No. 18-1700

United States Court of Appeals
for the Federal Circuit

BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM,
AND TISSUEGEN, INC.

Appellant,

v.

BOSTON SCIENTIFIC CORPORATION,

Appellee,

Appeal from the United States District Court for the Western District of Texas,
Judge Lee Yeakel, Case No. 1:17-cv-01103-LY

JOINT APPENDIX

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IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF TEXAS
AUSTIN DIVISION

BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM, AND TISSUEGEN, INC., PLAINTIFFS,	§	
V.	§	CAUSE NO. A-17-CV-1103-LY
BOSTON SCIENTIFIC CORP., DEFENDANT.	§	

ORDER

Before the court are Defendant Boston Scientific Corporation's Motion to Dismiss Plaintiffs' Complaint under Fed. R. Civ. P. 12(b)(3) filed February 1, 2018 (Doc. #11); Plaintiffs' Response in Opposition to Motion to Dismiss filed February 15, 2018 (Doc. #14); and Defendant Boston Scientific Corporation's Reply in Support of its Motion to Dismiss Plaintiffs' Complaint under Fed. R. Civ. P. 12(b)(3) filed February 22, 2018 (Doc. #16). Defendant Boston Scientific Corporation ("Boston Scientific") alternatively seeks transfer pursuant to Section 1400(b) of Title 28 of the United States Code. Having considered the motion, response, and reply, the court will grant the motion in the alternative and transfer the cause to the United States District Court for the District of Delaware for the reasons stated below.

Plaintiffs filed suit against Boston Scientific on November 20, 2017, alleging infringement of United States Patent Nos. 6,596,296 and 7,033,603 ("the asserted patents"). Plaintiffs claim that Boston Scientific infringed the asserted patents through the manufacture and sale of a range of coronary stent systems. Plaintiffs' complaint states that Boston Scientific is incorporated in the State of Delaware and headquartered in Boston, Massachusetts.

Boston Scientific does not own or lease any property in the Western District of Texas and does not maintain any business address in the Western District of Texas. Boston Scientific has approximately 46 employees in the Western District of Texas, all of whom maintain home offices and do not work in locations that are owned, leased, or otherwise controlled by Boston Scientific.

A defendant may request dismissal where venue is improper in the District where the case is filed. *See* FED. R. CIV. P. 12(b)(3). The patent venue statute, 28 U.S.C. § 1400(b), is the "sole and exclusive provision controlling venue in patent infringement actions." *TC Heartland LLC v. Kraft Foods Group Brands LLC*, ___ U.S. ___, 137 S. Ct. 1515–19 (2017).

"Any civil action for patent infringement may be brought in the judicial district where the defendant resides, or where the defendant has committed acts of infringement and has a regular and established place of business." 28 U.S.C. § 1400(b). The term "resides" refers only to a defendant's state of incorporation. *See TC Heartland*, 137 S. Ct. at 1519.

Whether a defendant has a "regular and established place of business" has three general requirements: "(1) there must be a physical place in the district; (2) it must be a regular and established place of business; and (3) it must be the place of the defendant." *In re Cray Inc.*, 871 F.3d 1355, 1360 (Fed. Cir. 2017). Although Boston Scientific has 46 employees working in the Western District of Texas, they all work from home. Because Boston Scientific does not own or lease a place of business in the Western District of Texas and does not operate or otherwise control its employees' homes, the court finds that Boston Scientific does not maintain a "regular and established place of business" in the Western District of Texas. *See id.* at 1365 (finding venue improper in district where defendant's employees merely worked from home).

In response, Plaintiffs assert that "[b]ecause this court has personal jurisdiction over Boston Scientific, venue considerations related to convenience or other factors cannot overcome The Board of Regents' sovereign right to control the forum for this dispute." The court disagrees. Sovereign immunity is a shield; it is not meant to be used as a sword. "The Eleventh Amendment applies to suits 'against' a state, not suits by a state." *Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1564–65 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998).[1] This case does not create an Eleventh Amendment jurisdictional issue where the question of sovereign immunity even arises. Plaintiffs have asserted patent-infringement claims against Boston Scientific. There is no claim or counterclaim against The Board of Regents that places it in the position of a defendant. *See id.* at 1565. "[W]here a state voluntarily become [sic] a party to a cause, and submits its rights for judicial determination, it would be bound thereby, and cannot escape the result of its own voluntary act by invoking the prohibitions of the 11th Amendment." *Gunter v. Atlantic Coast Line R.R.*, 200 U.S. 273, 284 (1906) (*citing Clark v. Barnard*, 108 U.S. 436, 477 (1883)).

Section 1400(b) provides that venue is proper where a corporation is incorporated. Boston Scientific is incorporated in the District of Delaware. Venue is proper in the District of Delaware. "Section 1406 of Title 28 is addressed to a case in which venue has been laid in an improper district. It authorizes either a dismissal on that ground or, if the court finds that the interest of justice would be served by a transfer, then a transfer instead." 28 U.S.C. § 1406, Commentary on 1996 Amendment of Section 1406 (West 2006). "The decision whether a transfer or dismissal is in the interest of justice rests within the sound discretion of the district court." *Naartex Consulting Corp.*

[1] In a patent suit, "the question of Eleventh Amendment waiver is a matter of Federal Circuit law." *Regents of Univ. of N.M. v. Knight*, 321 F.3d 1111, 1124 (Fed. Cir. 2003).

v. Watt, 722 F.2d 779, 789 (D.C. Cir. 1983). Transfer is typically considered more in the interest of justice than dismissal. Therefore,

IT IS ORDERED that Defendant Boston Scientific Corporation's Motion to Dismiss Plaintiffs' Complaint under Fed. R. Civ. P. 12(b)(3) filed February 1, 2018 (Doc. #11) is **GRANTED TO THE FOLLOWING EXTENT**: the above-styled cause of action is **TRANSFERRED** to the United States District Court for the District of Delaware.

SIGNED this 12th day of March, 2018.

LEE YEAKEL
UNITED STATES DISTRICT JUDGE

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF TEXAS
AUSTIN DIVISION

BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM, AND TISSUEGEN, INC.,	§	
PLAINTIFFS,	§	CAUSE NO. A-17-CV-1103-LY
v.	§	
BOSTON SCIENTIFIC CORPORATION,	§	
DEFENDANT.	§	

PLAINTIFFS' NOTICE OF APPEAL

Notice is hereby given that Board of Regents, The University of Texas System, and TissueGen, Inc. ("Plaintiffs") hereby appeal to the **United States Court of Appeals for the Federal Circuit** from the Order Granting Transfer to District of Delaware (Dkt. 27) dated March 12, 2018 and any other orders entered contrary to the interest of Plaintiffs entered in the above-referenced case.

This is a case arising under the patent laws of the United States, therefore the Federal Circuit has exclusive jurisdiction over all appellate proceedings. 28 U.S.C. § 1295(1). The Order is a final order of this Court and/or constitutes an order regarding the sovereign immunity and sovereign rights of an arm of The State of Texas, which is appealable under the collateral order doctrine.

Respectfully Submitted,

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COUNSEL FOR PLAINTIFFS BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM AND TISSUEGEN, INC.

CERTIFICATE OF SERVICE

I certify that on March 13, 2018, the foregoing instrument was electronically filed with the Clerk of the Court using the Court's CM/ECF system which will send notification of the filing to all counsel of record for parties.

/s/ Michael W. Shore
Michael W. Shore (Texas 18294915)

US006596296B1

(12) **United States Patent**
Nelson et al.

(10) **Patent No.: US 6,596,296 B1**
(45) **Date of Patent: Jul. 22, 2003**

(54) **DRUG RELEASING BIODEGRADABLE FIBER IMPLANT**

(75) Inventors: **Kevin D. Nelson**, Arlington, TX (US); **Andres A. Romero-Sanchez**, Arlington, TX (US); **George M. Smith**, Lexington, KY (US); **Nadir Alikacem**, Allen, TX (US); **Delia Radulescu**, Arlington, TX (US); **Paula Waggoner**, Burleson, TX (US); **Zhibing Hu**, Denton, TX (US)

(73) Assignee: **Board of Regents, The University of Texas System**, Austin, TX (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 14 days.

(21) Appl. No.: **09/632,457**

(22) Filed: **Aug. 4, 2000**

Related U.S. Application Data

(60) Provisional application No. 60/147,827, filed on Aug. 6, 1999.

(51) **Int. Cl.**[7] **A61F 2/02**; A61K 47/30

(52) **U.S. Cl.** **424/426**; 514/772.3

(58) **Field of Search** 424/426; 514/772.3

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,464,321	A		8/1984	Pittalis et al. 264/83
4,965,128	A		10/1990	Greidanus et al. 428/398
5,166,187	A		11/1992	Collombel et al. 514/21
5,263,984	A		11/1993	Li et al. 623/15
5,290,271	A		3/1994	Jernberg 604/891.1
5,342,348	A		8/1994	Kaplan 605/891.1
5,444,113	A	*	8/1995	Sinclair et al. 524/306
5,567,612	A		10/1996	Vacanti et al. 435/240.23

FOREIGN PATENT DOCUMENTS

EP	0 328 050	8/1989
WO	WO 98/20190	5/1998
WO	WO 00/47716	8/2000

OTHER PUBLICATIONS

Aigner et al., "Cartilage tissue engineering with novel nonwoven structured biomaterial based on hyaluronic acid benzyl ester," *J. of Biomed. Materials Res.*, 42:172–181, 1998.

Breitbart et al., "Tissue engineered bone repair of calvarial defects using cultured periosteal cells," *Plastic & Reconstructive Surgery*, 101:567–574, 1998.

Cao et al., "Comparative study of the use of poly(glycolic acid), calcium alginate and pluronics in the engineering of autologous porcine cartilage," *J. of Biomaterials Sci Polymer Edition*, 9:475–487, 1998.

Dillon et al., "The influence of physical structure and charge on neurite extension in a 3D hydrogel scaffold," *J. of Biomaterials Sci., Polymer Ed.*, 9:1049–1069, 1998.

Elcin et al., "Xenotransplantation of fetal porcine hepatocytes in rats using a tissue engineering approach," *Artificial Organs*, 23:146–152, 1999.

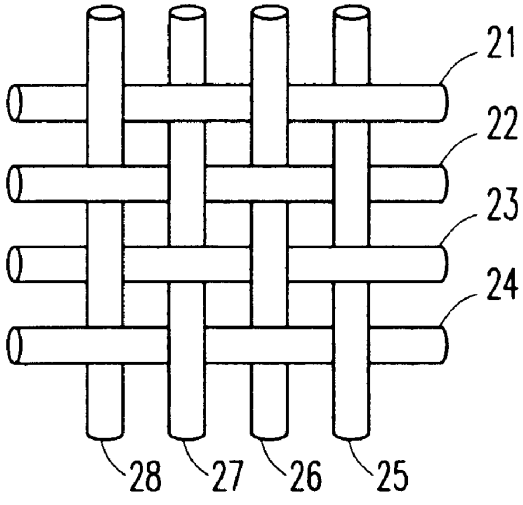
(List continued on next page.)

Primary Examiner—Carlos A. Azpuru
(74) *Attorney, Agent, or Firm*—Jenkens & Gilchrist, P.C.

(57) **ABSTRACT**

The invention provides tissue engineering compositions and methods wherein three-dimensional matrices for growing cells are prepared for in vitro and in vivo use. The matrices comprise biodegradable polymer fibers capable of the controlled delivery of therapeutic agents. The spatial and temporal distribution of released therapeutic agents is controlled by use of defined nonhomogeneous patterns of therapeutic agents in the matrices.

32 Claims, 11 Drawing Sheets



OTHER PUBLICATIONS

Estrera et al., "The cytoplasmic domain of C–CAM1 tumor suppressor is necessary and sufficient for suppressing the tumorigenicity of prostate cancer cells," *Biochem Biophys Res Commun*, 263:797–803, 1999.

Fauza et al., "Videofetoscopically assisted fetal tissue engineering: skin replacement," *J. of Pediatric Surgery*, 33:357–361, 1998.

Grande et al., "Evaluation of matrix scaffolds for tissue engineering of articular cartilage grafts," *J. of Biomed. Mat. Res.*, 34:211–220, 1997.

Heath and Rutkowski, "The development of bioartificial nerve grafts for peripheral–nerve regeneration," *TIBTECH*, 16:163–168, 1998.

Hoerstrup et al., "Fluorescence activated cell sorting: a reliable method in tissue engineering of a bioprosthetic heart valve," *Annals of Thoracic Surgery*, 66:1653–1657, 1998.

Hoerstrup et al., "Tissue engineering: a new approach in cardiovascular surgery–seeding of human fibroblasts on resorbable mesh," *Swiss Surgery*, 2:23–25, 1998.

Isogai et al., "Formation of phalanges and small joints by tissue–engineering," *J. of Bone & Joint Surgery*, 81A:306–316, 1999.

Martin et al., "In vitro differentiation of chick embryo bone marrow stromal cells into cartilaginous and bone–like tissues," *J. of Orthopaedic Res.*, 16:181–189, 1998.

Romero, Andres A., Home page posted at bme@mednet.swmed.edu.

Sacks et al., "Collagen fiber architecture of a cultured dermal tissue," *J. of Biomed. Engineering*, 119:124–127, 1997.

Shinoka et al., "Creation of viable pulmonary artery autografts through tissue engineering," *J. of Thoracic & Cardiovascular Surgery*, 115:536–546, 1998.

Sims et al., "Tissue engineered neocartilage using plasma derived polymer substrates and chondrocytes," *Plastic & Reconstructive Surgery*, 101:1580–1585, 1998.

Vunjak–Novakovic et al., "Dynamic cell seeding of polymer scaffolds for cartilage tissue engineering," *Biotechnology Progress*, 14:193–202, 1998.

Wong and Mooney, "Synthesis and properties of biodegradable polymers used as synthetic matrices for tissue engineering," *In: Synthetic Biodegradable Polymer Scaffolds*, (Atala and Mooney, eds.), Birkhauser Press, Boston, MA, pp. 51–82, 1997.

Yoo and Atala, "A novel gene delivery system using urothelial tissue engineered neoorgans," *J. of Urology*, 158:1066–1070, 1997.

