particularly aspect 56, wherein the cellulose nanofibers are chemically crosslinked with a crosslinker selected from glutaraldehyde, EDC, citric acid, epichlorohydrin, genipin, divinylsulfone (DVS), or combinations thereof.

[0191] Aspect 58. The method of any one of the aspects herein, particularly any one of aspects 48–57, wherein the cellulose nanofibers further comprise collagen, chitosan, gelatin, or combinations thereof.

[0192] Aspect 59. The method of any one of the aspects herein, particularly any one of aspects 48–58, wherein the cellulose nanofibers comprise cellulose having a number average molecular weight from about 1 kDa to about 100 kDa.

[0193] Aspect 60. The method of any one of the aspects herein, particularly any one of aspects 48–59, wherein the cellulose nanofibers have an average diameter from about 10 nm to about 100 nm.

[0194] Aspect 61. The method of any one of the aspects herein, particularly any one of aspects 48–60, wherein the biocompatible material is porous.

[0195] Aspect 62. The method of any one of the aspects herein, particularly aspect 61, wherein the biocompatible material has a density from about 0.05 to about 0.5 g/nm³ and a porosity from about 70% to about 99.9%.

[0196] Aspect 63. The method of any one of the aspects herein, particularly aspect 61, wherein the biocompatible material has a density from about 0.55 to about 0.95 g/nm³ and a porosity from about 20% to about 65%.

[0197] Aspect 64. The method of any one of the aspects herein, particularly any one of aspects 48–63, having anisotropic mechanical properties.

[0198] Aspect 65. The method of any one of the aspects herein, particularly aspect 64, wherein the biocompatible material has anisotropic properties with respect to strength, elastic modulus, permanent deformation, or combinations thereof.

[0199] Aspect 66. The method of any one of the aspects herein, particularly any one of aspects 48–65, wherein the biocompatible material exhibits a Young's modulus from about 0.5 MPa to about 100 MPa.

[0200] Aspect 67. The method of any one of the aspects herein, particularly any one of aspects 48–66, wherein the biocompatible material exhibits a tenacity from about 3 to about 5 g/denier.

[0201] Aspect 68. The method of any one of the aspects herein, particularly any one of aspects 48–67, wherein the biocompatible material exhibits an ultimate tensile strength from about 25 MPa to about 50 MPa.

[0202] Aspect 69. The method of any one of the aspects herein, particularly any one of aspects 48–68, wherein the biocompatible material exhibits an elongation at break from about 20% to about 500%.

[0203] Aspect 70. The method of any one of the aspects herein, particularly any one of aspects 48–69, wherein the biocompatible material is configured to be implanted into a patient body.

[0204] Aspect 71. The method of any one of the aspects herein, particularly aspect 70, wherein the biocompatible material exhibits substantially no calcification over a time of implantation within a patient body.

[0205] Aspect 72. The method of any one of the aspects herein, particularly any one of aspects 48–71, further comprising applying a coating to the biocompatible material.

[0206] Aspect 73. A biocompatible material prepared by the method of any one of the aspects herein, particularly any one of aspects 48–72.

[0207] Aspect 74. A method of making an implantable prosthetic valve comprising:

providing a leaflet structure, wherein at least a portion of the leaflet structure comprises the biocompatible material of any one of the aspects herein, particularly any one of aspects 1–25 or the biocomposite of any one of the aspects herein, particularly any one of aspects 26–38; and

coupling the leaflet structure within an annular frame, wherein the annular frame is configured to expand and contract.

[0208] Aspect 75. The method of any one of the aspects herein, particularly aspect 74, wherein the leaflet structure is formed by die cutting or laser cutting.

[0209] Aspect 76. The method of any one of the aspects herein, particularly aspect 74 or aspect 75, further comprising:

providing an inner skirt; and

positioning the inner skirt on an inner surface of the annular frame.

[0210] Aspect 77. The method of any one of the aspects herein, particularly aspect 76, wherein at least a portion of the inner skirt comprises the biocompatible material of any one of the aspects herein, particularly any one of aspects 1–25 or the biocomposite of any one of the aspects herein, particularly any one of aspects 26–38.

[0211] Aspect 78. The method of any one of the aspects herein, particularly any one of aspects 74–77, further comprising:

providing an outer skirt; and

positioning the outer skirt on an outer surface of the annular frame.

[0212] Aspect 79. The method of any one of the aspects herein, particularly aspect 78, wherein at least a portion of the outer skirt comprises the biocompatible material of any one of the aspects herein, particularly any one of aspects 1–25 or the biocomposite of any one of the aspects herein, particularly any one of aspects 26–38.