* cited by examiner

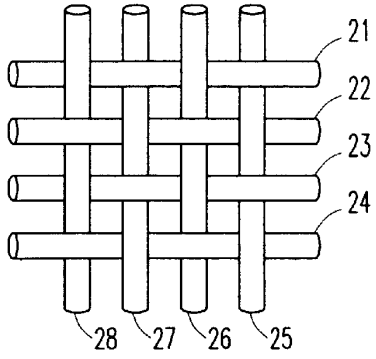


FIG. 1

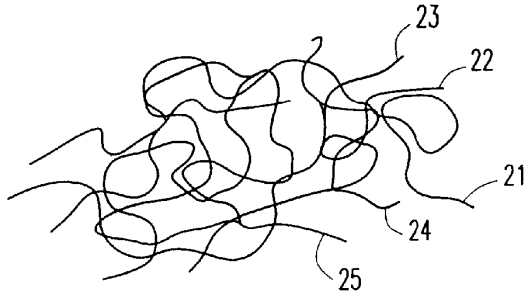


FIG. 2

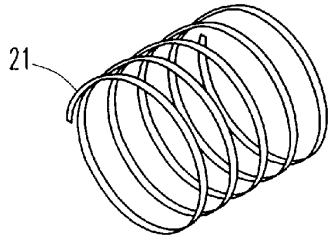


FIG. 3a

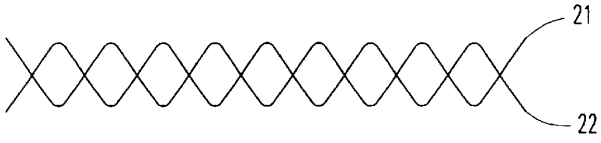


FIG. 3b

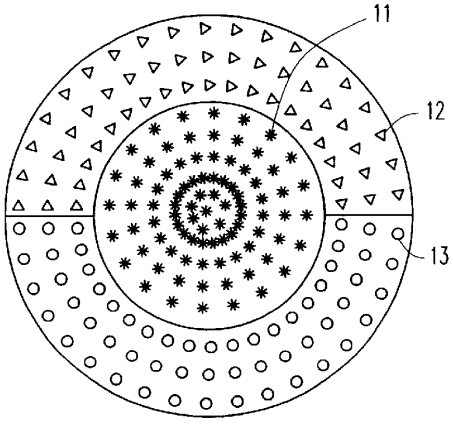


FIG. 4

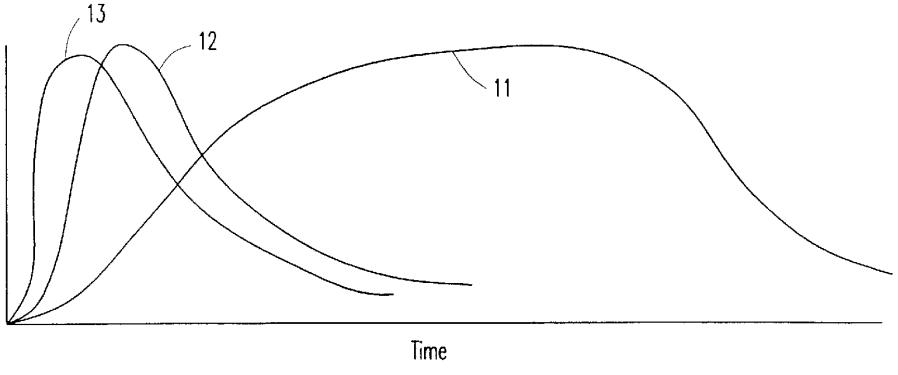


FIG. 5

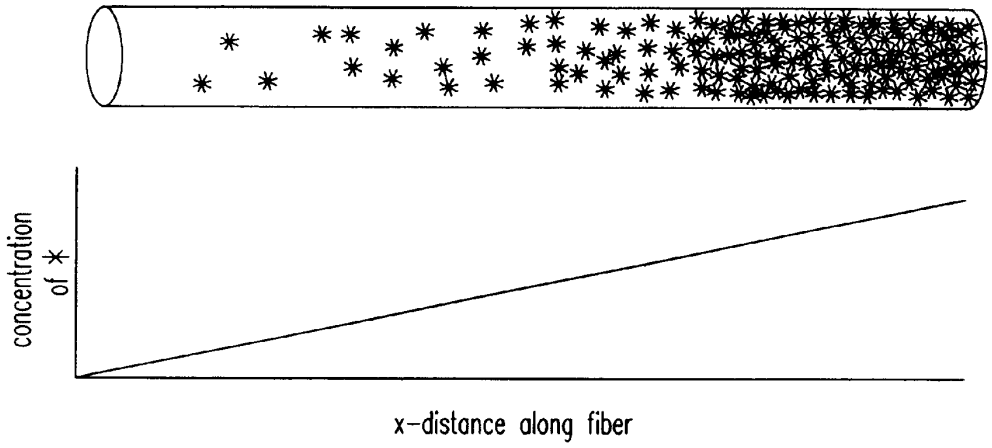


FIG. 6

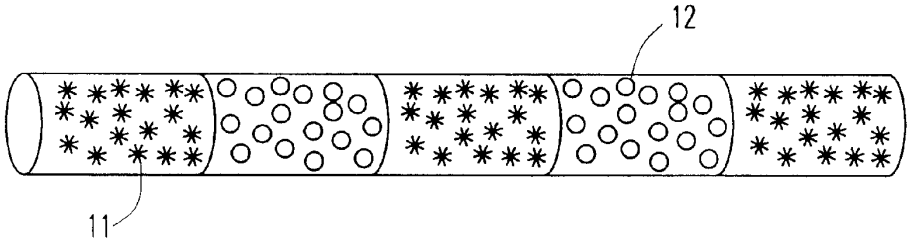


FIG. 7

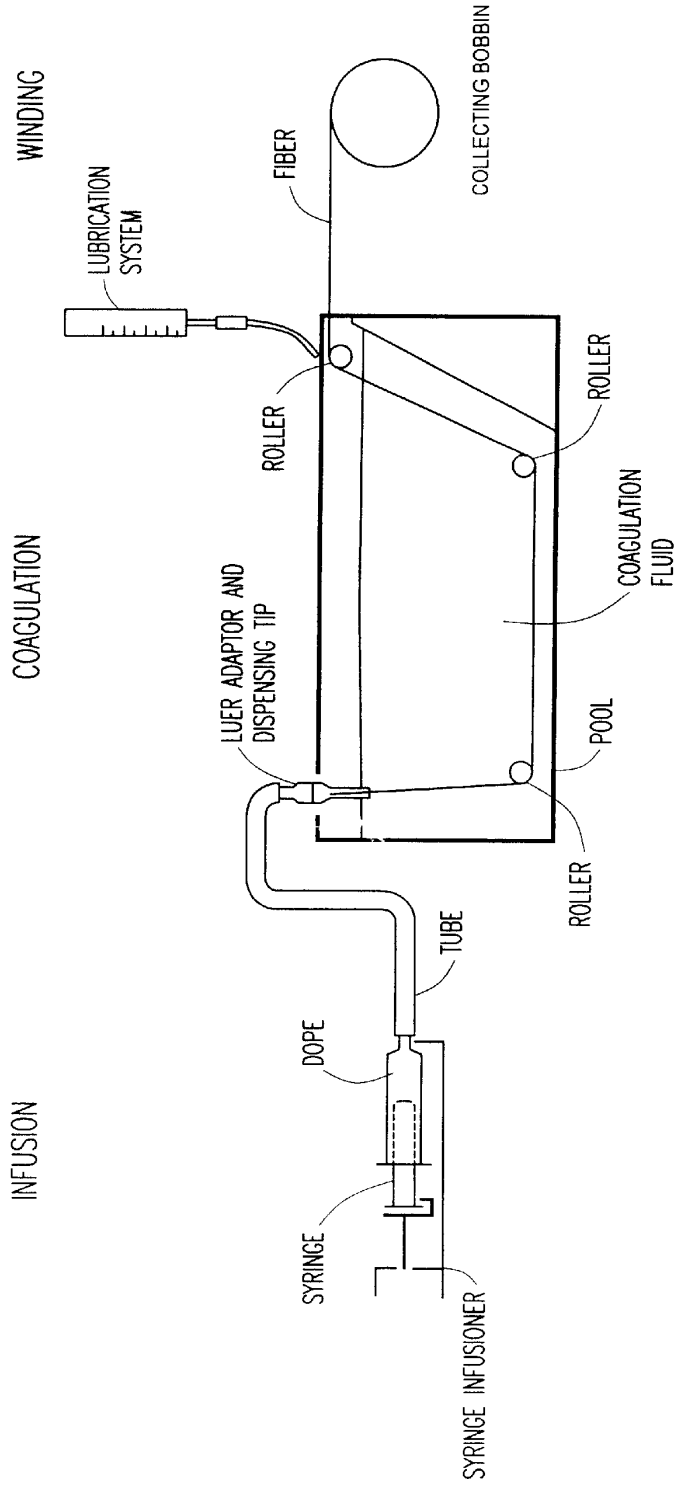

WINDING
COAGULATION
INFUSION
LUBRICATION SYSTEM
FIBER
COLLECTING BOBBIN
ROLLER
ROLLER
ROLLER
COAGULATION FLUID
LUER ADAPTOR AND DISPENSING TIP
POOL
TUBE
DOPE
SYRINGE
SYRINGE INFUSIONER

FIG. 8

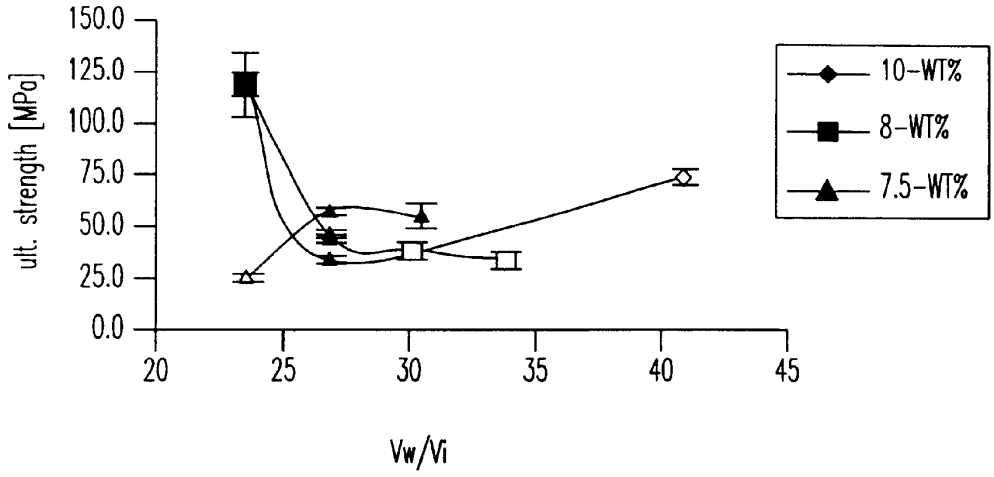

150.0
125.0
100.0
75.0
50.0
25.0
0.0
ult. strength [MPa]
20
25
30
35
40
45
Vw/Vi
10-WT%
8-WT%
7.5-WT%

FIG. 9a

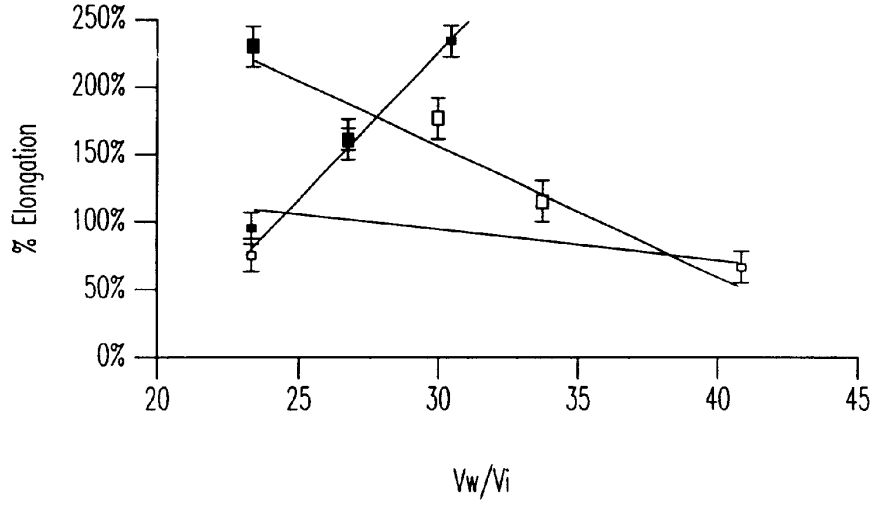

250%
200%
150%
100%
50%
0%
% Elongation
20
25
30
35
40
45
Vw/Vi

FIG. 9b

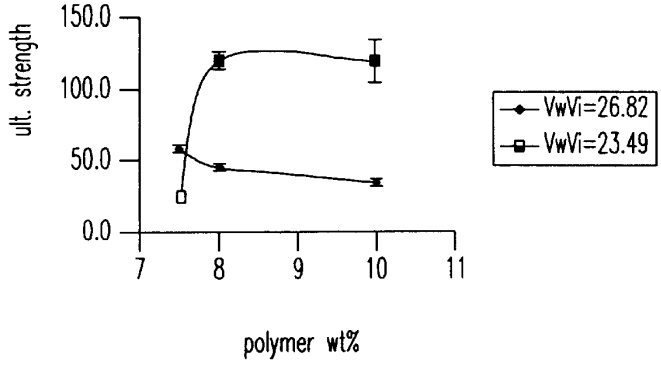


FIG. 10a

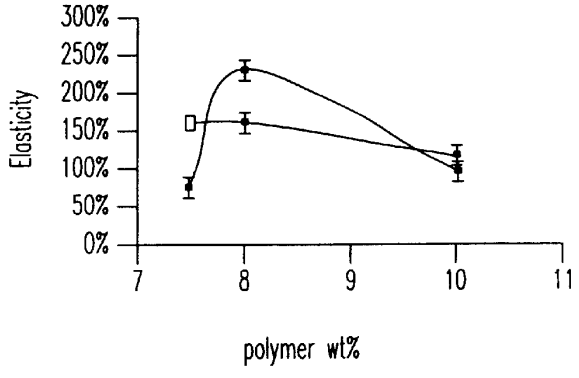


FIG. 10 b

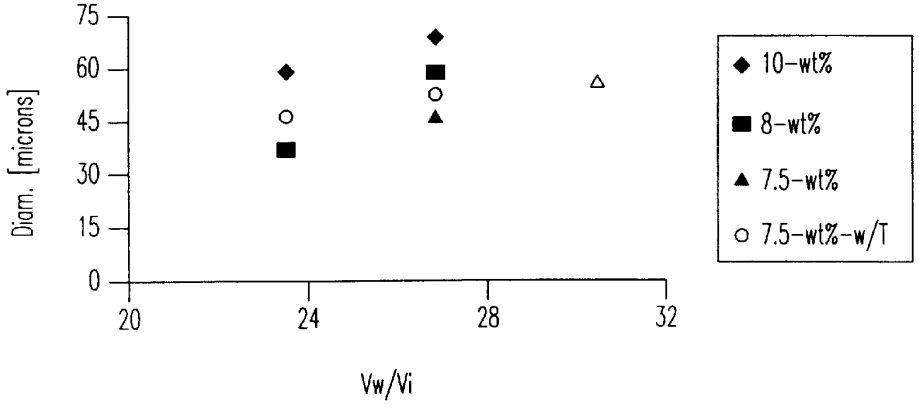


FIG. 12

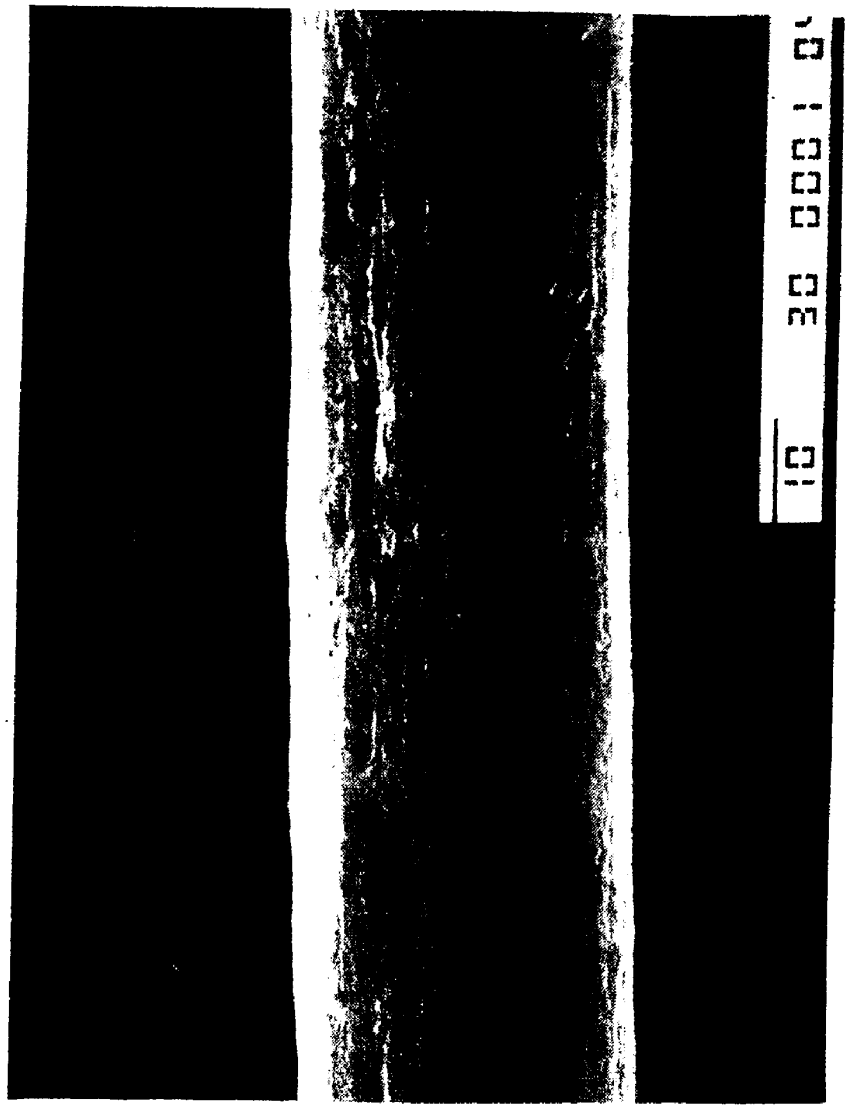


FIG. 11a

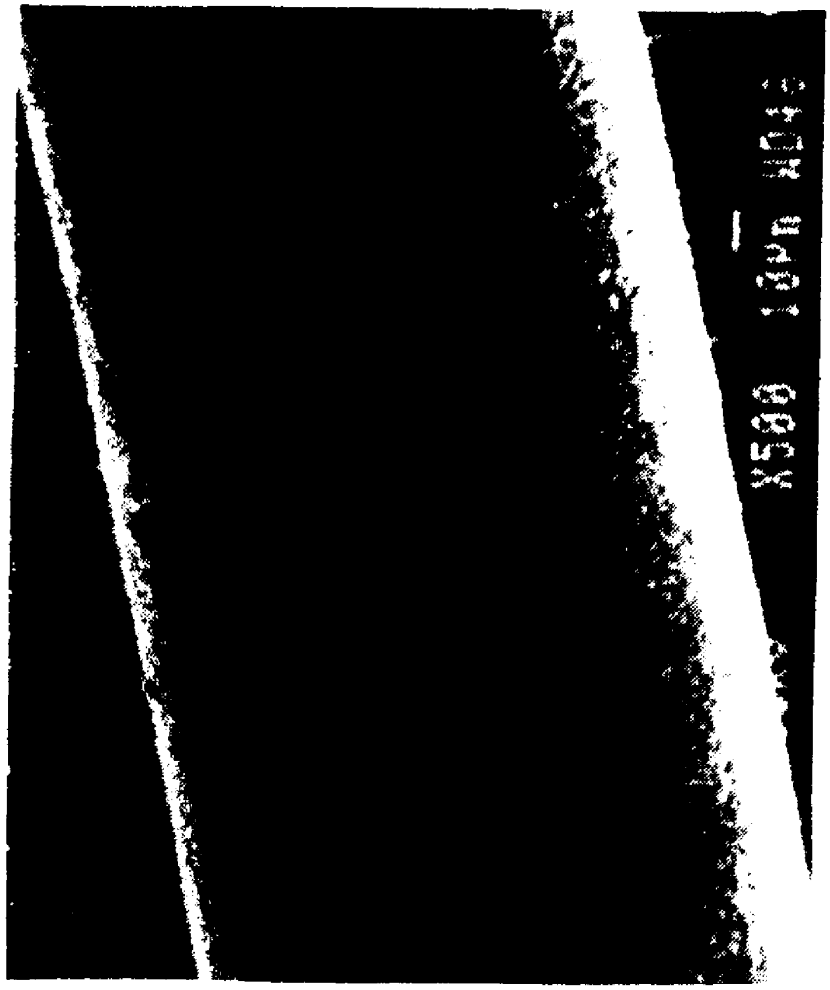


FIG. 11b

FIG. 11c

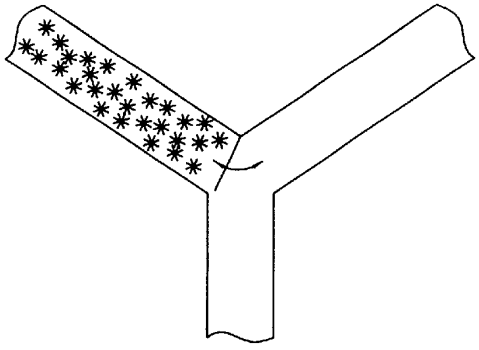


FIG. 13

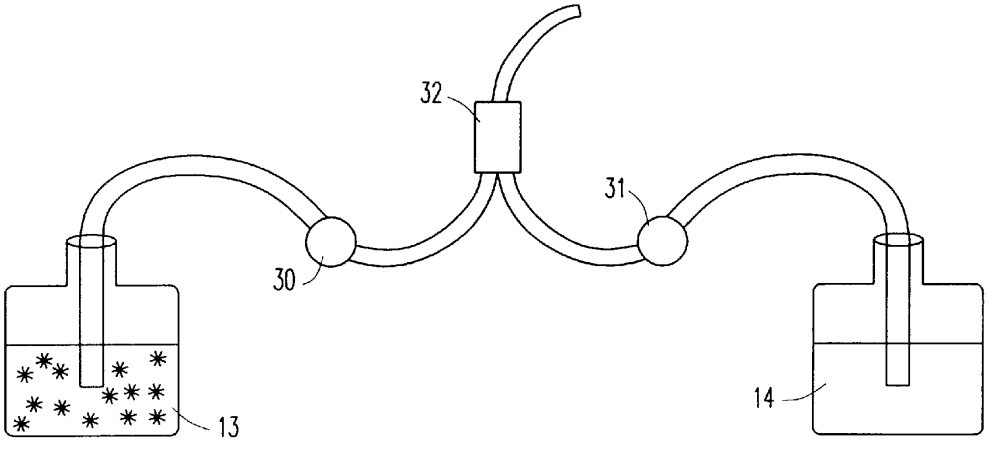


FIG. 14

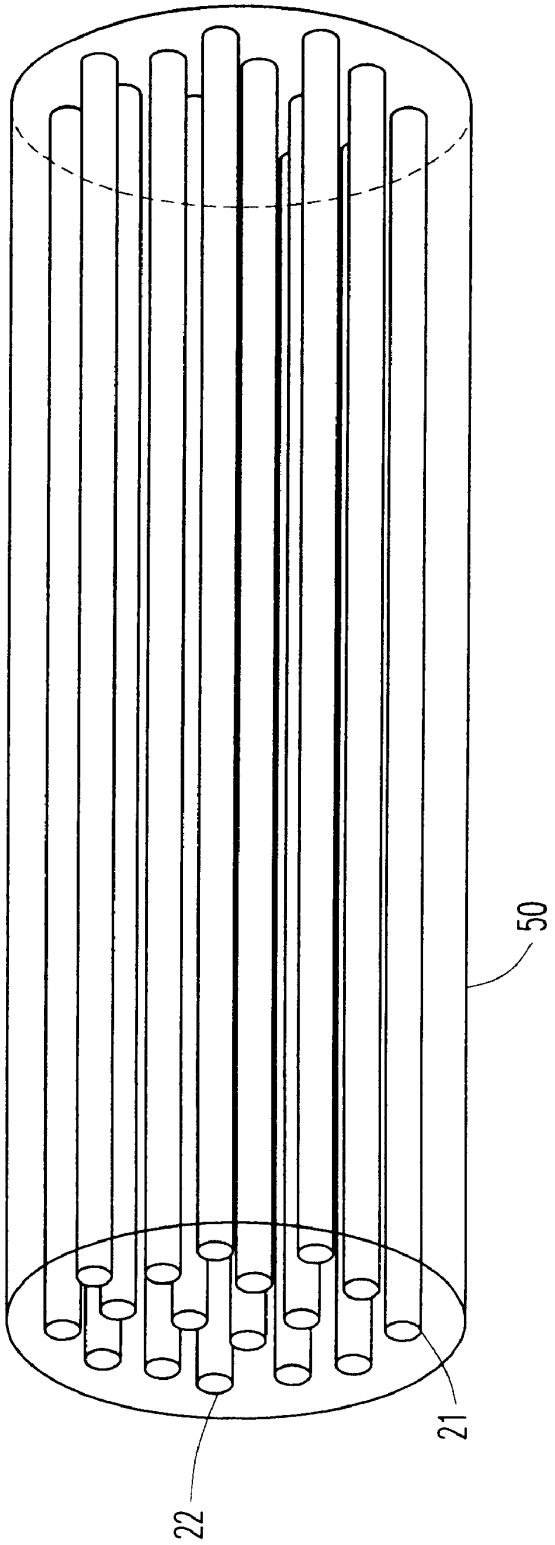


FIG. 15

DRUG RELEASING BIODEGRADABLE FIBER IMPLANT

The present invention claims priority to provisional application serial No. 60/147,827, filed Aug. 6, 1999.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to the field of medicine and tissue engineering, and in particular to drug releasing biodegradable implants.

2. Description of Related Art

Tissue engineering is a discipline wherein living cells are used to replace functional loss because of injury, disease, or birth defect in an animal or human. These replacement cells can be autologous, allogenic, or, in limited circumstances, xenogenic. The field of tissue engineering is a new area of medicine and optimal procedures have yet to be elucidated.

At present, there are several primary avenues investigators are using to engineer tissues. One is to harvest cells from a healthy donor, preferably from the same individual, or at least from an appropriate donor of the same species, and grow those cells on a scaffold in vitro. This scaffold is typically a three-dimensional polymer network, often composed of biodegradable fibers. Cells adherent to the polymer network can then typically be induced to multiply. This cell filled scaffold can be implanted into the impaired host with the goal that the cells will perform their physiological function and avoid destruction by the host immune system. To this end, it is important that purified cell lines are used, as the introduction of non-self immune cells can up-regulate a strong host immune attack. The difficulty with this approach is the scaffolding must be small, as no cell can survive more than a couple millimeters away from a source of oxygen and nutrients. Therefore, large scaffolds cannot be used, as the scaffold will not vascularize adequately in time to save the cells in the interior regions.

In another approach, an empty three-dimensional, biodegradable polymer scaffold is directly implanted in the patient, with the goal of inducing the correct type of cells from the host's body to migrate into the polymer scaffold. The benefit is that vascularization can happen simultaneously with migration of cells into the matrix. A major problem is that there is currently no way to ensure that the appropriate cell types will migrate into the scaffold, and that the mechanical and biological properties will be maintained to provide the patient's physiological need.

In both of the above approaches, the scaffold may be biodegradable, meaning that over time it will break down both chemically and mechanically. As this break down occurs, the cells secrete their own extracellular matrix, which plays a critical role in cell survival and function. In normal tissue, there is an active and dynamic reciprocal exchange between the constitutive cells of the tissue and the surrounding extracellular matrix. The extracellular matrix provides chemical signals that regulate the morphological properties and phenotypic traits of cells and may induce division, differentiation or even cell death. In addition, the cells are also constantly rearranging the extracellular matrix. Cells both degrade and rebuild the extracellular matrix and secrete chemicals into the matrix to be used later by themselves or other cells that may migrate into the area. It has also been discovered that the extracellular matrix is one of the most important components in embryological development. Pioneering cells secrete chemical signals that help following cells differentiate into the appropriate final phenotype. For example, such chemical signals cause the differentiation of neural crest cells into axons, smooth muscle cells or neurons.

The integrated relationship between extracellular matrix and tissue cells establishes the extracellular matrix as an important parameter in tissue engineering. If cells are desired to behave in a specific manner, then the extracellular matrix must provide the appropriate environment and appropriate chemical/biological signals to induce that behavior for that cell type. Currently it is not possible to faithfully reproducer a biologically active extracellular matrix. Consequently, some investigators use a biodegradable matrix that enables the cells to create their own extracellular matrix as the exogenous matrix degrades.

In the above-described approaches to tissue engineering, a polymer scaffolding provides not only the mechanical support, but also the three-dimensional shape that is desired for the new tissue or organ. Because cells must be close to a source of oxygen and nutrients in order to survive and function, a major current limitation is that of blood supply. Most current methodologies provide no specific means of actively assisting the incorporation of blood vessels into and throughout the polymer matrix. This places limitations on the physical size and shape of the polymer matrix. The only current tissue-engineering device that has made it into widespread clinical use is artificial skin, which by definition is of limited thickness. The present invention provides compositions and methods that promote the directed migration of appropriate cell types into the engineered extracellular matrix. By directing specific three-dimensional cell migration and functional patterns, directed vascularization can be induced, which overcomes the current limitations on the shape and size of polymer implants. It also ensures that appropriate cell types will be physically located in specific locations within the matrix. Compositions and methods are provided to modulate phenotypic expression as a function of both time and space.

SUMMARY OF THE INVENTION

The present invention provides tissue engineering compositions and methods wherein three-dimensional matrices for growing cells are prepared for in vitro and in vivo use. The matrices comprise biodegradable polymer fibers capable of the controlled delivery of therapeutic agents. The spatial and temporal distribution of released therapeutic agents is controlled by the use of predefined nonhomogeneous patterns of polymer fibers, which are capable of releasing one or more therapeutic agents as a function of time. The terms "scaffold," "scaffold matrix" and "fiber-scaffold" are also used herein to describe the three dimensional matrices of the invention. "Defined nonhomogeneous pattern" in the context of the current application means the incorporation of specific fibers into a scaffold matrix such that a desired three-dimensional distribution of one or more therapeutic agents within the scaffold matrix is achieved. The distribution of therapeutic agents within the matrix fibers controls the subsequent spatial distribution within the interstitial medium of the matrix following release of the agents from the polymer fibers. In this way, the spatial contours of desired concentration gradients can be created within the three dimensional matrix structure and in the immediate surroundings of the matrix. Temporal distribution is controlled by the polymer composition of the fiber and by the use of coaxial layers within a fiber.

One aspect of the present invention is a biocompatible implant composition comprising a scaffold of biodegradable

polymer fibers. In various embodiments of the present invention, the distance between the fibers may be about 50 microns, about 70 microns, about 90 microns, about 100 microns, about 120 microns, about 140 microns, about 160 microns, about 180 microns, about 200 microns, about 220 microns, about 240 microns, about 260 microns, about 280 microns, about 300 microns, about 320 microns, about 340 microns, about 360 microns, about 380 microns, about 400 microns, about 450 microns or about 500 microns. In various embodiments the distance between the fibers may be less than 50 microns or greater than 500 microns.

Additionally, it is envisioned that in various embodiments of the invention, the fibers will have a diameter of about 20 microns, about 40 microns, about 60 microns, about 80 microns, about 100 microns, about 120 microns, about 140 microns, about 160 microns, about 180 microns, about 200 microns, about 220 microns, about 240 microns, about 260 microns, about 280 microns, about 300 microns, about 320 microns, about 340 microns, about 360 microns, about 380 microns, about 400 microns, about 450 microns or about 500 microns (including intermediate lengths). In various embodiments the diameter of the fibers may be less than about 20 microns or greater than about 500 microns. Preferably, the diameter of the fibers will be from about 60 microns to about 80 microns.

"About", in this one context is intended to mean a range of from 1–10 microns, which includes the intermediate lengths within the range. It will be readily understood that "intermediate lengths", in this context, means any length between the quoted ranges, such as 21, 22, 23, 24, 25, 26, 27, 28, 29 etc.; 30, 31, 32, etc.; 50, 51, 52, 53, etc.; 100, 101, 102, 103, etc.; 150, 151, 152, 153, etc.; including all integers through the 200–500 range.

The inventors also contemplate that the matrix may be woven, non-woven, braided, knitted, or a combination of two or more such preparations. For example, potential applications such as artificial arteries may well use a combination of woven, non-woven and knitted preparations or a combination of all four preparations. In certain embodiments of the invention, braided compositions may find particular utility for use with tendons and ligaments. Such braiding may, for example, provide superior strength.

In certain embodiments of the invention, the fibers containing one or more therapeutic agents are distributed within the scaffold matrix in a defined nonhomogeneous pattern. In one embodiment, the fibers may comprise two or more subsets of fibers that differ in biodegradable polymer content. The fibers or subsets of fibers may comprise a plurality of co-axial biodegradable polymer layers.

In another embodiment of the present invention, the fibers or a subset of fibers, contain one or more therapeutic agents such that the concentration of the therapeutic agent or agents varies along the longitudinal axis of the fibers or subset of fibers. The concentration of the active agent or agents may vary linearly, exponentially or in any desired fashion, as a function of distance along the longitudinal axis of a fiber. The variation may be monodirectional, that is, the content of one or more therapeutic agents decreases from the first end of the fibers or subset of the fibers to the second end of the fibers or subset of the fibers. The content may also vary in a bidirection fashion, that is, the content of the therapeutic agent or agents increases from the first ends of the fibers or subset of the fibers to a maximum and then decreases towards the second ends of the fibers or subset of the fibers.

In certain embodiments of the present invention, a subset of fibers comprising the scaffold may contain no therapeutic agent. For fibers that contain one or more therapeutic agents, the agent or agents may include a growth factor, an immunodulator, a compound that promotes angiogenesis, a compound that inhibits angiogenesis, an anti-inflammatory compound, an antibiotic, a cytokine, an anti-coagulation agent, a procoagulation agent, a chemotactic agent, an agents that promotes apoptosis, an agent that inhibits apoptosis, a mitogenic agent, a radioactive agent, a contrast agent for imaging studies, a viral vector, a polynucleotide, therapeutic genes, DNA, RNA, a polypeptide, a glycosaminoglycan, a carbohydrate, a glycoprotein. The therapeutic agents may also include those drugs that are to be administered for long-term maintenance to patients such as cardiovascular drugs, including blood pressure, pacing, anti-arrhythmia, beta-blocking drugs, and calcium channel based drugs. Therapeutic agents of the present invention also include anti-tremor and other drugs for epilepsy or other movement disorders. These agents may also include long term medications such as contraceptives and fertility drugs. They could comprise neurologic agents such as dopamine and related drugs as well as psychological or other behavioral drugs. The therapeutic agents may also include chemical scavengers such as chelators, and antioxidants. Wherein the therapeutic agent promotes angiogenesis, that agent may be vascular endothelial growth factor. The therapeutic agents may be synthetic or natural drugs, proteins, DNA, RNA, or cells (genetically altered or not). As used in the specification and claims, following long-standing patent law practice, the terms "a" and "an," when used in conjunction with the word "comprising" or "including" means one or more.

In general, the present invention contemplates the use of any drug incorporated in the biodegradable polymer fibers of the invention. The word "drug" as used herein is defined as a chemical capable of administration to an organism, which modifies or alters the organism's physiology. More preferably the word "drug" as used herein is defined as any substance intended for use in the treatment or prevention of disease. Drug includes synthetic and naturally occurring toxins and bioaffecting substances as well as recognized pharmaceuticals, such as those listed in "The Physicians Desk Reference," 471st edition, pages 101–321; "Goodman and Gilman's The Pharmacological Basis of Therapeutics" 8th Edition (1990), pages 84–1614 and 1655–1715; and "The United States Pharmacopeia, The National Formulary", USP XXII NF XVII (1990), the compounds of these references being herein incorporated by reference. The term "drug" also includes compounds that have the indicated properties that are not yet discovered or available in the U.S. The term "drug" includes pro-active, activated, and metabolized forms of drugs.

The biodegradable polymer may be a single polymer or a co-polymer or blend of polymers and may comprise poly (L-lactic acid), poly(DL-lactic acid), polycaprolactone, poly (glycolic acid), polyanhydride, chitosan, or sulfonated chitosan, or natural polymers or polypeptides, such as reconstituted collagen or spider silk.

One aspect of the present invention is a drug-delivery fiber composition comprising a biodegradable polymer fiber containing one or more therapeutic agents. In one embodiment, the content of the one or more therapeutic agents within the fiber varies along the longitudinal axis of the fiber such that the content of the therapeutic agent or agents decreases from the first end of the fiber to the second end of the fiber. In another embodiment, the fiber comprises a plurality of co-axial layers of biodegradable polymers. The drug delivery fiber composition may be implanted into many

sites in the body including dermal tissues, cardiac tissue, soft tissues, nerves, bones, and the eye. Ocular implantation has particular use for treatment of cataracts, diabetically induced proliferative retinopathy and non-proliferative retinopathy, glaucoma, macular degeneration, and pigmentosa XXXX.

Another aspect of the present invention is a method of controlling the spatial and temporal concentration of one or more therapeutic agents within a fiber-scaffold implant, comprising implanting a fiber-scaffold into a host. The spatial concentrations may be provided across multiple fibers, or alternatively along a single fiber by imposing a concentration gradient along the length of a fiber. The fiber-scaffold typically comprises biodegradable polymer fibers containing one or more therapeutic agents, wherein the therapeutic agent or agents are distributed in the fiber-scaffold in a defined nonhomogeneous pattern. The host will typically be an animal, preferably a mammal and more preferably a human.

Yet another aspect of the present invention is a method of producing a fiber-scaffold for preparing an implant capable of controlling the spatial and temporal concentration of one or more therapeutic agents. This method generally comprises forming biodegradable polymer fibers into a three dimensional fiber-scaffold. The biodegradable polymer fibers contain one or more therapeutic agents. The therapeutic agent or agents are distributed in the fiber-scaffold in a defined nonhomogeneous pattern.

It is further envisioned that the scaffold of the invention may be used to direct and/or organize tissue structure, cell migration and matrix deposition and participate in or promote general wound healing.

In another embodiment of the invention, a method is provided for creating a drug releasing fiber from chitosan comprising use of hydrochloric acid as a solvent and Tris base as a coagulating bath. The hydrochloric acid concentration may be, for example, from about 0.25% to about 5%, or from about 1% to about 2%, including all concentrations within such ranges. In the method, the tris base concentration may be, for example, from about 2% to about 25%, from about 4% to about 17%, or from about 5% to about 15%, including all concentrations within such ranges. The method may, in one embodiment of the invention, comprise a heterogeneous mixture comprising chitosans with different degrees of deacetylation. The method may also comprise creating a drug releasing fiber comprising segments of chitosan with different degrees of deacetylation.

A drug releasing fiber in accordance with the invention may be created, for example, from chitosan and extracellular matrix. In creating a drug releasing fiber in accordance with the invention, the chitosan concentration may be, for example, from about 0.5 wt. % to about 10 wt. %, from about 1 wt. % to about 7 wt. %, from about 2 wt. % to about 5 wt. %, from about 3 wt. % to about 4 wt. %, or about 3.5 wt. %. In one embodiment of the invention, the Matrigel. The extracellular matrix concentration may be from about 1 vol. % to about 20 vol. %, from about 2 vol. % to about 15 vol. %, from about 3 vol. % to about 10 vol. %, or from about 4 vol. % to about 6 vol. %, including about 5 vol. %. In the method, the fiber may be coated with said extracellular matrix.

Chitosan used in accordance with the invention may be sulfated or unsulfated. In one embodiment of the invention, when sulfated chitosan is used the concentration may be from about 0.025 wt. % to about 2 wt. %, from about 0.05 wt. % to about 1 wt. %, from about 0.1 wt. % to about 0.5 wt. %, or from about 0.15 wt. % to about 0.3 wt. %, including about 0.2 wt. %. In the method, chitosan and sulfated chitosan may be extruded into a fiber.

In still another embodiment of the invention, a method is provided of creating a drug releasing fiber, the method comprising adding poly(L-lactic acid) microspheres to chitosan in acid and a coagulation bath. In the method, the acid may be, for example, acetic acid or hydrochloric acid. Where the acid is hydrochloric acid, the concentration may be, for example, from about 0.25% to about 5%, or from about 1% to about 2%, including 1.2 vol. % and all other concentrations within such ranges. The chitosan concentration may be, for example, from about 0.5 wt. % to about 10 wt. %, from about 1 wt. % to about 7 wt. %, from about 2 wt. % to about 5 wt. %, from about 3 wt. % to about 4 wt. %, or about 3.5 wt. %. The coagulation bath may comprise sodium hydroxide, for example, in a concentration of about 1 vol. % to about 20 vol. %, 2 vol. % to about 15 vol. %, 3 vol. % to about 10 vol. %, 4 vol. % to about 7 vol. %, or about 4 vol. % to about 6 vol. %, including about 5 vol. %. In one embodiment of the invention, the method comprises adding poly(L-lactic acid) microspheres to a solution of about 3.5 wt. % chitosan in from about 1 vol. % hydrochloric acid to about 2 vol. % hydrochloric acid and using a coagulation bath comprising from about 5 vol. % tris base to about 15 vol. % tris base. The method may further comprise adding a surfactant to the solution, including albumin, for example, from about 1 wt. % to about 5 wt. % of said albumin, including about 3 wt. %. In yet another embodiment of the invention, a composition of chitosan fibers is provided comprising microspheres of a second polymer, said microspheres comprising one or more biological molecules. The composition may comprise a surfactant that is a biological molecule.

In yet another embodiment of the invention, a composition is provided comprising a fiber containing chitosan and an extracellular matrix. The chitosan may be sulfated or non-sulfated.

In yet another embodiment of the invention, a composition is provided comprising a three-dimensional scaffold, said scaffold comprising fibers that are woven, non-woven, or knitted, wherein said fibers comprise any of the compositions described herein above. A composition in accordance with the invention may, in one embodiment, comprise fibers containing chitosan, extracellular matrix and a biological molecule. The chitosan may sulfated non-sulfated.

In yet another embodiment of the invention, a composition is provided comprising a heterogeneous scaffold of fibers a biological molecule as described above, wherein the biological molecule not the same for all fibers of the scaffold. In the composition, the degree of deacetylation may vary as a function of distance along the fiber. The composition may an extracellular matrix. The composition may also, in certain embodiments of the invention, comprise sulfated or non-sulfated chitosan.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIG. **1**: Shows fibers configured in a complex three-dimensional woven scaffolding with patterning. Each of the individual fibers may be loaded with one or more therapeutic agents. The numerals **21–27** denote fibers loaded with therapeutic agents.