[0213] In view of the many possible aspects to which the principles of the disclosed disclosure can be applied, it should be recognized that the illustrated aspects are only preferred examples of the disclosure and should not be taken as limiting the scope of the disclosure. Rather, the scope of the disclosure is defined by the following claims. We, therefore, claim as our disclosure all that comes within the scope and spirit of these claims.

[0214] The compositions and methods of the appended claims are not limited in scope by the specific compositions and methods described herein, which are intended as illustrations of a few aspects of the claims and any compositions and methods that are

functionally equivalent are intended to fall within the scope of the claims. Various modifications of the compositions and methods in addition to those shown and described herein are intended to fall within the scope of the appended claims. Further, while only certain representative compositions and method steps disclosed herein are specifically described, other combinations of the compositions and method steps also are intended to fall within the scope of the appended claims, even if not specifically recited. Thus, a combination of steps, elements, components, or constituents may be explicitly mentioned herein; however, other combinations of steps, elements, components, and constituents are included, even though not explicitly stated.

WHAT IS CLAIMED IS:

1. A biocompatible material comprising a plurality of nanolayers, wherein each nanolayer within the plurality of nanolayers comprises a plurality of cellulose nanofibers, the plurality of cellulose nanofibers within each nanolayer being substantially disposed along a direction that is substantially unparallel to a direction of a plurality of cellulose nanofibers within a nanolayer below or above.
2. The biocompatible material of claim 1, wherein the cellulose nanofibers comprise natural cellulose nanofibers.
3. The biocompatible material of claim 2, wherein the natural cellulose nanofibers comprise bacterial cellulose.
4. The biocompatible material of claim 3, wherein the bacterial cellulose is derived from a bacterium selected from *Acetobacter*, *Agrobacterium*, *Alcaligenes*, *Azotobacter*, *Komagataeibacter*, *Pseudomonas*, *Rhizobium*, *Salmonella*, and *Sarcina*.
5. The biocompatible material of any one of claims 1–4, wherein the cellulose nanofibers are crosslinked.
6. The biocompatible material of claim 5, wherein the cellulose nanofibers are enzymatically crosslinked or chemically crosslinked.
7. The biocompatible material of any one of claims 1–6, wherein the cellulose nanofibers comprise cellulose having a number average molecular weight from about 1 kDa to about 100 kDa.
8. The biocompatible material of any one of claims 1–7, wherein the cellulose nanofibers have an average diameter from about 10 nm to about 100 nm.
9. The biocompatible material of any one of claims 1–8, wherein the biocompatible material is porous.
10. The biocompatible material of claim 9, wherein the biocompatible material has a density from about 0.05 to about 0.5 g/nm³ and a porosity from about 70% to about 99.9%.
11. The biocompatible material of any one of claims 1–10, having anisotropic mechanical properties.
12. The biocompatible material of any one of claims 1–11, wherein the biocompatible material is configured to be implanted into a patient body.

13. The biocompatible material of any one of claims 1–12, further comprising a backing material or a coating.

14. A biocomposite comprising:

a first layer comprising a biocompatible material of any one of claims 1–13;
a second layer comprising a plurality of manufactured cellulose nanofibers; and
a filler dispersed within the first layer and/or the second layer.

15. The biocompatible material of any one of claims 1–13 or the biocomposite of claim 14 formed into a leaflet structure.

16. An implantable medical device comprising the biocompatible material of any one of claims 1–13 or the biocomposite of claim 14.

17. The implantable medical device of claim 16 selected from a surgical aortic valve replacement, a transcatheter mitral valve replacement, a cardiovascular patch, and a vascular graft.

18. An implantable prosthetic valve comprising:

an annular frame having an inner surface and an outer surface wherein the frame has an inflow end and an outflow end, and a central longitudinal axis extending from the inflow end to the outflow end; and
a leaflet structure having an inner surface and an outer surface and positioned at the inner surface of the annular frame;
wherein at least a portion of the leaflet structure comprises the biocompatible material of any one of claims 1–13 or the biocomposite of claim 14;
wherein the annular frame is configured to expand and contract.

19. A method of manufacturing a biocompatible material comprising:

depositing a first plurality of cellulose nanofibers to be substantially arranged along a first direction to form a first nanolayer; and
depositing a second plurality of cellulose nanofibers to be substantially arranged along a second direction to form a second nanolayer disposed upon the first nanolayer, wherein the second direction is substantially unparallel to the first direction.

20. A method of making an implantable prosthetic valve comprising

providing a leaflet structure, wherein at least a portion of the leaflet structure comprises the biocompatible material of any one of claims 1–14 or the biocomposite of claim 14; and

coupling the leaflet structure within an annular frame, wherein the annular frame is configured to expand and contract.