FIG. **2**: Shows fibers configured in a three-dimensional non-woven scaffolding without patterning. Each of the individual fibers may be loaded with one or more therapeutic agents. All fibers may contain the same therapeutic agent(s) or, a variety of different agents may be used in other fibers in the same scaffolding. The numerals **21–25** denote fibers loaded with therapeutic agents.

FIG. **3**A and FIG. **3**B: Fibers can provide the body with short term mechanical support in such applications as stents. FIG. **3**A illustrates that a single polymer fiber can maintain the lumen of any tubular body, such as arteries, veins, or ducts. FIG. **3**B illustrates that multiple polymer fibers can maintain the lumen of tubular bodies. The numerals **21–25** denote fibers loaded with therapeutic agents.

FIG. **4**: Fibers can be coated to form co-axial fibers. FIG. **4** shows that a fiber may have multiple component coatings, with each component loaded with different therapeutic agents. The numerals **11–13** denote therapeutic agents.

FIG. **5**: Shows the release kinetics of a coated fiber, as shown in FIG. **4**, having a two component coating with each component loaded with different therapeutic agents. The numerals **11–13** denote therapeutic agents.

FIG. **6**: Fibers may contain linear gradients of therapeutic agents along their length. FIG. **6** illustrates a fiber containing a linear gradient of therapeutic agent along its length (top) and graphically illustrates the linear gradient (bottom).

FIG. **7**: Shows a banded fiber having more than one therapeutic agent with possibly varying concentrations along its length. The distribution and frequency of the bands can be changed as desired. The numerals **11–12** denote therapeutic agents.

FIG. **8**: Depicts an apparatus for fabrication of polymer fibers containing therapeutic agents.

FIG. **9**A and FIG. **9**B: By varying the ratio of the infusion speed of the polymer emulsion into the coagulating bath to the linear winding speed of the lathe, very surprising changes in the mechanical properties was observed. FIG. **9**A graphically illustrates changes in the ultimate strength [Mpa] when the ratio of winding speed to the infusion speed is varied. Results shown are for polymers having 10-wt %, 8-wt %, and 7.5-wt %. FIG. **9**B graphically illustrates changes in percent elongation with varying ratios of winding velocity (Vw) to infusion velocity (Vi).

FIG. **10**A and FIG. **10**B: The mechanical properties of fibers change as a function of polymer solvent(s), coagulating bath solvent(s), interaction of the solvent system, winding speed to infusion speed ratio, total time in the coagulating bath, ratio of aqueous phase to polymer solution phase in emulsion, and the quality of the surfactant. FIG. **10**A graphically illustrates changes in ultimate strength with polymer concentration (wt %) when the winding speed to infusion speed ratio (Vw/Vi) is 26.82 and 23.49. FIG. **10**B illustrates changes in elasticity with polymer weight percent for the same ratios.

FIG. **11**A, FIG. **11**B and FIG. **11**C: Fibers have been produced with varying surface textures. FIG. **11**A shows a fiber having a smooth surface texture. FIG. **11**B shows a fiber having a veloured surface texture. FIG. **11**C shows a fiber having a longitudinally grooved surface texture.

FIG. **12**: Illustrates variations in the diameter of fibers as a function of the winding speed to infusion speed ratio (Vw/Vi) and of weight percent.

FIG. **13**: Illustrates the use of a butterfly valve at a "Y" junction to gradually change the ratio of two solutions to achieve a concentration gradient down the length of a fiber.

FIG. **14**: Illustrates the use of independent pumps and a mixing chamber to establish a well-controlled gradient with known change in concentration per centimeter length. The numerals **13** and **14** denote polymer solutions, with and without therapeutic agents respectively; **30** denotes Pump **1**, **31** denotes Pump **2** and **32** denotes the mixing chamber in place.

FIG. **15**: Illustrates parallel arrays of fibers packed into silicon rubber of other suitable material tubes and loaded with neurotrophins for axonal growth. The numeral **21** denotes fibers loaded with neutrophins, **22** denotes fibers loaded with other cytokines or growth factors, and **50** denotes a tube (made from silicone rubber or other material) to hold the fiber bundle in place.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The present invention provides compositions and methods to create a heterogeneous, woven, knitted, or non-woven or braided three-dimensional matrix for growing cells in tissue engineering applications. These scaffolds can be used in vitro and in vivo, and due to their heterogeneity can create both spatial and temporal distributions of therapeutic agents. In this invention, therapeutic agents may include drugs, proteins, peptides, mono- and di-saccharides, polysaccharides, glycoproteins, DNA, RNA, viruses, or other biological molecules of interest. The term therapeutic agent in this invention also includes radioactive materials used to help destroy harmful tissues such as tumors in the local area, or to inhibit growth of healthy tissues, such as in current stent applications; or markers to be used in imaging studies.

A. Three Dimensional Fiber Matrix

To create the heterogeneous scaffolds of the present invention, the therapeutic agents are encapsulated into individual fibers of the matrix by methods to be described herein. The therapeutic agents are released from each individual fiber slowly, and in a controlled manner. The fiber format has many advantages as a drug delivery platform over other slow drug-releasing agents known to those familiar in the art such as microspheres, porous plugs or patches. The primary advantage of fibers is that they can provide complex three-dimensional woven (FIG. **1**), or non-woven (FIG. **2**) scaffolding, with or without patterning, to allow cells to attach, spread, differentiate, and mature into appropriately functioning cells. Because they can form patterns, a "smart fabric" can be woven to induce cells of specific types to migrate to specific regions of the scaffold due to specific chemotactic factors being released. This scaffold mimics the function of the extracellular matrix material both during embryological development and in post-embryological tissues. Additionally, filaments could be formed into a unique scaffold that provides a growth substrate for tissue repair or reconstruction that is not reminiscent of a natural like structure.

Because of the ability to weave patterns to induce appropriate cell types into specific regions, it is possible to incorporate strands that will induce the formation of blood vessels into the fabric. This may be accomplished by providing fibers that release growth factors such as vascular endothelial growth factor (VEGF). By appropriate spacing of VEGF containing-fibers into the weave pattern, large tissues may be engineered, and the cells in such tissues can be provided with a sufficient blood supply and thereby receive oxygen and nutrients and enable the removal of waste products.

Fibers also have the advantage of providing the body with short term mechanical support in such applications as stents

(FIGS. **3**A and **3**B), wherein the polymer fiber can maintain the lumen of any tubular body, such as arteries, veins, ducts (e.g. bile duct, ureter, urethra, trachea, etc.), organs of the digestive track such as esophagus, intestine, colon, and connective tissue such as tendons, ligaments, muscle and bone. The fibers provide a useful structure to support mechanical strength or tension during the healing process. Fibers may also be useful to promote neural regeneration or reconstruction of nerves or spinal cord.

Further, fibers can be coated, forming co-axial fibers as shown in FIG. **4**. Each coating can be of a different polymer material, or combination of polymers, and each layer can release a different therapeutic agent or combination of therapeutic agents. The coating can also be physically divided into multiple sections, meaning that if desired, different therapeutic agents can be released in various directions. For example, as depicted in FIG. **4**, a fiber may have a two component coating, with each component loaded with different therapeutic agents. Therefore, not only is spatial distribution of various therapeutic agents possible, as described above, but these agents may have different release kinetics, thus yielding temporal distribution of therapeutic agents. The release kinetics of such a coated fiber is characterized in FIG. **5**. For example, if a fiber has two coatings over the core polymer, then three different therapeutic agents or combinations of therapeutic agents can be released. The outside coating will release its therapeutic agents followed by the inner coating material and finally from the core fiber. Therefore, each polymer system has its own release kinetics profile that can be adjusted by polymer type and processing conditions for that particular coating layer. Each coating can consist of different polymers as well as being loaded with different molecules. This provides the ability to control release kinetics at each layer. The ability to release different agents at different times is particularly important in tissue engineering, because cells that are rapidly dividing often do not display the specialized functions of non-dividing cells of the same type of class. With the present invention, it is possible, by release of the appropriate therapeutic agents, to induce cells to first migrate to a specific location, then enter a rapid division phase to fill the tissue space, and then differentiate into a functional form.

Additionally, cells are known to follow concentration gradients. It is the change in concentration of a particular factor that appears to be important for directed cell migration. Therefore, the present invention provides a method of achieving gradients of therapeutic agents along the length of the fibers. A linear gradient is depicted in FIGS. **6**A and **6**B. By methods disclosed in this invention, this concentration gradient can be linear, exponential, or any other shape as a function of distance along the length of the fiber. It can also be bidirectional, meaning that it can be low at both ends and reach a maximum in the middle for example. This induces the cells to migrate and grow in specific directions along the fibers. By extension, by methods disclosed in this invention, a banded fiber can also be produced, as shown in FIG. **7**. The distribution and frequency of these bands can be changed as desired. Therefore, the therapeutic agents delivery aspect of this invention goes far beyond simple drug-delivery microspheres or plugs, and the fiber based "smart scaffold" exceeds typical fiber based matrices into orchestrating the development of viable tissue, providing a three-dimensional biological architecture as well as mechanical support.

B. Biodegradable Polymers

Preferred polymers for use in the present invention include single polymer, co-polymer or a blend of polymers of poly(L-lactic acid), poly(DL-lactic acid), polycaprolactone, poly(glycolic acid), polyanhydride, chitosan, or sulfonated chitosan. Naturally occurring polymers may also be used such as reconstituted collagen or natural silks. Those of skill in the art will understand that these polymers are just examples of a class of biodegradable polymer matrices that may be used in this invention. Further biodegradable matrices include polyanhydrides, polyorthoesters, and poly(amino acids) (Peppas and Langer, 1994). Any such matrix may be utilized to fabricate a biodegradable polymer matrix with controlled properties for use in this invention. Further biodegradable polymers that produce non-toxic degradation products are listed in Table 1.

TABLE 1

Main Polymers Recognized as Biodegradable
Synthetic
Polypeptides
Polydepsipeptides
Nylon-2/nylon-6 copolyamides
Aliphatic polyesters
Poly(glycolic acid) (PGA) and copolymers
Poly(lactic acid) (PLA) and copolymer
Poly(alkylene succinates)
Poly(hydroxy butyrate) (PHB)
Poly(butylene diglycolate)
Poly(ϵ-capro1actone) and copolymers
Polydihydropyrans
Polyphosphazenes
Poly(ortho ester)
Poly(cyano acrylates)
Natural
Modified polysaccharides
cellulose, starch, chitin
Modified proteins
collagen, fibrin

Adapted from Wong and Mooney, 1997.

C. Agents That Promote Angiogenesis

One class of therapeutic agents to be encapsulated by the polymer fibers of the present invention are therapeutic agents that promote angiogenesis. The successful engineering of new tissue requires the establishment of a vascular network. The induction of angiogenesis is mediated by a variety of factors, any of which may be used in conjunction with the present invention (Folkman and Klagsbrun, 1987, and references cited therein, each incorporated herein in their entirety by reference). Examples of angiogenic factors includes, but is not limited to: vascular endothelial growth factor (VEGF) or vascular permeability factor (VPF); members of the fibroblast growth factor family, including acidic fibroblast growth factor (AFGF) and basic fibroblast growth factor (bFGF); interleukin-8 (IL-8); epidermal growth factor (EGF); platelet-derived growth factor (PDGF) or platelet-derived endothelial cell growth factor (PD-ECGF); transforming growth factors alpha and beta (TGF-α, TGF-β); tumor necrosis factor alpha (TNF-α); hepatocyte growth factor (HGF); granulocyte-macrophage colony stimulating factor (GM-CSF); insulin growth factor-1 (IGF−1); angiogenin; angiotropin; fibrin and nicotinamide (Folkman, 1986, 1995; Auerbach and Auerbach, 1994; Fidler and Ellis, 1994; Folkman and Klagsbrun, 1987; Nagy et al., 1995)

D. Cytokines

In certain embodiments the use of particular cytokines incorporated in the polymer fibers of the present invention is contemplated. Table 2 below is an exemplary, but not limiting, list of cytokines and related factors contemplated for use in the present invention.

TABLE 2

Cytokine	Reference
Human IL-1	March et al., Nature, 315:641, 1985
Murine IL-1	Lomedico et al., Nature, 312:458, 1984
Human IL-I	March et al., Nature, 315:641, 1985; Auron et al., Proc. Natl. Acad. Sci. USA, 81:7907, 1984
Murine IL-1	Gray, J. Immunol., 137:3644, 1986; Telford, NAR, 14:9955, 1986
Human IL-1ra	Eisenberg et al., Nature, 343:341, 1990
Human IL-2	Taniguchi et al., Nature, 302:305, 1983; Maeda et al., Biochem. Biophys. Res. Commun., 115:1040, 1983
Human IL-2	Taniguchi et al., Nature, 302:305, 1983
Human IL-3	Yang et al., Cell, 47:3, 1986
Murine IL-3	Yokota et al., Proc. Natl. Acad. Sci. USA, 81:1070, 1984; Fung et al., Nature, 307:233, 1984; Miyatake et al., Proc. Natl. Acad. Sci. USA, 82:316, 1985
Human IL-4	Yokota et al., Proc. Natl. Acad. Sci. USA, 83:5894, 1986
Murine IL-4	Norma et al., Nature, 319:640, 1986; Lee et al., Proc. Natl. Acad. Sci. USA, 83:2061, 1986
Human IL-5	Azuma et al., Nuc. Acids Res., 14:9149, 1986
Murine IL-5	Kinashi et al., Nature, 324:70, 1986; Mizuta et al., Growth Factors, 1:51, 1988
Human IL-6	Hirano et al., Nature, 324:73, 1986
Murine IL-6	Van Snick et al., Eur. J. Immunol., 18:193, 1988
Human IL-7	Goodwin et al., Proc. Natl. Acad. Sci. USA, 86:302, 1989
Murine IL-7	Namen et al., Nature, 333:571, 1988
Human IL-8	Schmid et al., J. Immunol., 139:250, 1987; Matsushima et al., J Exp. Med., 167:1883, 1988; Lindley et al., Proc. Natl. Acad. Sci. USA, 85:9199, 1988
Human IL-9	Renauld et al., J. Immunol., 144:4235, 1990
Murine IL-9	Renauld et al., J. Immunol., 144:4235, 1990
Human Angiogenin	Kurachi et al., Biochemistry, 24:5494, 1985
Human GRO	Richmond et al., EMBO J., 7:2025, 1988
Munne MIP-1	Davatelis et al., J. Exp. Med., 167:1939, 1988
Murine MIP-1	Sherry et al., J. Exp. Med., 168:2251, 1988
Human MIF	Weiser et al., Proc. Natl. Acad. Sci. USA, 86:7522, 1989
Human G-CSF	Nagata et al., Nature, 319:415, 1986; Souza et al., Science, 232:61, 1986
Human GM-CSF	Cantrell et al., Proc. Natl. Acad. Sci. USA, 82:6250, 1985; Lee et al., Proc. Natl. Acad. Sci. USA, 82:4360, 1985; Wong et a1., Science, 228:810, 1985
Murine GM-CSF	Gough et al., EMBO J., 4:645, 1985
Human M-CSF	Wong, Science, 235:1504, 1987; Kawasaki, Science, 230; 291, 1985; Ladner, EMBO J., 6:2693, 1987
Human EGF	Smith et al., Nuc. Acids Res., 10:4467, 1982; Bell et al., NAR, 14:8427, 1986
Human TGF-	Derynck et al., Cell, 38:287, 1984
Human FGF acidic	Jaye et al., Science, 233:541, 1986; Gimenez-Gallego et al., Biochem. Biophys. Res. Commun., 138:611, 1986; Harper et al, Biochem., 25:4097, 1986
Human -ECGF	Jaye et al., Science, 233:541, 1986
Human FGF basic	Abraham et a1., EMBO J., 5:2523, 1986; Sommer et al., Biochem. Biophys. Res. Comm., 144:543, 1987
Murine IFN-	Higashi et al., J. Biol. Chem., 258:9522, 1983; Kuga, NAR, 17:3291, 1989
Human IFN-	Gray et al., Nature, 295:503, 1982; Devos et al., NAR, 10:2487, 1982; Rinderknecht, J. Biol. Chem., 259:6790, 1984
Human IGF-I	Jansen et al., Nature, 306:609, 1983; Rotwein et al., J. Biol. Chem., 261:4828, 1986
Human IGF-II	Bell et al., Nature, 310:775, 1984
Human -NGF chain	Ullrich et al., Nature, 303:821, 1983
Human NT-3	Huang EJ. Et al., Development. 126(10):2191–203, 1999 May.
Human PDGF A chain	Betsholtz et al., Nature, 320:695, 1986
Human PDGF B chain	Johnsson et al., EMBO J., 3:921, 1984; Collins et al., Nature, 316:748, 1985
Human TGF-1	Derynck et al., Nature, 316:701, 1985
Human TNF-	Pennica et al., Nature, 312:724, 1984; Fransen et al., Nuc. Acids Res., 13:4417, 1985
Human TNF-	Gray et al., Nature, 312:721, 1984
Murine TNF-	Gray et al., Nucl. Acids Res., 15:3937, 1987
Human E-Selectin	Bevilacqua et al., Science, 243:1160, 1989; Hensley et al., J. Biol. Chem., 269:23949, 1994
Human ICAM-1	Simmons et al., Nature, 331:624, 1988
Human PECAM	Simmons et al., J. Exp. Med., 171:2147, 1990
Human VCAM-1	Hession et al., J. Biol. Chem., 266:6682; Osborn et al., Cell, 59:1203, 1989
Human L-Selectin	Ord et al., J. Biol. Chem., 265:7760, 1990; Tedder et al.,

TABLE 2-continued

Cytokine	Reference
(membrane bound)	J. Exp. Med., 170:123, 1989
Human L-Selectin	Ord et al., J. Biol. Chem., 265:7760, 1990; Tedder et al.,
(soluble form)	J. Exp. Med., 170:123, 1989
Human Calcitonin	Le Moullec et al., FEBS Lett., 167:93, 1984
Human Hirudin	Dodt et al., FEBS Lett., 165:180, 1984
(*E. coli* optimized)	

E. Polynucelotides

The polynucleotides to be incorporated within the polymer fibers of the present invention, extend to the full variety of nucleic acid molecules. The nucleic acids thus include genomic DNA, cDNAs, single stranded DNA, double stranded DNA, triple stranded DNA, oligonucleotides, Z-DNA, mRNA, tRNA and other RNAs. DNA molecules are generally preferred, even where the DNA is used to express a therapeutic RNA, such as a ribozyme or antisense RNA.

A "gene" or DNA segment encoding a selected protein or RNA, generally refers to a DNA segment that contains sequences encoding the selected protein or RNA, but is isolated away from, or purified free from, total genomic DNA of the species from which the DNA is obtained. Included within the terms "gene" and "DNA segment", are DNA segments and smaller fragments of such segments, and also recombinant vectors, including, for example, plasmids, cosmids, phage, retroviruses, adenoviruses, and the like.

The term "gene" is used for simplicity to refer to a functional protein or peptide encoding unit. As will be understood by those in the art, this functional term includes both genomic sequences and cDNA sequences. "Isolated substantially away from other coding sequences" means that the gene of interest forms the significant part of the coding region of the DNA segment, and that the DNA segment does not contain large portions of naturally-occurring coding DNA, such as large chromosomal fragments or other functional genes or cDNA coding regions. Of course, this refers to the DNA segment as originally isolated, and does not exclude genes or coding regions, such as sequences encoding leader peptides or targeting sequences, later added to the segment by the hand of man.