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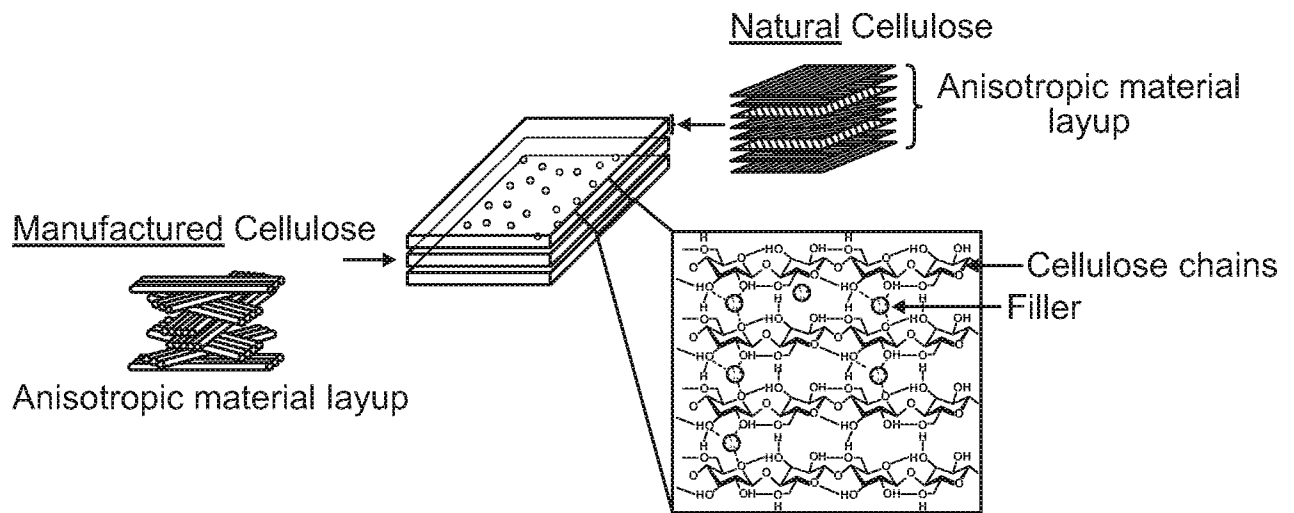


FIG. 1

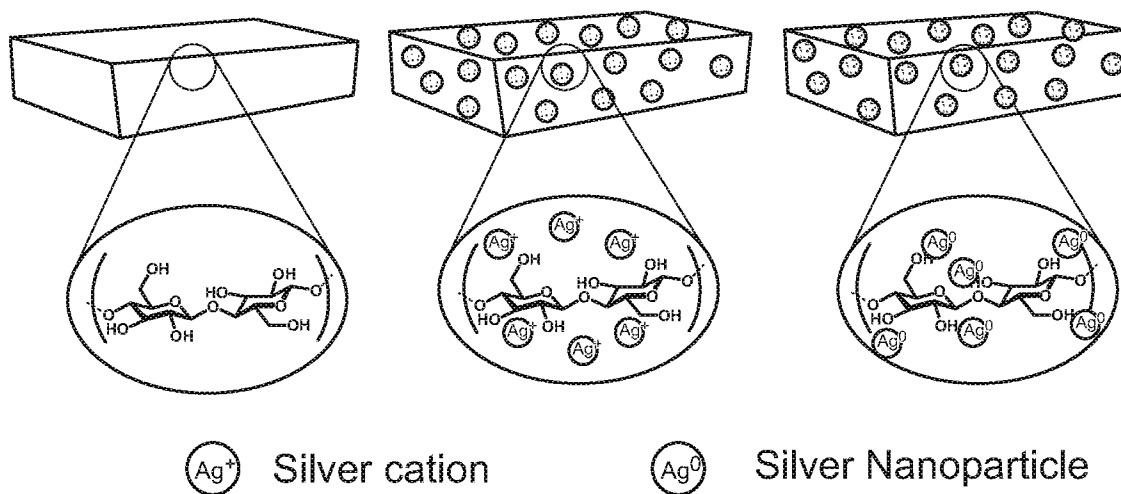


FIG. 2

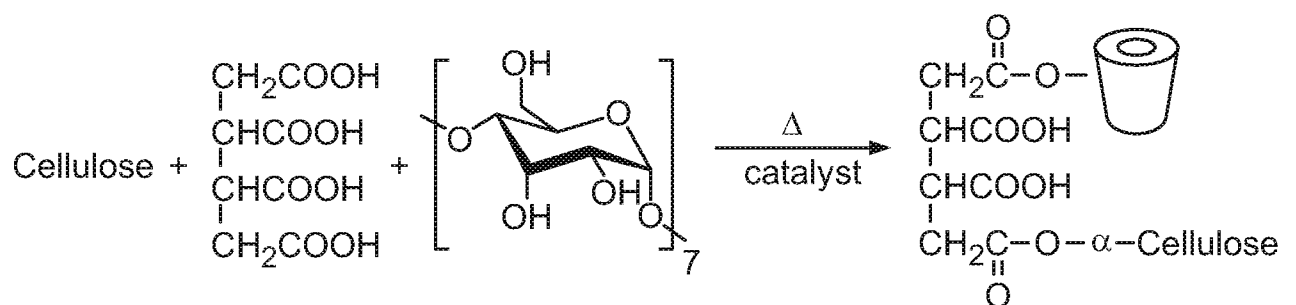


FIG. 3