The present invention does not require that highly purified DNA or vectors be used, so long as any coding segment employed encodes a selected protein or RNA and does not include any coding or regulatory sequences that would have a significant adverse effect on the target cells. Therefore, it will also be understood that useful nucleic acid sequences may include additional residues, such as additional non-coding sequences flanking either of the 5' or 3' portions of the coding region or may include various internal sequences, i.e., introns, that are known to occur within genes.

Many suitable DNA segments may be obtained from existing, including commercial sources. One may also obtain a new DNA segment encoding a protein of interest using any one or more of a variety of molecular biological techniques generally known to those skilled in the art. For example, cDNA or genomic libraries may be screened using primers or probes with designed sequences. Polymerase chain reaction (PCR) may also be used to generate a DNA fragment encoding a protein of interest.

After identifying an appropriate selected gene or DNA molecule, it may be inserted into any one of the many vectors currently known in the art, so that it will direct the expression and production of the selected protein when incorporated into a target cell. In a recombinant expression vector, the coding portion of the DNA segment is positioned under the control of a promoter/enhancer element. The promoter may be in the form of the promoter that is naturally associated with a selected gene, as may be obtained by isolating the 5' non-coding sequences located upstream of the coding segment or exon, for example, using recombinant cloning and/or PCR technology.

In other embodiments, it is contemplated that certain advantages will be gained by positioning the coding DNA segment under the control of a recombinant, or heterologous, promoter. As used herein, a recombinant or heterologous promoter is intended to refer to a promoter that is not normally associated with a selected gene in its natural environment. Such promoters may include those normally associated with other selected genes, and/or promoters isolated from any other bacterial, viral, eukaryotic, or mammalian cell. Naturally, it will be important to employ a promoter that effectively directs the expression of the DNA segment in the chosen target cells.

The use of recombinant promoters to achieve protein expression is generally known to those of skill in the art of molecular biology, for example, see Sambrook et al. (1989; incorporated herein by reference). The promoters employed may be constitutive, or inducible, and can be used under the appropriate conditions to direct high level or regulated expression of the introduced DNA segment. Expression of genes under the control of constitutive promoters does not require the presence of a specific substrate to induce gene expression and will occur under all conditions of cell growth. In contrast, expression of genes controlled by inducible promoters is responsive to the presence or absence of an inducing agent.

Promoters isolated from the genome of viruses that grow in mammalian cells, e.g., RSV, vaccinia virus 7.5K, SV40, HSV, adenoviruses MLP, MMTV LTR and CMV promoters, may be used herewith, as well as promoters produced by recombinant DNA or synthetic techniques. Currently preferred promoters are those such as CMV, RSV LTR, the SV40 promoter alone, and the SV40 promoter in combination with the SV40 enhancer.

Exemplary tissue specific promoter/enhancer elements and transcriptional control regions that exhibit tissue specificity include, but are not limited to: the elastase I gene control region that is active in pancreatic acinar cells; the insulin gene control region that is active in pancreatic cells; the immunoglobulin gene control region that is active in lymphoid cells; the albumin, 1-antitrypsin and -fetoprotein gene control regions that are active in liver; the -globin gene control region that is active in myeloid cells; the myelin basic protein gene control region that is active in oligodendrocyte cells in the brain; the myosin light chain-2 gene control region that is active in skeletal muscle; and the gonadotropic releasing hormone gene control region that is active in the hypothalamus. U.S. application Ser. No. 08/631,334, filed Apr. 12, 1996 and PCT Application Serial

No. PCT/US97/07301, filed Apr. 11, 1997, are both incorporated herein by reference for the purposes of incorporating references even further describing the foregoing elements.

Specific initiation signals may also be required for sufficient translation of inserted protein coding sequences. These signals include the ATG initiation codon and adjacent sequences. In cases where the entire coding sequence, including the initiation codon and adjacent sequences are inserted into the appropriate expression vectors, no additional translational control signals may be needed. However, in cases where only a portion of the coding sequence is inserted, exogenous translational control signals, including the ATG initiation codon should be provided. The initiation codon must be in phase with the reading frame of the protein coding sequences to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency and control of expression may be enhanced by the inclusion of transcription attenuation sequences, enhancer elements, etc.

A variety of vectors may be used including, but not limited to, those derived from recombinant bacteriophage DNA, plasmid DNA or cosmid DNA. For example, plasmid vectors such as pBR322, pUC 19/18, pUC 118, 119 and the M13 mp series of vectors may be used. Bacteriophage vectors may include gt10, gt11, gt18–23, ZAP/R and the EMBL series of bacteriophage vectors. Cosmid vectors that may be utilized include, but are not limited to, pJB8, pCV 103, pCV 107, pCV 108, pTM, pMCS, pNNL, pHSG274, COS202, COS203, pWE15, pWE16 and the charomid 9 series of vectors. Vectors that allow for the in vitro transcription of RNA, such as SP6 vectors, may also be used to produce large quantities of RNA that may be incorporated into matrices.

The selected genes and DNA segments may also be in the form of a DNA insert located within the genome of a recombinant virus, such as, for example a recombinant herpes virus, retroviruses, vaccinia viruses, adenoviruses, adeno-associated viruses or bovine papilloma virus. While integrating vectors may be used, non-integrating systems, which do not transmit the gene product to daughter cells for many generations will often be preferred. In this way, the gene product is expressed during a defined biological process, e.g., a wound healing process, and as the gene is diluted out in progeny generations, the amount of expressed gene product is diminished.

In such embodiments, to place the gene in contact with a target cell, one would prepare the recombinant viral particles, the genome of which includes the gene insert, and contact the target cells or tissues via release from the polymer fiber of the present ,invention, whereby the virus infects the cells and transfers the genetic material. The following U.S. patents are each incorporated herein by reference for even further exemplification of viral gene therapy: U.S. Pat. No. 5,747,469, concerning adenovirus, retrovirus, adeno-associated virus, herpes virus and cytomegalovirus gene therapy; U.S. Pat. No. 5,631,236, concerning adenovirus gene therapy; and U.S. Pat. No. 5,672,344, concerning herpesvirus gene therapy.

Genes with sequences that vary from those described in the literature are also contemplated for use in the invention, so long as the altered or modified gene still encodes a protein that functions to effect the target cells in the desired (direct or indirect) manner. These sequences include those caused by point mutations, those due to the degeneracies of the genetic code or naturally occurring allelic variants, and further modifications that have been introduced by genetic engineering, i.e., by the hand of man.

Techniques for introducing changes in nucleotide sequences that are designed to alter the functional properties of the encoded proteins or polypeptides are well known in the art, e.g., U.S. Pat. No. 4,518,584, incorporated herein by reference, which techniques are also described in further detail herein. Such modifications include the deletion, insertion or substitution of bases, and thus, changes in the amino acid sequence. Changes may be made to increase the activity of a protein, to increase its biological stability or half-life, to change its glycosylation pattern, confer temperature sensitivity or to alter the expression pattern of the protein, and the like. All such modifications to the nucleotide sequences are encompassed by this invention.

It is an advantage of the present invention that one or more than one selected gene may be used in the gene transfer methods and compositions. The nucleic acid delivery methods may thus entail the administration of one, two, three, or more, selected genes. The maximum number of genes that may be applied is limited only by practical considerations, such as the effort involved in simultaneously preparing a large number of gene constructs or even the possibility of eliciting an adverse cytotoxic effect. The particular combination of genes may be chosen to alter the same, or different, biochemical pathways. For example, a growth factor gene may be combined with a hormone gene; or a first hormone and/or growth factor gene may be combined with a gene encoding a cell surface receptor capable of interacting with the polypeptide product of the first gene.

In using multiple genes, they may be combined on a single genetic construct under control of one or more promoters, or they may be prepared as separate constructs of the same of different types. Thus, an almost endless combination of different genes and genetic constructs may be employed. Certain gene combinations may be designed to, or their use may otherwise result in, achieving synergistic effects on cell stimulation and tissue growth, any and all such combinations are intended to fall within the scope of the present invention. Indeed, many synergistic effects have been described in the scientific literature, so that one of ordinary skill in the art would readily be able to identify likely synergistic gene combinations, or even gene-protein combinations.

It will also be understood that, if desired, the nucleic segment or gene could be administered in combination with further agents, such as, e.g. proteins or polypeptides or various pharmaceutically active agents. So long as genetic material forms part of the composition, there is virtually no limit to other components which may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or tissues. The nucleic acids may thus be delivered along with various other agents, for example, in certain embodiments one may wish to administer an angiogenic factor as disclosed in U.S. Pat. No. 5,270,300 and incorporated herein by reference.

As the chemical nature of genes, i.e., as a string of nucleotides, is essentially invariant, and as the process of gene transfer and expression are fundamentally the same, it will be understood that the type of genes transferred by the fiber matrices of the present invention is virtually limitless. This extends from the transfer of a mixture of genetic material expressing antigenic or immunogenic fragments for use in DNA vaccination; to the stimulation of cell function, as in wound-healing; to aspects of cell killing, such as in transferring tumor suppressor genes, antisense oncogenes or apoptosis-inducing genes to cancer cells.

By way of example only, genes to be supplied by the invention include, but are not limited to, those encoding and

expressing: hormones, growth factors, growth factor receptors, interferons, interleukins, chemokines, cytokines, colony stimulating factors and chemotactic factors; transcription and elongation factors, cell cycle control proteins, including kinases and phosphatases, DNA repair proteins, apoptosis-inducing genes; apoptosis-inhibiting genes, oncogenes, antisense oncogenes, tumor suppressor genes; angiogenic and anti-angiogenic proteins; immune response stimulating and modulating proteins; cell surface receptors, accessory signaling molecules and transport proteins; enzymes; and anti-bacterial and anti-viral proteins.

F. Kits

All the essential materials and reagents required for the various aspects of the present invention may be assembled together in a kit. The kits of the present invention also will typically include a means for containing the vials comprising the desired components in close confinement for commercial sale such as, e.g., injection or blow-molded plastic containers into which the desired vials are retained. Irrespective of the number or type of containers, the kits of the invention are typically packaged with instructions for use of the kit components.

G. EXAMPLES

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Example 1

Fabrication of Polymer Fibers Containing Therapeutic Agents

In one embodiment of the present invention, the following procedure is used to create the drug-releasing fibers. The apparatus is depicted in FIG. **8**. First, a biodegradable polymer such as poly(L-lactic acid) (PLLA), poly(DL-lactic acid), polycaprolactone, poly(glycolic acid), polyanhydride, or copolymers or blends of these or other biodegradable polymers are dissolved in some appropriate solvent (A) at concentrations ranging from 5 to 30 wt % depending on the type of polymer, 10 wt % being preferred for PLLA. In this embodiment, solvent (A) has low miscibility with water, and is very miscible with the coagulation bath solvent (B). Preferred choices of solvent (A) include chloroform and methylene chloride. Once the polymer is dissolved, an aqueous solution containing both the biomolecules(s) of interest and a surfactant, is added to the polymer solution. The concentration of the aqueous emulsion is typically in the range of 1 to 50% v/v of the polymer solution, 4–10% being most typical for monofilament PLLA fibers. The surfactant can be one or a combination of substances familiar to those skilled in the art, such as bovine serum albumin (BSA), poly(vinyl alcohol), pluronics, or biological surfactants such as the family of phospholipids. Other surfactants not specifically mentioned here, but known to those skilled in the art are included by extension. In a typical use, BSA is used as the surfactant at concentrations ranging from about 10 fold to 100 fold higher than the biological molecule of interest, with typical concentrations ranging from 10 wt % to 50 wt % of the aqueous phase.

Using some form of mechanical energy such as sonication, vortexing, or shear forces generated by forcing the liquid through a small orifice, a water-in-oil type emulsion is formed between the aqueous and organic phases. This emulsion must be stable for periods far in excess of time required for extrusion. The size of the dispersed aqueous phase droplets is primarily dependent on the quality of the surfactant, and the amount of mechanical energy imparted to the system in forming the emulsion. The aqueous phase size is an important variable in both release kinetics and mechanical properties of the fiber.

The emulsion is then extruded into a coagulating bath containing solvent (B). The polymer emulsion is extruded into the coagulation bath through a dispensing tip ranging in size from 16 gage down to 30 gage. Solvent (B) must be highly miscible with solvent (A), and must be a non-solvent for the polymer; isopropyl alcohol is the most typical choice but any solvent that is a non-solvent for the polymer and highly miscible with solvent (A) will work. For example hexane is very miscible with methylene chloride yet is a non-solvent for the polymer, therefore, methylene chloride and hexane make a good solvent and coagulating bath combination. Because solvent (A) is highly miscible with coagulating bath solvent (B), it freely diffuses from the polymer solution stream, into the coagulating bath. The polymer, however, is not soluble in solvent (B), and therefore begins to precipitate upon itself, forming the outer sheath of a fiber and trapping virtually all of the dispersed aqueous phase of the emulsion within the forming fiber. In this way, the fiber is loaded with the drug or protein of interest. The forming fiber may be passed over a series of rollers within the coagulation bath to provide a fixed path length through the coagulation bath should a fixed path length be desired. The fiber is drawn from the coagulation bath at a determined rate. In the laboratory, the inventors have used a cylinder attached to a modified variable-speed lathe that can accurately maintain its angular velocity. The drawn and extruded fiber is then removed from the cylinder and either freeze-dried, frozen, or oven dried and placed in a desecrator or freezer, depending upon recommended storage conditions of the loaded biomolecules.

By varying the ratio of the infusion speed of the polymer emulsion into the coagulating bath to the linear winding speed of the of the lathe, very surprising changes in the mechanical properties of the fibers have been found, as shown in FIGS. **9**A and **9**B. The mechanical properties of the fibers change as a function of the following variables: polymer solvent(s), coagulating bath solvent(s), intermiscibility of the solvent system, winding speed to infusion speed ratio, total time in the coagulating bath, ratio of aqueous phase to polymer solution phase in the emulsion, and the quality of the surfactant. Changes in mechanical properties as a function of several of these variables are shown in FIGS. **10**A and **10**B.

Another surprising discovery was that the surface texture of the finished fiber could also be controlled by appropriate choices of solvent and polymer systems. The inventors have produced fibers with surface textures that vary from smooth, to veloured, to longitudinally grooved as shown in FIGS. **11**A–**11**C. These changes in surface texture have practical applications to cell growth in providing surfaces with greater adhesive properties in the case of the veloured texture, and better contact guidance in the case of the longitudinally grooved fibers. All of the changes in mechanical properties and surface texture significantly affect the release kinetics of therapeutic agents.

The diameter of the fibers has been controlled by processing conditions as shown in FIG. **12**. Because the pro-

cessing parameters that control the mechanical properties, surface texture, diameter, and release kinetics are known fibers with specific properties for specific uses can be tailor made

That biological therapeutic agents retain biological activity throughout this fabrication process can be shown with a sandwich ELISA where the agent loaded into the fiber was the Fab fragment of mouse IgG. For the ELISA to detect the presence of the Fab fragment, the biological activity of both binding epitopes must be maintained.

In another embodiment of the fabrication process, a poor solvent for the polymer is added to the polymer solution such as toluene. The addition of the poor solvent changes the mechanical properties of the fiber.

In another fabrication embodiment, up to 20% v/v of the polymer solvent is added to the coagulation bath solvent. The addition of the polymer solvent decreases the concentration gradient from inside the fiber to outside the fiber. This changes the diffusion rate and hence the rate at which the outer sheath of the fiber forms. The rate of this outer sheath formation is critical to the surface texture of the fibers and the mechanical properties of the fiber, and to the release kinetics of the biomolecule.

In another fabrication embodiment, a thickening solution, such as glycerol, is added to the coagulation bath. This increases the viscosity of the coagulation bath, and changes the specific gravity of the coagulation bath. Both of these variables have resulted in substantially increased ability to form loaded fibers. The concentration of glycerol varies from 8 to 20% v/v.

Alternatively, coaxial fibers can be fabricated in a single process by methods familiar to those skilled in the art of extrusion. Using these techniques, various polymer(s) and biomolecule(s) can be added in each layer of the coaxial fiber.

Example 2

Fabrication of Polymer Fibers Containing Variable Concentrations of Therapeutic Agents

In another fabrication embodiment, the process is similar to that described in Example 1, with the exception that a concentration gradient is applied down the length of the fiber. This is accomplished by having two solutions. One is a polymer emulsion containing the therapeutic agent(s) of interest, and the other does not contain therapeutic agents, or contains different biomolecules. The gradient is accomplished by continuously changing the ratio of the two solutions during the extrusion process. This can be accomplished in a number of ways including a butterfly valve at a "Y" junction as shown in FIG. **13**, or using independent pumps with or without a mixing chamber as shown in FIG. **14**. In this way, a well-controlled gradient is established with known change in concentration per centimeter length. Another embodiment of the present invention is the creation of "banded" fibers. In banded fibers, there are several possible configurations; in one embodiment, both polymer solutions are emulsions containing different biomolecules. This is accomplished in the same way as the gradient, where the gradient is a series of step-functions, switching alternately from emulsion A to emulsion B.

In a second embodiment, one of the bands if from a polymer emulsion containing one or more biomolecules as in other embodiments described herein. The other band is a polymer segment that acts as a sealant so that the finished fibers can be cut to pre-specified lengths so that each end of the finished fibers will be sealed at both ends. In each of these embodiments, the band lengths are independently adjustable. These gradient and banded fibers may be used with or without a concentric coating as described in the next example.

Example 3

Fabrication of Polymer Fibers With Concentric Coatings

In yet another fabrication embodiment, a pre-existing fiber is loaded through a spinneret and through the coagulation bath. The liquid polymer emulsion is added in a "T" or "Y" junction and coats the fiber before entering a coagulation bath. Thus concentric coatings are applied to the fiber, with each coating having the ability to contain a different therapeutic agent(s) as shown in FIG. **4**. The coating polymer may be the same or different from the core polymer. There may be molecules attached to the core fiber to increase the adhesion of the coating polymer. For example, a thin layer of BSA, may improve the adhesion of chitosan to poly(L-lactic acid). By an intricate spinneret, two or more polymer emulsions each containing a different biomolecule can be put in the coating. This is accomplished by bringing all coating materials into the spinneret, with baffles separating each coating polymer stream. This allows fibers to release different molecules as a function of angular position around the fiber. In certain embodiments, the spinneret may have a non-circular shape, thereby forming fibers with any desired cross-sectional shape. This is true of the core fiber as well as the coating polymers.

An alternative fabrication technique is to use specially designed multilumen spinnerets to create standard fiber structures well known to those familiar in the art, such as core and sheath, islands in the sea, etc.