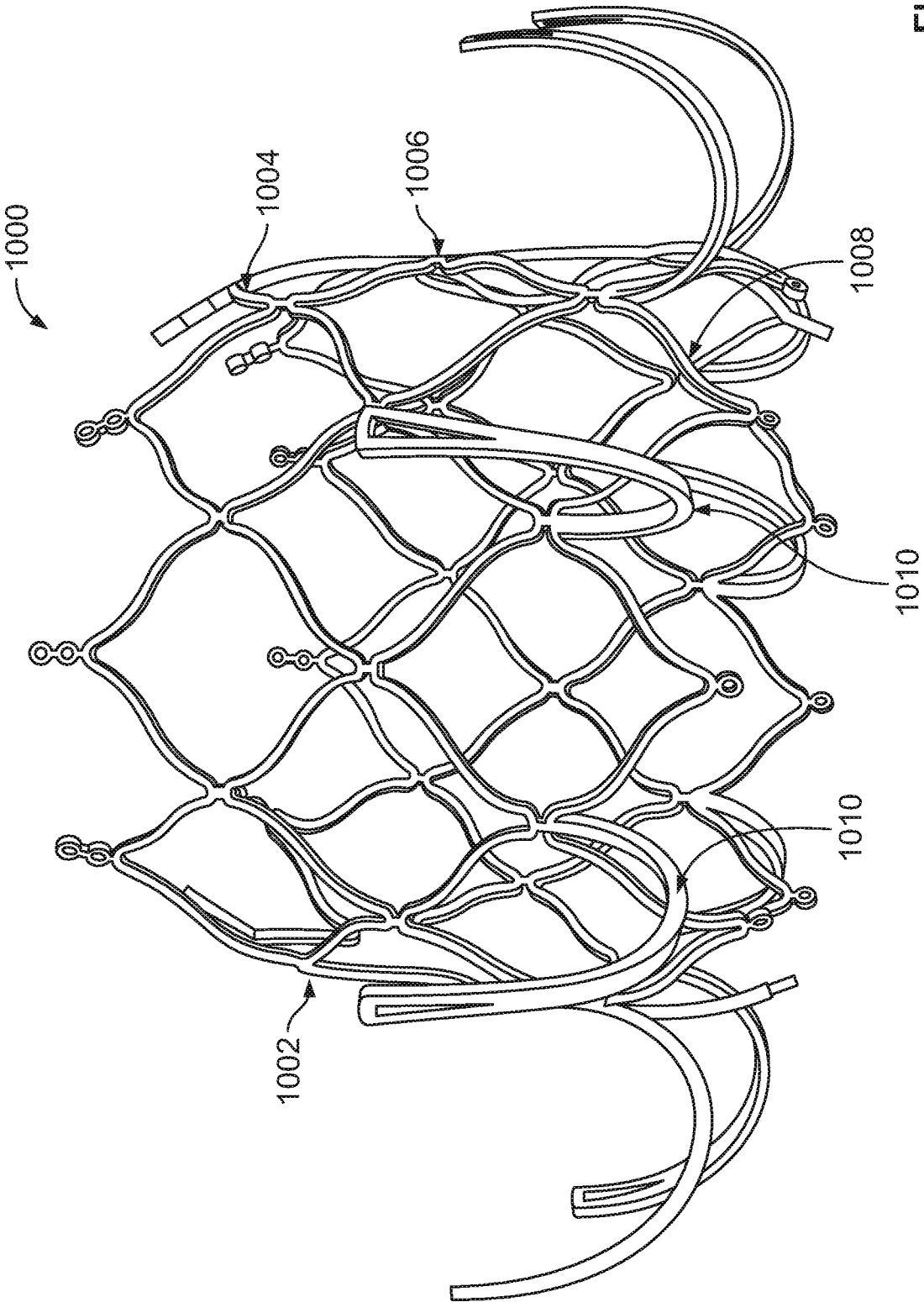


FIG. 4

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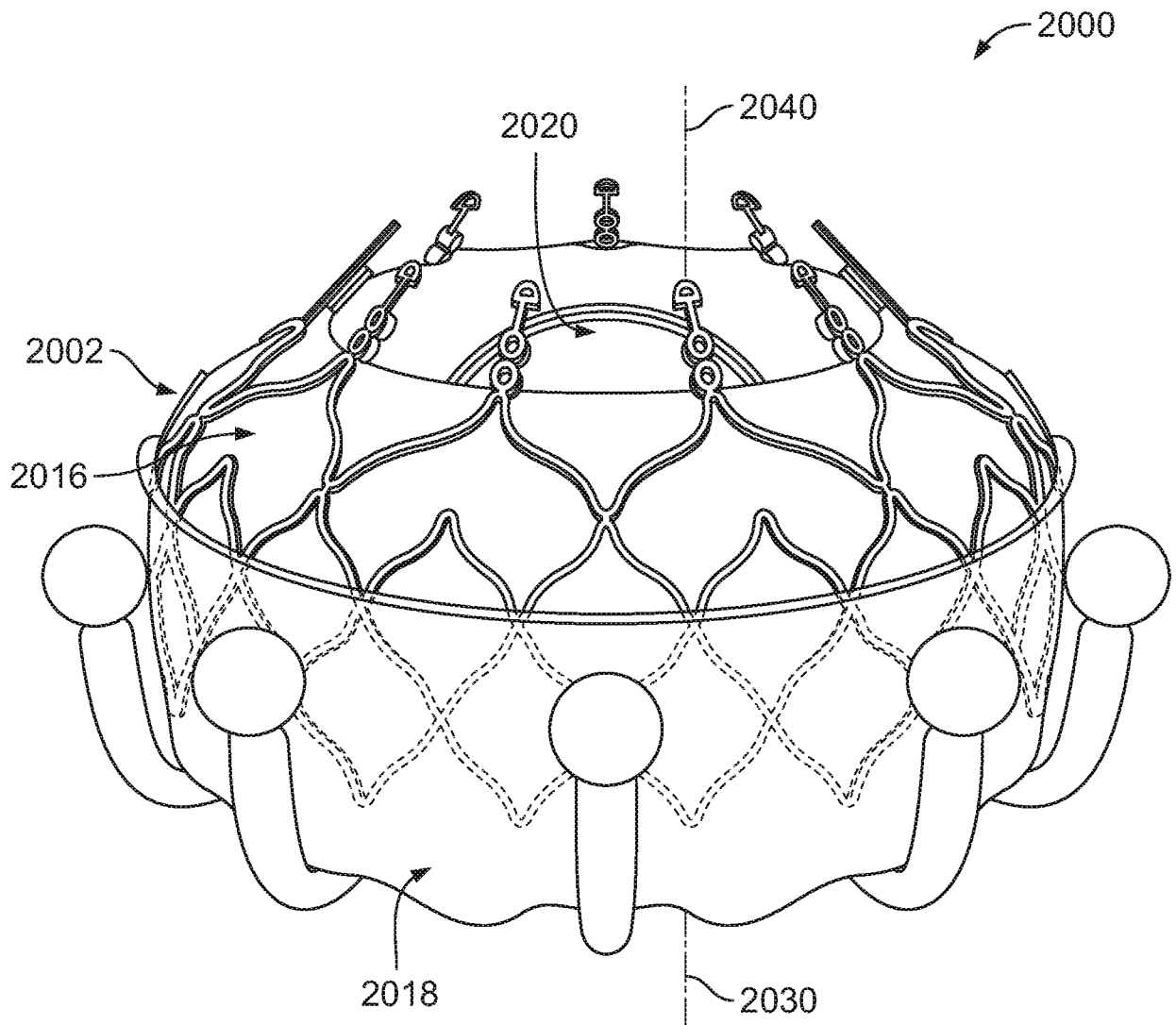