Example 4

Fabrication of Environmentally Responsive Polymer Gel Fibers

In a different fabrication embodiment, environmentally responsive polymer hydrogels are formed in nanosphere size by emulsion polymerization or other methods. Such nanospheres are then incorporated into fibers. "Environmentally responsive gels" are intended to represent polymer gels that exhibit a substantial change in their physical characteristics as the environment surrounding the gels undergoes relatively small changes. Polymer hydrogels that have been found to be useful in the present invention include poly(N-isopropylacrylamide) (NIPA) and poly(acrylic acid) (PAA) gels. For example, NIPA gels have the ability to undergo dramatic volume changes of 100 fold in response to a small (2–3C) temperature change. These nanospheres may be loaded with biological molecules by soaking them in an aqueous solution of the biomolecules. These loaded nanospheres are then dried and added to the polymer solution with or without forming an emulsion. All other fabrication processes are the same. This process then creates a fiber that is temperature sensitive. The NIPA phase transition can be adjusted by those skilled in the art to occur at 38–39C. This now provides a fiber that is responsive to the physiological state of the patient. It has a dramatic increase in release kinetics if the patient begins to run a fever, and because this is a reversible phenomenon, the release kinetics slow down again once body temperature returns to normal.

Example 5

Chitosan Based Fibers

In another fabrication embodiment, rather than ester based synthetic polymers described above, naturally occurring polysaccharides such as chitosan may be used as the polymer system. It is well known in the art that chitosan fibers can be made by dissolving the chitosan in 3% acetic acid, and using 5% sodium hydroxide as the coagulation bath. The inventors have found that one can use 1% hydrochloric acid to dissolve the chitosan, that the chitosan concentrations can go as low as 2.5 wt %, and good quality fibers are obtained if the coagulation bath consists of Tris base in concentrations ranging from 5 to 15% (FIG. **1**). This is the first reporting of chitosan fibers extruded under these conditions.

Chitosan is a biodegradable polymer. Chitosan is enzymatically degraded by lysozyme, which is present in plasma, in the interstitial fluid, as well as intracellularly. Since the action of lysozyme on chitosan is dependent on the presence of acetyl groups on the polymer backbone, one can modulate, under specific circumstances, the release rate of the fibers described above by two alternative ways: a) one is to extrude fibers as described above from a heterogeneous mixture consisting of chitosan polymers each with a different degree of deacetylation. In this way, one can maintain the level of released drug in the optimal range for the necessary period of time; b) another possibility is to extrude segmented fibers of chitosan, wherein each segment is made from chitosan having a different degree of deacetylation as described in FIG. **2**. This latter approach can have applications for migratory cells by creating a temporal gradient along the fiber.

The inventors have also mixed reconstituted basement membrane extract (matrigel, Becton Dickinson, Bedford, Mass.) with chitosan dissolved in hydrochloric acid, and have demonstrated the ability to extrude good quality fibers using a coagulation bath consisting of Tris base in concentrations ranging from 10 to 15%. In this case, it was found that axonal extension was improved over chitosan alone. ELISA confirmed the presence of the two major proteins of matrigel (laminin and collagen type IV) in the fibers. These proteins also retained biological activity as demonstrated by in vitro neuron attachment and axonal extension. Another possibility is to coat the same Tris base extruded chitosan fibers with matrigel.

In a surprising finding, if the inventors sulfate the chitosan prior to adding the matrigel, neuron attachment and axon extension are improved dramatically compared to the case of matrigel and untreated chitosan (FIG. **3**, FIG. **4**). Using the same chemical extrusion conditions, the inventors could extrude polymer fibers made of 0.2% sulfated chitosan with 3.2% unmodified chitosan with or without matrigel as a co-extruded substance.

It is well known in the art that sulfated chitosan has heparin-like, anticoagulant properties due to their similar chemical structure. The fibers made of unmodified chitosan dissolved in hydrochloric acid and extruded in Tris base can be coated with sulfated chitosan or with matrigel and sulfated chitosan. This may yield fibers with inherent anticoagulant properties that can also be loaded with active drugs. This may have substantial clinical application in fabricating vascular stents and other medical devices that come in direct contact with blood, and require mechanical strength, and/or the ability to deliver drugs.

The relatively harsh acidic and basic environment in which chitosan fibers are extruded as described above substantially limits the range of biomolecules that can be incorporated into the fiber to only those biomolecules that can withstand very large pH transitions. Therefore, to overcome this inherent limitation, the inventors have developed a new approach to retain the bioactivity of even the most sensitive biomolecules loaded into chitosan fibers. In this embodiment, sensitive biomolecules of interest are loaded into PLLA microspheres using solvent evaporation or other techniques well known in the drug delivery literature. These PLLA microspheres are then mixed with 3.5 wt % chitosan solution and extruded as described above. A chitosan fiber loaded with PLLA microspheres will form when this mixture is extruded using either acetic acid and sodium hydroxide or 1.2% hydrochloric acid and 10 to 15% Tris base. The PLLA microspheres can protect the sensitive biomolecules from the harsh processing conditions of the chitosan fibers.

Example 6

Neural Tissue Engineering

In this aspect of the present invention, parallel arrays of fibers are packed into silicon rubber or other suitable material tubes and loaded with neurotrophins for axonal growth as shown in FIG. **15**. These bundles of fibers are placed in severed peripheral or central nerves. The neurotrophins may be loaded in a linear or some other appropriate gradient. This device is implanted bridging the gap between the ends of the nerve stumps. As the fibers release neurotrophins, axons begin to migrate out of the proximal end, across the fiber bundle and into the distal nerve end. Once in the distal end, guidance cues are provided by existing Schwann or glial cells and reconnections can then be made. It has been previously found that axons receive contact guidance by these fiber bundles and are able to traverse at least 1.8 cm in a rat sciatic nerve resection using non-loaded fibers. The optimal density of unloaded fibers in the tube is approximately 32 fibers in a 1.5 mm diameter tube for rat sciatic nerve growth.

Example 7

Preparation and Use of Polymer Fiber Stents

In another embodiment, fibers can be loaded with a drug of interest and used in stents or other medical devices where mechanical strength is required. The stents can be woven in such a manner as to have loaded fibers intermingled with unloaded fibers if needed for mechanical properties.

Fibers can also be used in conjunction with commercially available stents to deliver drugs at the placement site. In this case, the fibers would not provide any mechanical support, but would only serve as a drug delivery reservoir.

Example 8

Preparation and Use of Wound Dressings

In another embodiment, a gauze or dressing can be made from these fibers. This dressing can have two sides, an upper surface that will release molecules for re-epithelialization and provide a substrate for these cells. The bottom surface will promote regeneration of dermal tissue. This dressing is designed for dermal wound healing, including burns, full thickness dermal wounds and chronic or non-healing wounds and sores. Each fiber can be coated to provide temporal release of drugs or factors to correspond to the three phases of dermal wound healing.

For example, in the case of a dressing designed for trauma patients, the first chemical to be released could be a pro-

coagulant to help stop the bleeding. The next layer could then release cytokines to help recruit neutrophils and macrophages for the next phase of wound healing. Finally, a release of factors to help with reducing excessive scar tissue and to inhibit contractions, which are particularly disabling to burn patients.

Example 9

Fabrication of Artificial Arteries

It may be possible to construct an artificial artery using techniques described herein. A series of hollow, cylindrical sections can be knitted, woven, braided or fabricated using non-woven technology with fibers loaded with various biological agents. The innermost cylinder is preferably tightly woven and contains drugs or agents to promote migrating, spreading and functioning of an intact endothelial cell layer. The next cylinder is composed of a woven or knitted architecture with fibers predominately circumferentially wound around the inner cylinder. This layer will induce the migration and proliferation of smooth muscle fibers, and promote the expression of elastin to create the internal elastic media. The next cylinder is composed of knitted or non-woven fibers and will contain drugs to promote the ingrowth of fibroblasts, macrophages and the creation of extracellular matrix. The last layer will compose longitudinal fibers that will promote the vascularization of the arterial cells via an artificial vasa vasorum, created by VEGF releasing fibers, or other promoters of angiogenesis.

Example 10

Drug Delivery Scaffold

In another application embodiment, these fibers can be used for drug delivery scaffolds in places where a fiber format is preferred to that of a microsphere. For example, for drug delivery directly to the blood stream, a fiber can be attached to a vessel wall, and be contained entirely within the blood vessel. Microspheres cannot flow through the circulatory system, as they will become trapped at some level, potentially compromising the downstream tissue. The fibers, however, can release drugs and not cause any problems with occluding downstream branches so long as the fiber remains intact. Other locations where a fiber may make more sense than microspheres may include the eye, where the spheres may be more likely to interfere with the subject's vision. A fiber could be tacked down and not float into the field of view. Fibers may be able to stay in place better than microspheres, particularly within a space where the fiber can be coiled. In this way, the mechanical tension within the fiber will cause it to push against the sides of the tissue space and thus remain in position.

Example 11

In Situ Arteriogenesis

Similar in scope to example 9, is in situ arteriogenesis. In this embodiment, a fiber bundle containing VEGF or a similar substitute is placed into the body with both ends of the fiber bundle near or touching an existing blood vessel. As the fiber begins to release VEGF or its substitute, endothelial cells from the existing blood vessel will be induced to migrate out from the existing vessel following a process similar to normal angiogenesis. The leading endothelial cells will traverse the path of the fiber bundle, thus creating a new blood vessel along the path of the fiber bundle. This fiber bundle may have several forms, it may exist of single or a few fibers that only release VEGF or its substitute, or it may be a tube with VEGF or similar growth factor that is chemotactic for endothelial cells on the inside, and a different factor for smooth muscles on the outside. In this way, the size of the created vessel may be determined. In this application, cells are guided into initially cell-free scaffoldings by cell-specific growth factors.

Example 12

Bone Fracture Healing

In another wound healing embodiment, proteins known to enhance bone fracture healing are loaded into a fiber. This fiber can then be wrapped around the bone at the site of the fracture, releasing the growth factors and enhancing the rate of fracture repair.

These fibers can either be in a helical structure (single or multiple helix), or they may be woven into a loose, open weave. Either in the helical or in the woven format, the fibers are placed around the bone fragments, holding them in place while releasing their growth factors.

In the case of a non-healing fracture that is due to lost or poor blood supply to the fracture site, a fiber or set of fibers containing VEGF or its equivalent may be used to enhance blood supply to the fractured area.

In this embodiment, bone fractures may be healed at accelerated rates compared to non-treated fractures, and non-unions may be healed in certain cases.

Example 13

Skin Ulcer Healing

Similar to example 8 which described one form of dermal wound healing, another important example of this technology is the potential of healing chronic skin ulcers of various origins, such as diabetic foot ulcers, venous ulcers and general pressure sores. These conditions, and potentially other similar conditions may be healed based on creating a non-woven mesh of fibers that release factors known to accelerate dermal wound healing, for example, platelet derived growth factor (PDGF), transforming growth factor-beta (TGF-beta), and VEGF or similar protein. This non-woven mesh can be inserted or packed directly into the ulcer or wound, where these growth factors can help accelerate the wound-healing process. These dressings can be designed for healing dermal sores and ulcers. In this case, there is little need to reduce bleeding; rather one of the biggest needs of these patients, particularly those with diabetic ulcers is lack of blood supply to the wound site. Therefore, factors that induce angiogenesis may be able to increase circulation and help to rejuvenate the tissue at the site of the sore or ulcer.

Each dressing can be designed for the particular needs of the various types of wounds or sores by altering the biomolecules that are released, and the kinetics at which they are released.

Example 14

Muscle Grafts

In another embodiment, parallel arrays of fibers may be loaded with muscle stem cells. These stem cells can be of cardiac, smooth or skeletal muscle origin. Once these muscle stem cells are seeded onto the fiber array, the fibers can be mechanically stretched in vitro to help these cells

align and differentiate properly. Alignment may also be achieved by using fibers of very small diameter. Our experience with axons indicates that with fibers on the order of 50 μm diameter tend to help cells align parallel to the axis of the fibers. Other fibers in this bundle can release angiogenic factors to create a vascular supply for the muscle cells. In the case of skeletal or smooth muscle tissue, fibers for nerve growth can also be included to induce the formation of neuromuscular junctions. Various experimental conditions used to harvest, isolate, reproduce and differentiate these stem cells are known to those skilled in the art, and is not a part of this patent.

Example 15

Alternative Fiber Fabrication Procedure 1

To fabricate small volumes of polymer on the order of 100 μl of polymer solution, the following method has been developed. Create the emulsion as described in example 1. Add this emulsion to a small container, such as a 1 ml FALCON® tube that has been modified by inserting a 20 to 30 gauge needle through the bottom of the tube, 23 gauge being most typical. Place this tube into a modified 50 ml tube that is full of the coagulating bath solvent. Place the tubes in a centrifuge and spin between 500 to 1200 rpm, 700 being most typical. The centrifugal force will push the small volume of polymer emulsion through the needle and into the coagulating fluid. By similar solvent exchanges as described in example 1, a fiber is formed. This method uses substantially less polymer emulsion with very little wasted emulsion.

Example 16

Alternative Fiber Fabrication Procedure 2

As an alternative fabrication procedure, the coagulation solvent(s) are flowed through long vertical tubes at a prescribed rate and the polymer solution is extruded into the flowing stream of coagulation solvent(s). The flow from the tube exits into a bath. The fiber passes over one or more bobbins and is taken from the bath and wound onto a spool. The solvent flow rate, the rate of polymer extrusion, the composition of the polymer solution/emulsion, the composition of the coagulating bath solvent(s), the rate at which the fiber is wound, any drawing that may take place between successive bobbins, and any additional baths or treatments will affect the fiber mechanical and chemical properties as well as the release kinetics of the loaded biological materials.

Example 17

Treatment of Glaucoma

Similar to drug delivery in the eye, described in example 10, and the neural stent described briefly in example 6, glaucoma may be treated by combining an intraocular drug delivery with a neural treatment applied to the optic nerve. Retinal ganglion cells undergo apoptosis leading to death of the axons of the optic nerve. It is hypothesized that if the cells could be supported both within the eye as well as along the path of the optic nerve, the cells may be able to survive. A fiber bundle that releases growth factors such as NT-4, BDNF, CNTF, may be applied topically to the exterior of the optic nerve. Simultaneously, fibers that release apoptosis inhibitors, or factors to support the retinal ganglion cells are implanted within the eye. This combined effort may prolong or save the sight of those suffering from glaucoma.

As is seen from the preceding examples, other tissues, organs, or structures are possible to weave once the basic physiologic structure is understood. This can be extended to organs of the digestive system, musculoskeletal system, urological system, circulatory system, nervous system.

All of the compositions and methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

REFERENCES

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

Aigner, Tegeler, Hutzler, Campoccia, Pavesio, Hammer, Kastenbauer, Naumann, "Cartilage tissue engineering with novel nonwoven structured biomaterial based on hyaluronic acid benzyl ester," *J. of Biomed. Materials Res.*, 42(2):172–81, 1998.

Auerbach and Auerbach, "Angiogenesis inhibition: a review," *Pharmac. Ther.*, 63:265, 1994.

Breitbart, Grande, Kessler, Ryaby, Fitzsimmons, Grant, "Tissue engineered bone repair of calvarial defects using cultured periosteal cells," *Plastic & Reconstructive Surgery*, 101(3):567–74, 1998.

Cao, Rodriguez, Vacanti, Ibarra, Arevalo, Vacanti, "Comparative study of the use of poly(glycolic acid), calcium alginate and pluronics in the engineering of autologous porcine cartilage," *J. of Biomaterials Sci., Polymer Edition*, 9(5):475–87, 1998.

Dillon, Yu, Sridharan, Ranieri, Bellamkonda, "The influence of physical structure and charge on neurite extension in a 3D hydrogel scaffold," *J. of Biomaterials Sci., Polymer Ed.*, 9(10):1049–69, 1998.

Elcin, Dixit, Lewin, Gitnick, "Xenotransplantation of fetal porcine hepatocytes in rats using atissue engineering approach," *Artificial Organs*, 23(2):146–52, 1999.

Fauza, Fishman, Mehegan, Atala, "Videofetoscopically assisted fetal tissue engineering: skin replacement," *J. of Pediatric Surgery*, 33(2):357–61, 1998.

Fidler and Ellis, "The implications of angiogenesis for the biology and therapy of cancer metastasis," *Cell*, 79:185, 1994.

Folkman and Klagsbrun, "Angiogenic factors," *Science*, 235:442–447, 1987.

Folkman, "How is blood vessel growth regulated in normal and neoplastic tissue," *Cancer Res.*, 46:467, 1986.

Folkman, J., "Angiogenesis in cancer, vascular, rheumatoid and other disease," *Nature Med.*, 1:27, 1995.

Grande, Halberstadt, Naughton, Schwartz, Manji, "Evaluation of matrix scaffolds for tissue engineering of articular cartilage grafts," *J. of Biomed. Mat. Res.*, 34(2):211–20, 1997.

Gutsche, Lo, Zurlo, Yager, Leong, "Engineering of a sugar-derivatized porous network for hepatocyte culture," *Biomaterials*, 17(3):387–93, 1996.

Hoerstrup, Zund, Lachat, Schoeberlein, Uhlschmid, Vogt, Turina, "Tissue engineering: a new approach in cardiovascular surgery-seeding of human fibroblasts on resorbable mesh," *Swiss Surgery*, (Suppl.), 2:23–5, 1998.

Hoerstrup, Zund, Schoeberlein, Ye, Vogt, Turina, "Fluorescence activated cell sorting: a reliable method in tissue engineering of a bioprosthetic heart valve," *Annals of Thoracic Surgery*, 665(5):1653–7, 1998.

Isogai, Landis, Kim, Gerstenfeld, Upton, Vacanti, "Formation of phalanges and small joints by tissue-engineering," *J. of Bone & Joint Surgery, American Vol.*, 81(3):306–16, 1999.

Martin, Padera, Vunjak-Novakovic, Freed, "In vitro differentiation of chick embryo bone marrow stromal cells into cartilaginous and bone-like tissues," *J. of Orthopaedic Res.*, 16(2):181–9, 1998.

Nagy et al., "Pathogenesis of ascites tumor growth: vascular permeability factor, vascular hyperpermeability, and ascites fluid accumulation," *Cancer Res.*, 55:360, 1995.

Peppas and Langer, "New challenges in biomaterials," *Science*, 263:1715–1720, 1994.

Peter, Miller, Yasko, Yaszemski, Mikos, "Polymer concepts in tissue engineering," *J. of Biomed. Materials Res.*, 43(4):422–7, 1998.

Sacks, Chuong, Petroll, Kwan, Halberstadt, "Collagen fiber architecture of a cultured dermal tissue," *J. of Biomed. Engineering*, 119(1):124–7, 1997. Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989.

Shinoka, Shum-Tim, Ma, Tanel, Isogai, Langer, Vacanti, Mayer, "Creation of viable pulmonary artery autografts through tissue engineering," *J. of Thoracic & Cardiovascular Surgery*, 115(3):536–45, 1998.

Sims, Butler, Cao, Casanova, Randolph, Black, Vacanti, Yaremchuk, "Tissue engineered neocartilage using plasma derived polymer substrates and chondrocytes," *Plastic & Reconstructive Surgery*, 101(6):1580–5, 1998.

Vunjak-Novakovic, Obradovic, Martin, Bursac, Langer, Freed, "Dynamic cell seeding of polymer scaffolds for cartilage tissue engineering," *Biotechnology Progress*, 14(2):193–202, 1998.

Whang, Tsai, Nam, Aitken, Sprague, Patel, Healy, "Ectopic bone formation via rhBMP-2 delivery from porous bioabsorbably polymer scaffolds," *J. of Biomed. Materials Res.*, 42(4):491–9, 1998.