FIG. 5

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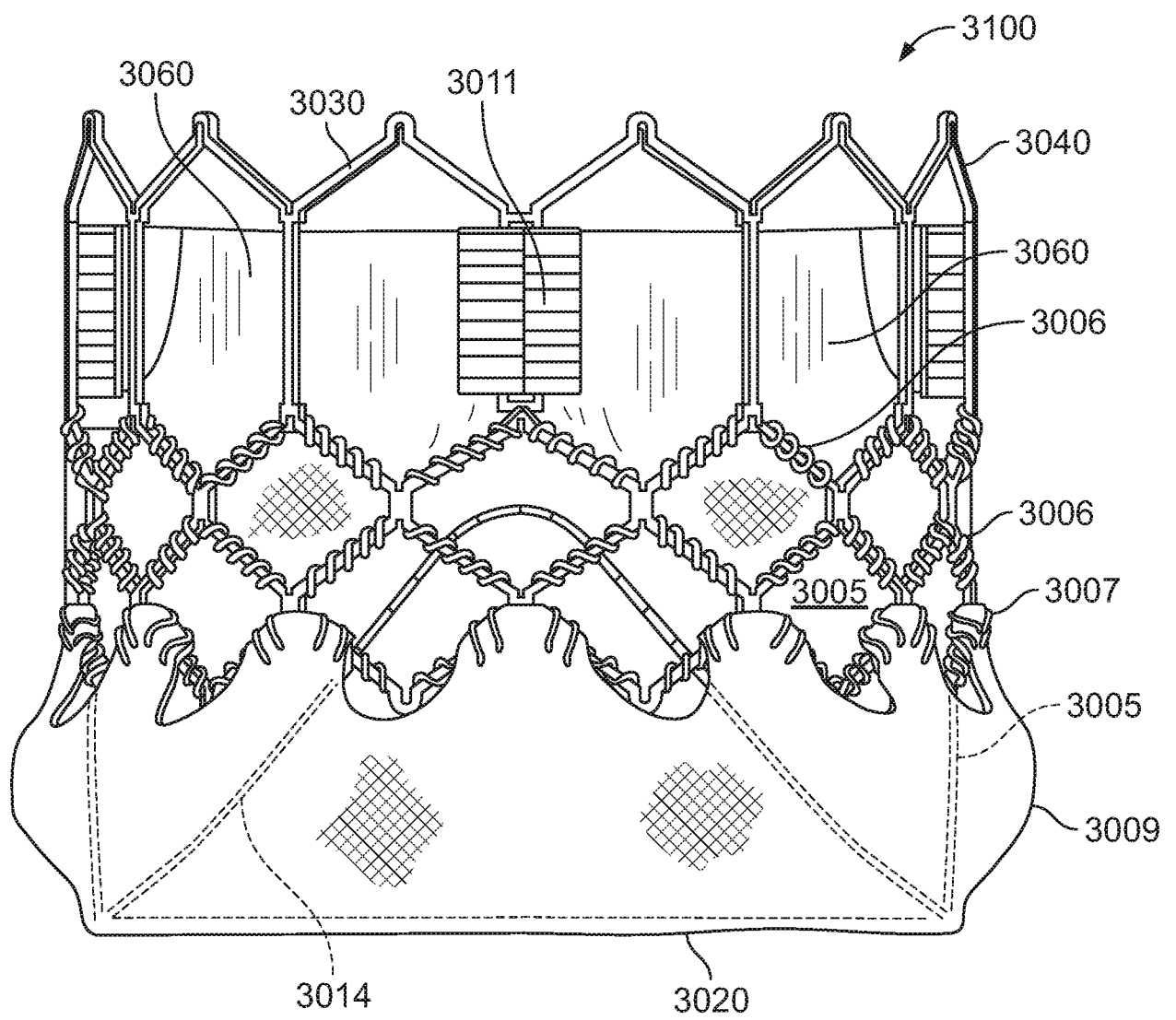