Wong and Mooney, "Synthesis and properties of biodegradable polymers used in tissue engineering," In: *Synthetic Biodegradable Polymer Scaffolds*, (Atala and Mooney, eds.), Birkhauser Press, Boston, Mass., pp. 51–82, 1997.

Yoo and Atala, "A novel gene delivery system using urothelial tissue engineered neoorgans," *J. of Urology*, 158(3 Pt 2):1066–70, 1997.

What is claimed is:

1. A composition comprising at least one biodegradable polymer fiber wherein said fiber is composed of a first phase and a second phase, the first and second phases being immiscible, and wherein the second phase comprises one or more therapeutic agents.

2. The composition of claim **1**, wherein said second phase is derived from an aqueous solution, a hydrogel or polymer.

3. The composition of claim **1**, wherein said fiber forms a scaffold and further wherein, said second phase is manipulated to form an internal porous structure within the fiber.

4. The composition of claim **1**, wherein said fiber is woven, braided or knitted in an assembly with other fibers, and at least one fiber in the assembly comprises one or more therapeutic agents.

5. The composition of claim **1**, wherein the one or more therapeutic agents are distributed within the second phase in a nonhomogenous pattern.

6. The composition of claim **1**, wherein the concentration of said one or more therapeutic agents varies along the longitudinal axis of the fiber.

7. The composition of claim **6**, wherein the concentration of said one or more therapeutic agents varies linearly, exponentially or in any desired fashion, as a function of distance along the longitudinal axis of the fiber.

8. The composition of claim **1**, wherein the concentration of said one or more therapeutic agents decreases from a first end of the fiber to a second end of the fiber.

9. The composition of claim **1**, wherein said one or more therapeutic agents vary in a bidirectional manner, and the content of said one or more therapeutic agents increases from the first end of said fiber to a maximum and then decreases towards the second end of said fiber.

10. The composition of claim **1**, further comprising at least one biodegradable polymer fiber containing no therapeutic agent.

11. The composition of claim **1**, wherein said one or more therapeutic agents are selected from the group consisting of drugs, proteins, enzymes, growth factors, immunomodulators, compounds promoting angiogenesis, compounds inhibiting angiogenesis, anti-inflammatory compounds, antibiotics, cytokines, anti-coagulation agents, procoagulation agents, chemotactic agents, agents to promote apoptosis, agents to inhibit apoptosis, and mitogenic agents.

12. The composition of claim **1**, wherein said one or more therapeutic agents include a radioactive agent or a contrast agent for imaging studies.

13. The composition of claim **1**, wherein said one or more therapeutic agents is selected from the group consisting of viral vector, polynucleotide and polypeptide.

14. The composition of claim **1**, wherein said one or more therapeutic agents comprise an angiogenesis-promoting agent.

15. The composition of claim **14**, wherein said angiogenesis-promoting agent is vascular endothelial growth factor.

16. The composition of claim **1**, wherein said biodegradable polymer is a single polymer, a co-polymer, or a mixture of polymers selected from the group consisting of polypeptides, polydepsipeptides, nylon copolyamides, aliphatic polyesters, polydihydropyrans, polyphosphazenes, poly(ortho ester), poly(cyano acrylates), polyanhydride, modified polysaccharides and modified proteins.

17. The composition of claim **16**, wherein said aliphatic polyesters are selected from the group consisting of poly (glycolic acid), poly(lactic acid), poly(alkylene succinates) poly(hydroxybutyrate), poly(butylene diglycolate), poly (epsilon-caprolactone) and copolymers, blends and mixtures thereof.

18. The composition of claim **16**, wherein said modified polysaccharides are selected from the group consisting of cellulose, starch-alginate and the glycosaminoglycans, chondroitin sulfate, heparin, heparin sulfate, dextran, dextran sulfate, chitin, chitosan and chitosan sulfate.

19. The composition of claim **16**, wherein said modified proteins are selected from the group consisting of collagen and fibrin.

20. The composition of claim **1**, wherein said fiber comprises a plurality of polymer layers, wherein an outer layer circumscribes an adjacent inner layer.

21. The composition of claim **20**, wherein said plurality of layers optionally contain one or more therapeutic agents.

22. The composition of claim **21**, wherein said one or more therapeutic agents are released over time from said plurality of layers.

23. The composition of claim **1**, wherein the fiber contains more than one therapeutic agent along its length.

24. The composition of claim **23**, wherein the concentration of said more than one therapeutic agent varies along the length of said subset of fibers.

25. The composition of claim **23**, wherein said more than one therapeutic agents are released at varying rates over time from said fiber.

26. The composition of claim **1**, wherein said one or more therapeutic agents are released at varying rates over time from said fiber.

27. A composition comprising a three-dimensional scaffold, said scaffold comprising fibers that are woven, non-woven, or knitted, or braided, wherein said fibers comprise fibers containing chitosan or a reconstituted extracellular matrix composition.

28. The composition of claim **27**, wherein said chitosan is sulfated chitosan.

29. A composition comprising fibers containing chitosan, reconstituted extracellular matrix composition and a therapeutic agent.

30. The composition of claim **29**, wherein said chitosan is sulfated chitosan.

31. The composition of claim **21**, wherein said one or more therapeutic agents are distributed within the plurality of layers in a nonhomogenous pattern.

32. The composition of claim **31**, wherein the concentration of said one or more therapeutic agents varies linearly, exponentially or in any desired fashion, as a function of distance within the plurality of layers.

* * * * *

US007033603B2

(12) **United States Patent**
Nelson et al.

(10) **Patent No.: US 7,033,603 B2**
(45) **Date of Patent: *Apr. 25, 2006**

(54) **DRUG RELEASING BIODEGRADABLE FIBER FOR DELIVERY OF THERAPEUTICS**

(75) Inventors: **Kevin D. Nelson**, Arlington, TX (US); **Brent B. Crow**, Fort Worth, TX (US)

(73) Assignee: **Board of Regents The University of Texas**, Austin, TX (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 54 days.

This patent is subject to a terminal disclaimer.

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(22) Filed: **May 2, 2003**

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Related U.S. Application Data

(63) Continuation-in-part of application No. 09/632,457, filed on Aug. 4, 2000, now Pat. No. 6,596,296.

(60) Provisional application No. 60/147,827, filed on Aug. 6, 1999.

(51) **Int. Cl.**
A61F 2/02 (2006.01)
A61K 47/30 (2006.01)

(52) **U.S. Cl.** **424/426**; 514/772.3

(58) **Field of Classification Search** 424/426; 514/772.3

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,464,321	A	8/1984	Pittalis et al.	264/83
4,965,128	A	10/1990	Greidanus et al.	428/398
5,166,187	A	11/1992	Collombel et al.	514/21
5,263,984	A	11/1993	Li et al.	623/15
5,270,300	A	12/1993	Hunziker	514/12
5,290,271	A	3/1994	Jernberg	604/891.1
5,342,348	A	8/1994	Kaplan	605/891.1
5,567,612	A	10/1996	Vacanti et al.	435/240.23
6,596,296	B1 *	7/2003	Nelson et al.	424/426

FOREIGN PATENT DOCUMENTS

EP	0 328 050 A2	8/1989
WO	WO 98/20190	5/1998
WO	WO 00/47716	8/2000

OTHER PUBLICATIONS

Aigner et al., "Cartilage tissue engineering with novel nonwoven structured biomaterial based on hyaluronic acid benzyl ester," *J. of Biomed. Materials Res.*, 42(2):172-81, 1998.

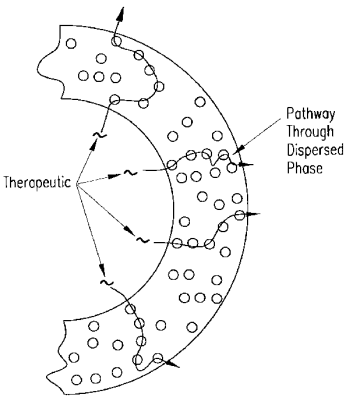
(Continued)

Primary Examiner—Carlos A. Azpuru
(74) *Attorney, Agent, or Firm*—Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

The present invention relates to fiber compositions comprising gels or hydrogels. The invention further relates to the composition of a gel or hydrogel loaded biodegradable fiber and methods of fabricating such fibers. The present invention further provides tissue engineering and drug-delivery compositions and methods wherein three-dimensional matrices for growing cells are prepared for in vitro and in vivo use. The invention also relates to methods of manipulating the rate of therapeutic agent release by changing both the biodegradable polymer properties as well as altering the properties of the incorporated gel or hydrogel.

34 Claims, 11 Drawing Sheets



OTHER PUBLICATIONS

Auerbach and Auerbach, "Angiogenesis inhibition: a review," *Pharmac. Ther*., 63:265, 1994.
Breitbart et al., "Tissue engineered bone repair of calvarial defects using cultured periosteal cells," *Plastic & Reconstructive Surgery*, 101(3):567-74, 1998.
Cao et al., "Comparative study of the use of poly(glycolic acid), calcium alginate and pluronics in the engineering of autologous porcine cartilage," *J. of Biomaterials Sci., Polymer Edition*, 9(5):475-87, 1998.
Dillon et al., "The influence of physical structure and charge on neurite extension in a 3D hydrogel scaffold," *J. of Biomaterials Sci., Polymer Ed*., 9(10):1049-69, 1998.
Elcin et al., "Xenotransplantation of fetal porcine hepatocytes in rats using a tissue engineering approach," *Artificial Organs*, 23(2):146-52, 1999.
Fidler and Ellis, "The implications of angiogenesis for the biology and therapy of cancer metastasis," *Cell*, 79:185, 1994.
Folkman and Klagsbrun, "Angiogenic factors," *Science*, 235:442-447, 1987.
Folkman, "How is blood vessel growth regulated in normal and neoplastic tissue," *CancerRes*., 46:467, 1986.
Folkman, J., "Angiogenesis in cancer, vascular, rheumatoid and other disease," *NatureMed*., 1:27, 1995.
Grande et al., "Evaluation of matrix scaffolds for tissue engineering of articular cartilage grafts," *J. of Biomed. Mat. Res*., 34(2):211-20, 1997.
Gutsche et al., "Engineering of a sugar-derivatized porous network for hepatocyte culture," *Biomaterials*, 17(3):387-93, 1996.
Hoerstrup et al., "Tissue engineering: a new approach in cardiovascular surgery-seeding of human fibroblasts on resorbable mesh," *Swiss Surgery*, (Suppl.), 2:23-5, 1998.
Hoerstrup et al., " Fluorescence activated cell sorting: a reliable method in tissue engineering of a bioprosthetic heart valve," *Annals of Thoracic Surgery*, 665(5):1653-7, 1998.
Isogai et al., "Formation of phalanges and small joints by tissue-engineering," *J. of Bone & Joint Surgery, American* vol., 81(3):306-16, 1999.
Martin et al., "In vitro differentiation of chick embryo bone marrow stromal cells into cartilaginous and bone-like tissues," *J. of Orthopaedic Res*., 16(2):181-9, 1998.
Nagy et al., "Pathogenesis of ascites tumor growth: vascular permeability factor, vascular hyperpermeability, and ascites fluid accumulation," *Cancer Res*., 55:360, 1995.
Peppas and Langer, "New challenges in biomaterials," *Science*, 263:1715-1720, 1994.
Peter et al., "Polymer concepts in tissue engineering," *J. of Biomed. Materials Res*., 43(4):422-7, 1998.
Sacks et al., "Collagen fiber architecture of a cultured dermal tissue," *J. of Biomed. Engineering*, 119(1):124-7, 1997.
Shinoka et al., "Creation of viable pulmonary artery autografts through tissue engineering," *J. of Thoracic & Cardiovascular Surgery*, 115(3):536-45, 1998.
Sims et al., "Tissue engineered neocartilage using plasma derived polymer substrates and chondrocytes," *Plastic & Reconstructive Surgery*, 101(6):1580-5, 1998.
Vunjak-Novakovic et al., "Dynamic cell seeding of polymer scaffolds for cartilage tissue engineering," *Biotechnology Progress*, 14(2):193-202, 1998.
Whang et al., "Ectopic bone formation via rhBMP-2 delivery from porous bioabsorbably polymer scaffolds," *J. of Biomed. Materials Res*., 42(4):491-9, 1998.
Wong and Mooney, "Synthesis and properties of biodegradable polymers used in tissue engineering," *In: Synthetic Biodegradable Polymer Scaffolds*, (Atala and Mooney, eds.), Birkhauser Press, Boston, MA, pp. 51-82, 1997.
Yoo and Atala, "A novel gene delivery system using urothelial tissue engineered neoorgans," *J. of Urology*, 158(3 Pt 2):1066-70, 1997.
Fauza et al., "Videofetoscopically assisted fetal tissue engineering: skin replacement," *J. of Pediatric Surgery*, 33(2):357-61, 1998.