FIG. 6A

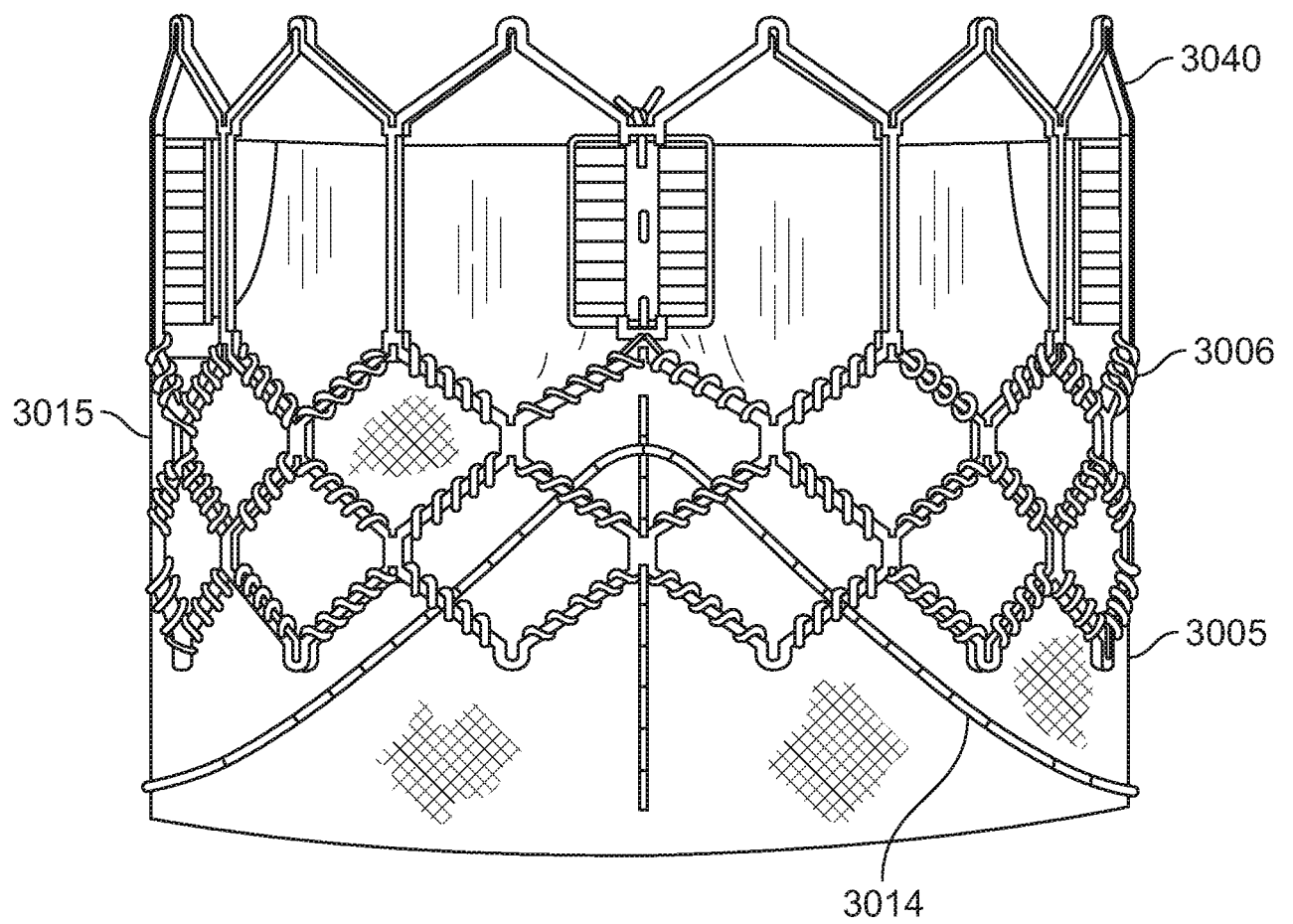


FIG. 6B

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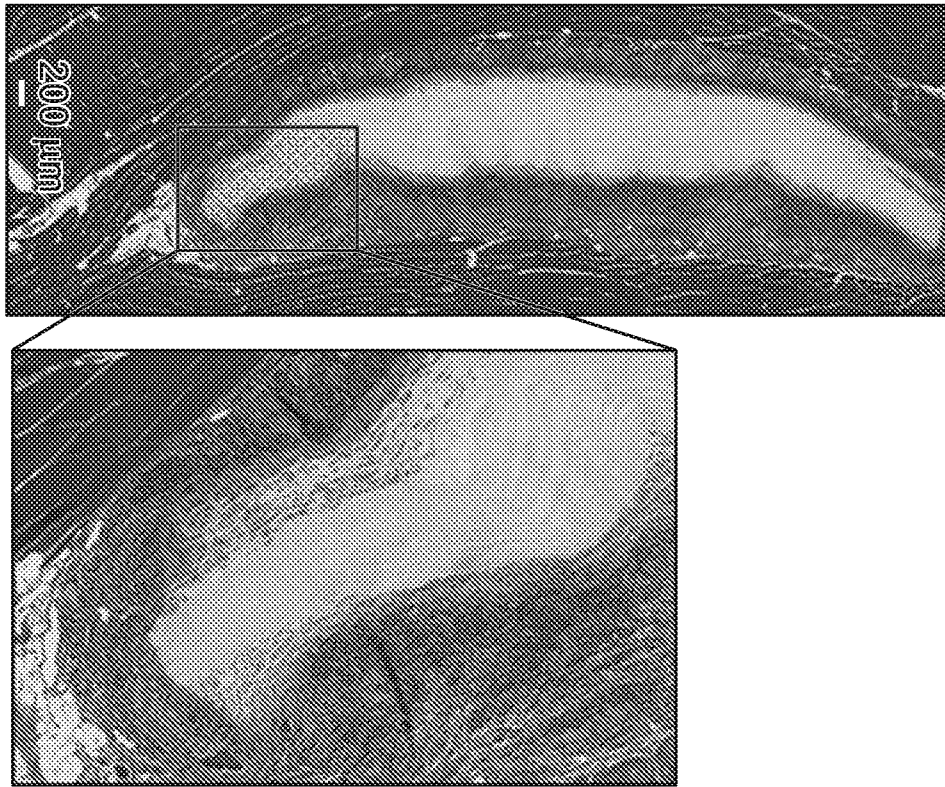


FIG. 7

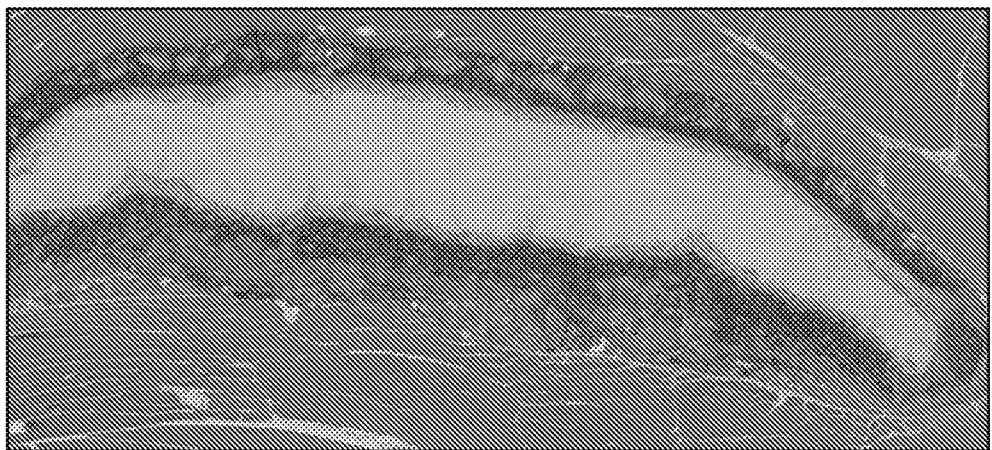


FIG. 8

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2024/060709

A. CLASSIFICATION OF SUBJECT MATTERINV. A61L27/34 A61F2/24 A61L27/48 A61L27/56 C08L1/02
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61L A61F C09J C08L

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

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

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2023/089010 A1 (BIOTRONIK AG [CH]) 25 May 2023 (2023-05-25) claims; examples -----	15-18, 20
X	CN 105 332 163 B (BEIJING INST TECHNOLOGY ET AL.) 1 May 2018 (2018-05-01) claims; figures; examples -----	1-14, 19
A	US 2019/358031 A1 (RZANY ALEXANDER [DE] ET AL) 28 November 2019 (2019-11-28) the whole document -----	1-20
A	EP 3 223 873 B1 (BIOTRONIK AG [CH]) 8 April 2020 (2020-04-08) paragraphs [[0014], [0015]], [[0022] - [0024]]; claims; examples ----- -/-	1-20

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search

7 April 2025

Date of mailing of the international search report

14/04/2025

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Derrien, Anne-Cécile

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/060709

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 11 559 394 B2 (BOSTON SCIENT SCIMED INC [US]) 24 January 2023 (2023-01-24) claims; examples -----	1-20
A	RAJWADE J M ET AL: "Applications of bacterial cellulose and its composites in biomedicine", APPLIED MICROBIOLOGY AND BIOTECHNOLOGY, SPRINGER BERLIN HEIDELBERG, BERLIN/HEIDELBERG, vol. 99, no. 6, 11 February 2015 (2015-02-11), pages 2491-2511, XP035459116, ISSN: 0175-7598, DOI: 10.1007/S00253-015-6426-3 [retrieved on 2015-02-11] the whole document -----	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2024/060709

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2023089010	A1	25-05-2023	EP 4433106 A1	25-09-2024
			US 2025001055 A1	02-01-2025
			WO 2023089010 A1	25-05-2023

CN 105332163	B	01-05-2018	NONE	

US 2019358031	A1	28-11-2019	EP 3572043 A1	27-11-2019
			US 2019358031 A1	28-11-2019

EP 3223873	B1	08-04-2020	EP 3223873 A1	04-10-2017
			EP 3223874 A1	04-10-2017
			US 2017312398 A1	02-11-2017
			US 2017354765 A1	14-12-2017
			US 2020353130 A1	12-11-2020
			WO 2016083351 A1	02-06-2016
			WO 2016083352 A1	02-06-2016

US 11559394	B2	24-01-2023	CN 109475409 A	15-03-2019
			EP 3457989 A1	27-03-2019
			US 2017333185 A1	23-11-2017
			US 2019350703 A1	21-11-2019
			WO 2017200920 A1	23-11-2017