* cited by examiner

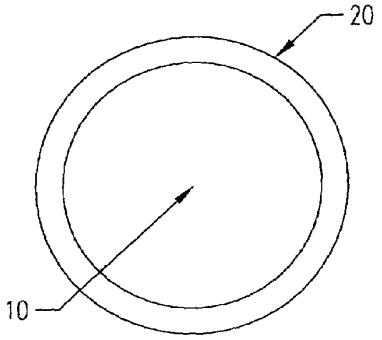


FIG. 1A

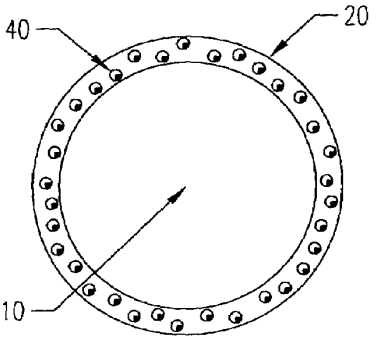


FIG. 1C

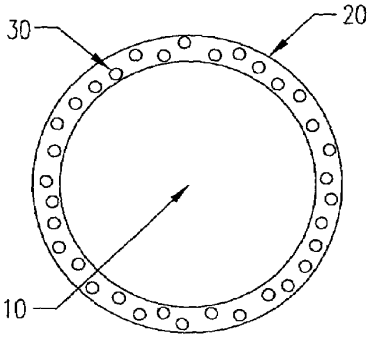


FIG. 1B

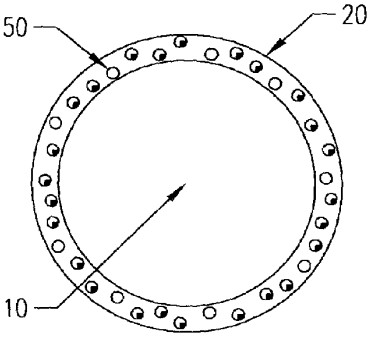


FIG. 1D

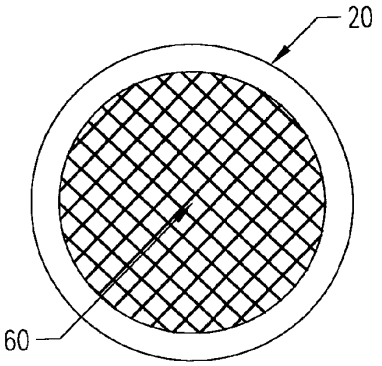


FIG. 2A

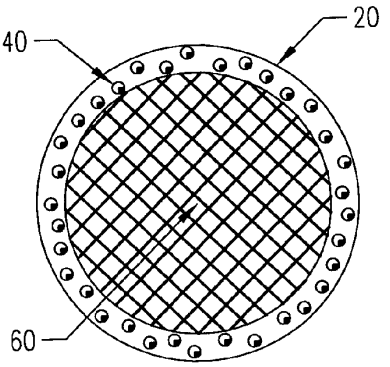


FIG. 2C

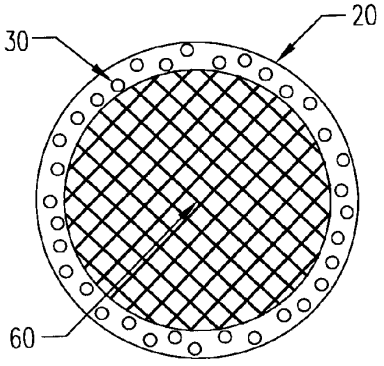


FIG. 2B

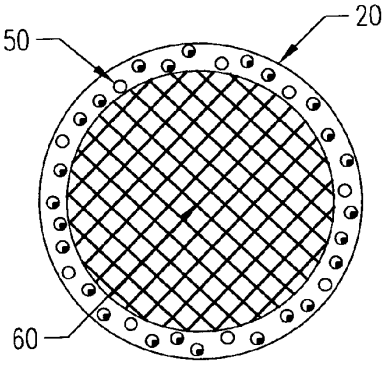


FIG. 2D

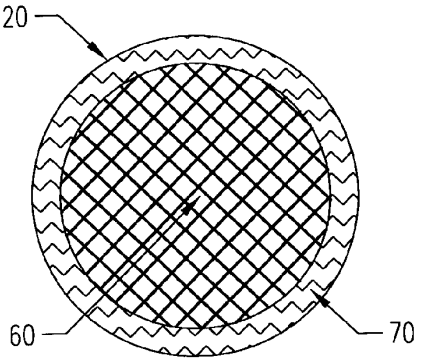


FIG. 3A

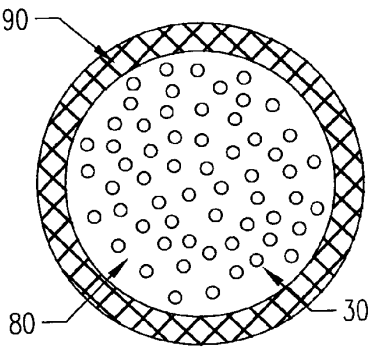


FIG. 3C

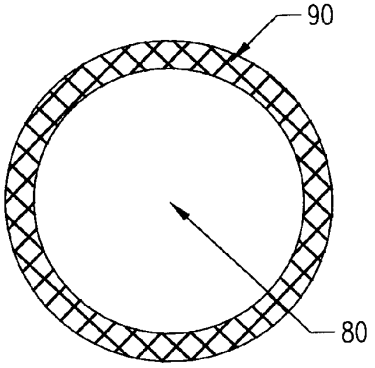


FIG. 3B

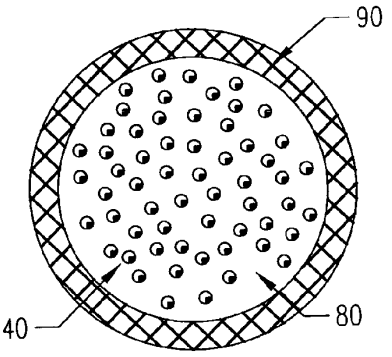


FIG. 3D

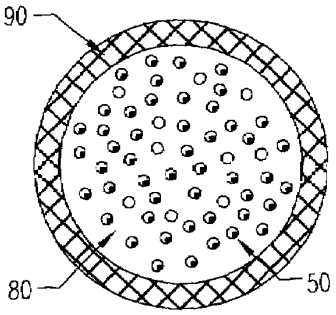


FIG. 4A

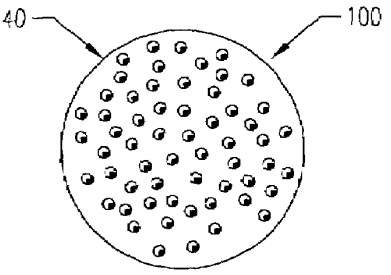


FIG. 4C

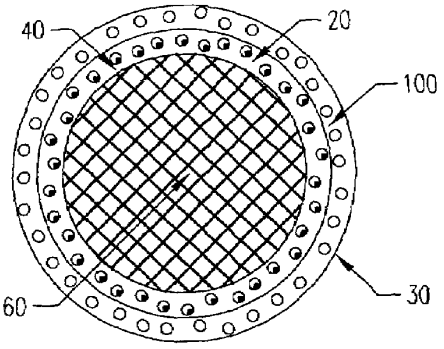


FIG. 4B

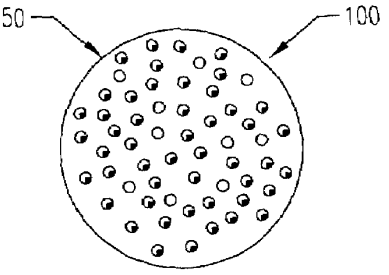


FIG. 4D

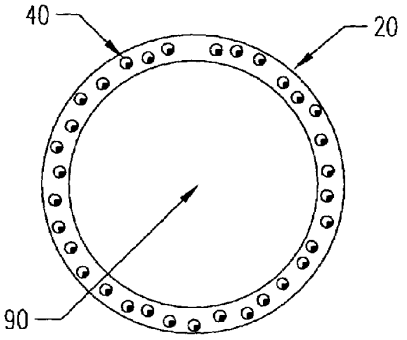


FIG. 5A

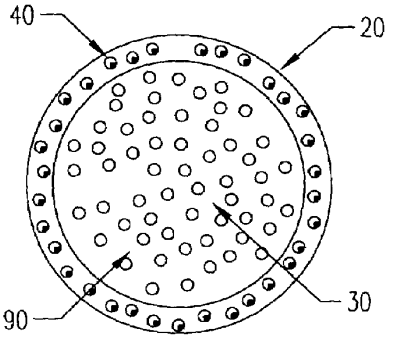


FIG. 5C

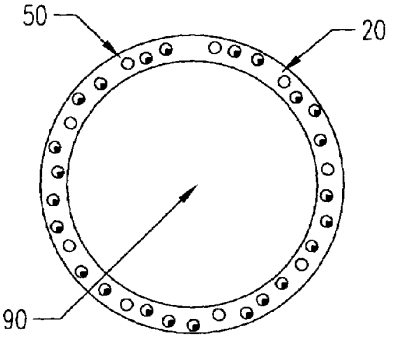


FIG. 5B

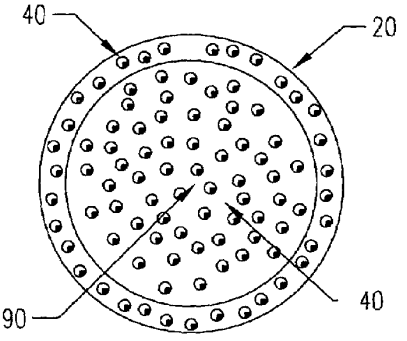


FIG. 5D

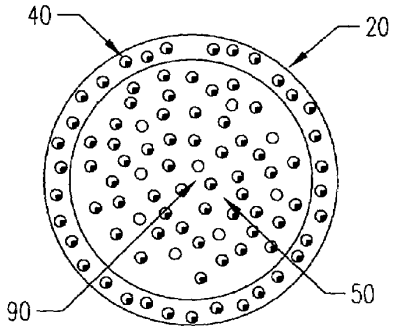


FIG. 6A

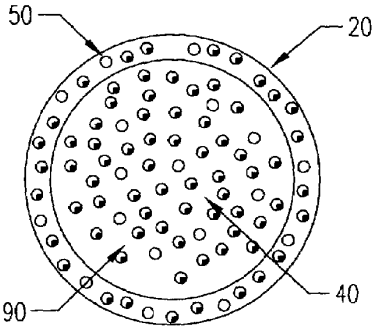


FIG. 6C

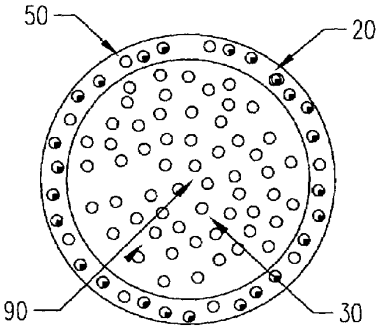


FIG. 6B

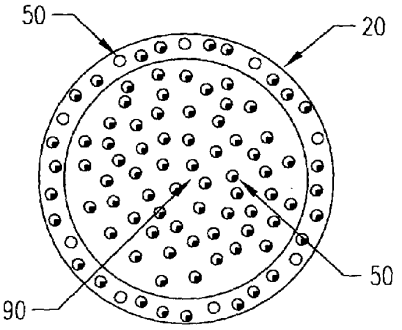


FIG. 6D

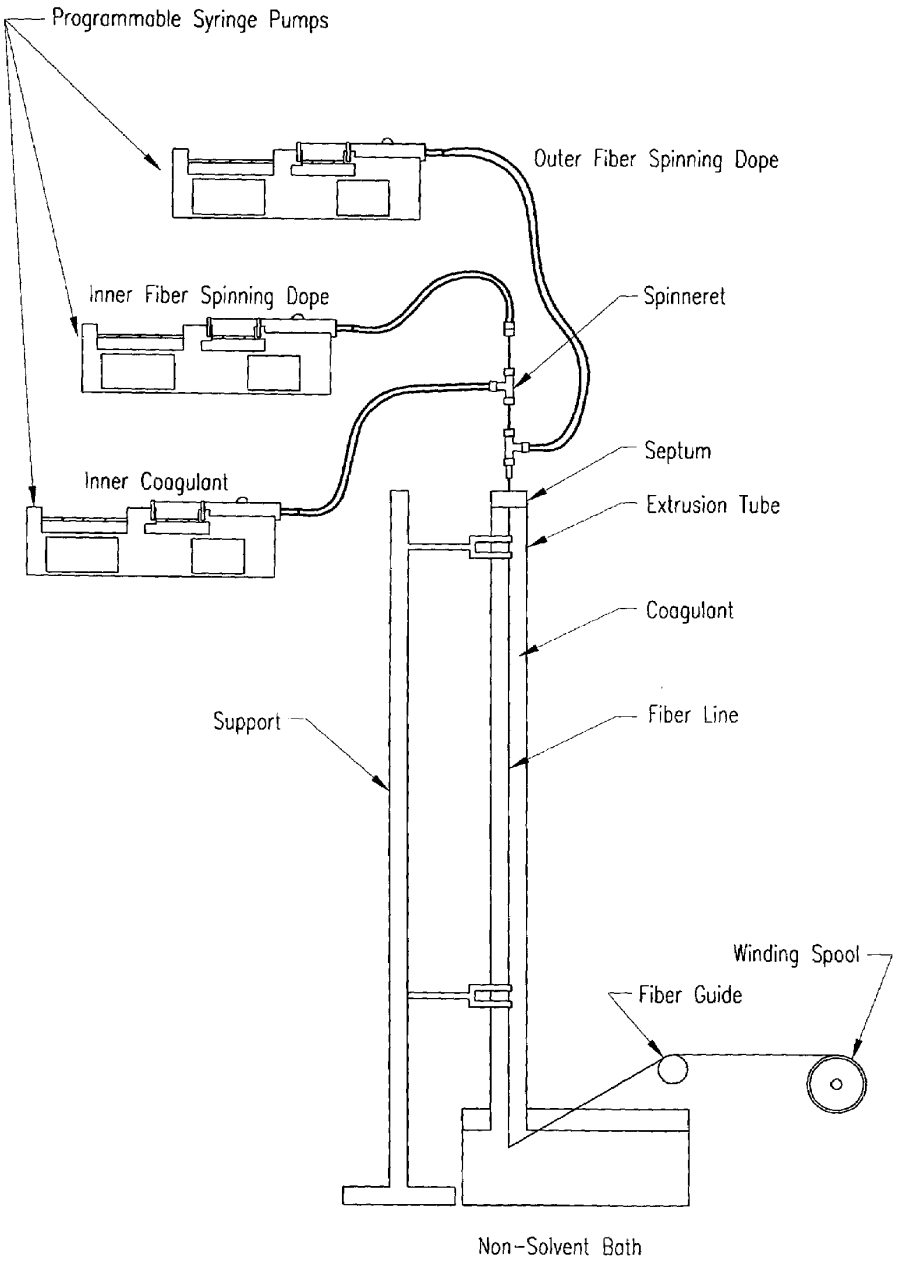

Programmable Syringe Pumps
Outer Fiber Spinning Dope
Inner Fiber Spinning Dope
Spinneret
Septum
Inner Coagulant
Extrusion Tube
Coagulant
Support
Fiber Line
Winding Spool
Fiber Guide
Non-Solvent Bath

FIG. 7

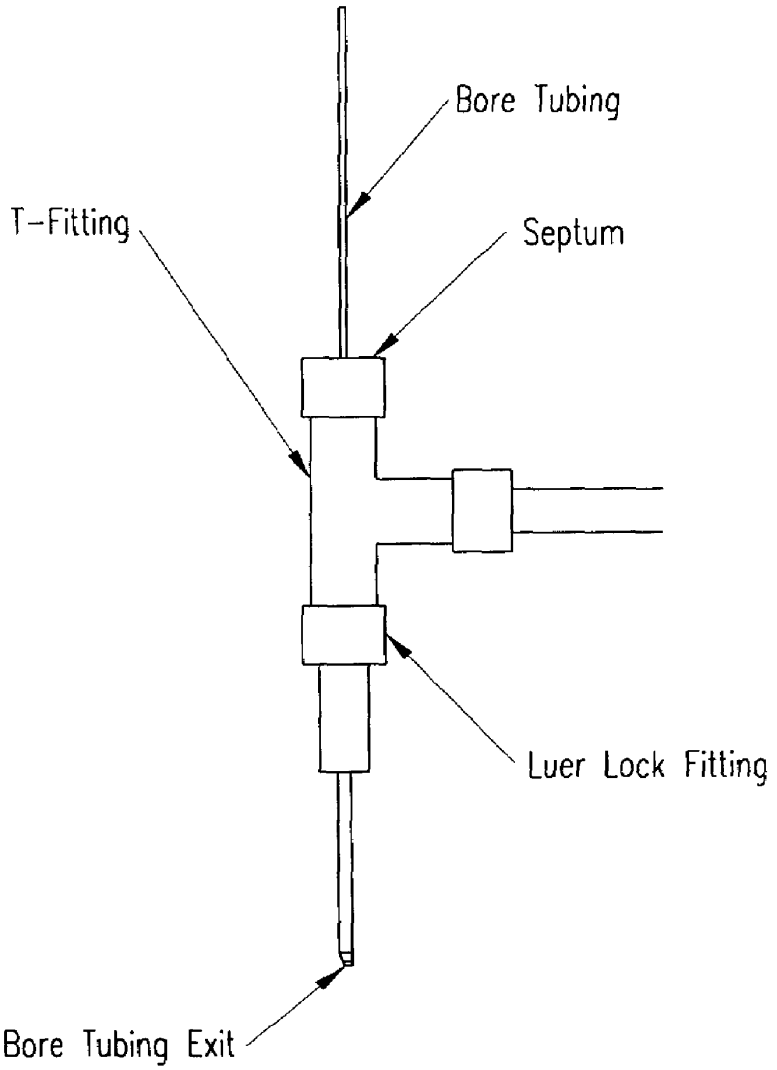

Bore Tubing
T-Fitting
Septum
Luer Lock Fitting
Bore Tubing Exit

FIG. 8

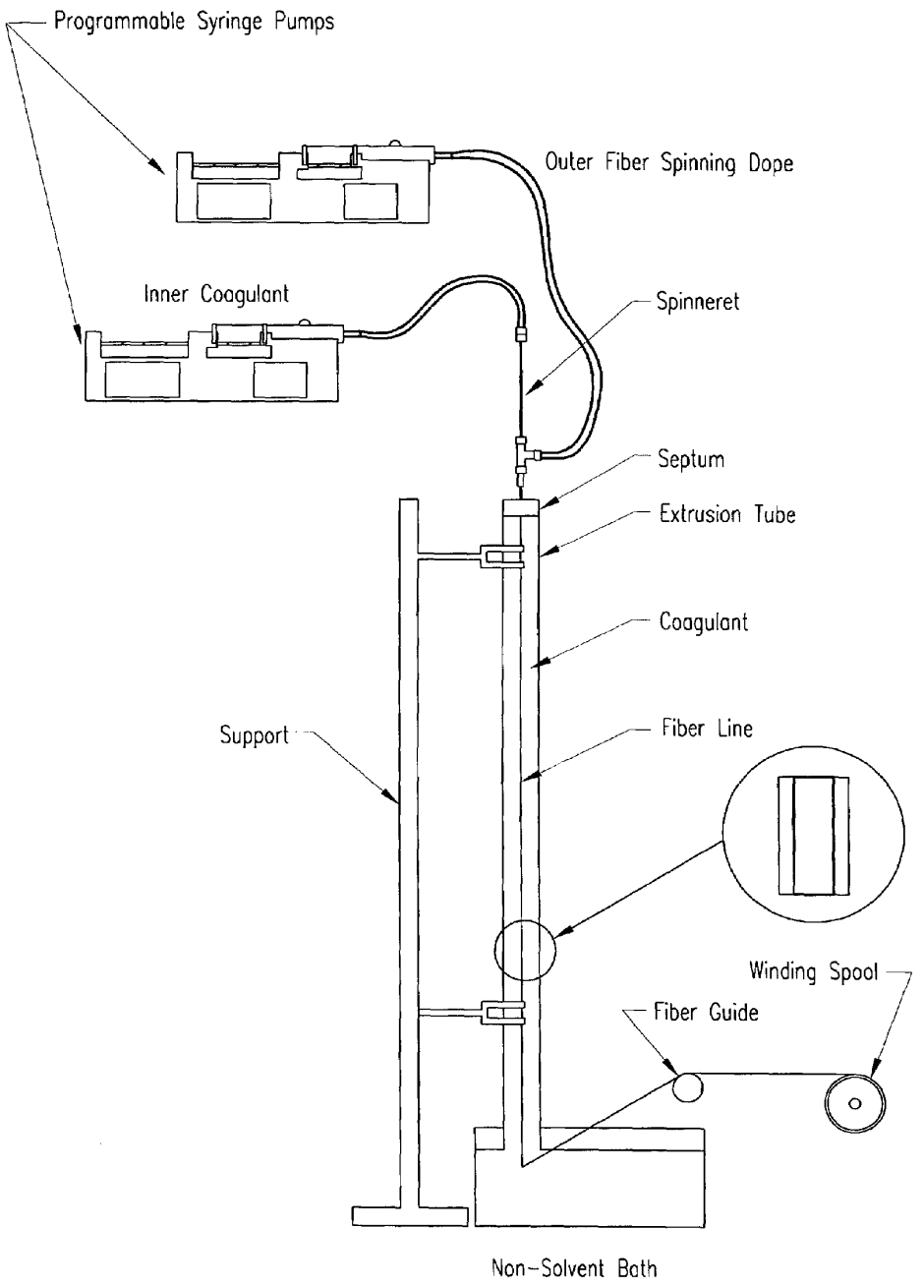

Programmable Syringe Pumps
Outer Fiber Spinning Dope
Inner Coagulant
Spinneret
Septum
Extrusion Tube
Coagulant
Support
Fiber Line
Winding Spool
Fiber Guide
Non-Solvent Bath

FIG. 9

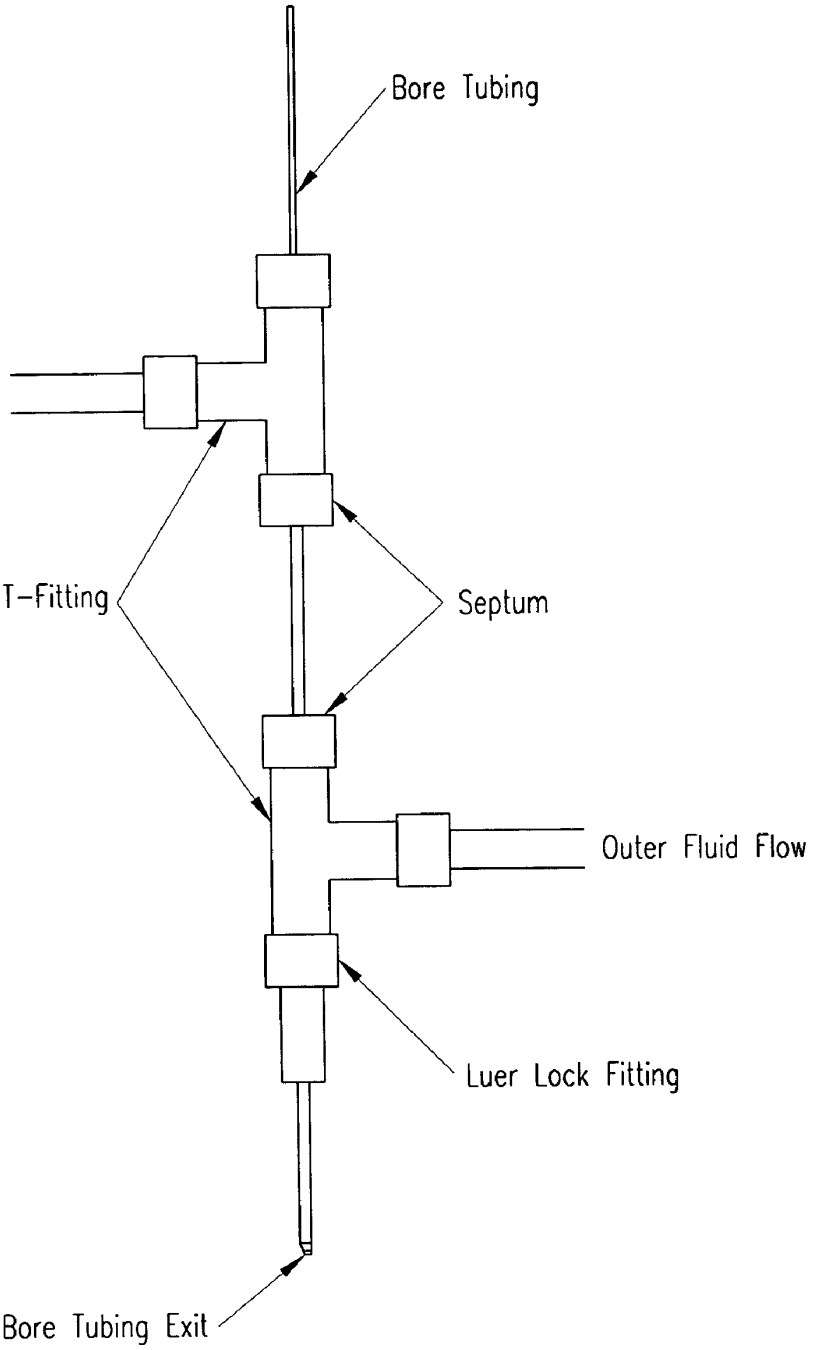

Bore Tubing
T-Fitting
Septum
Outer Fluid Flow
Luer Lock Fitting
Bore Tubing Exit

FIG. 10

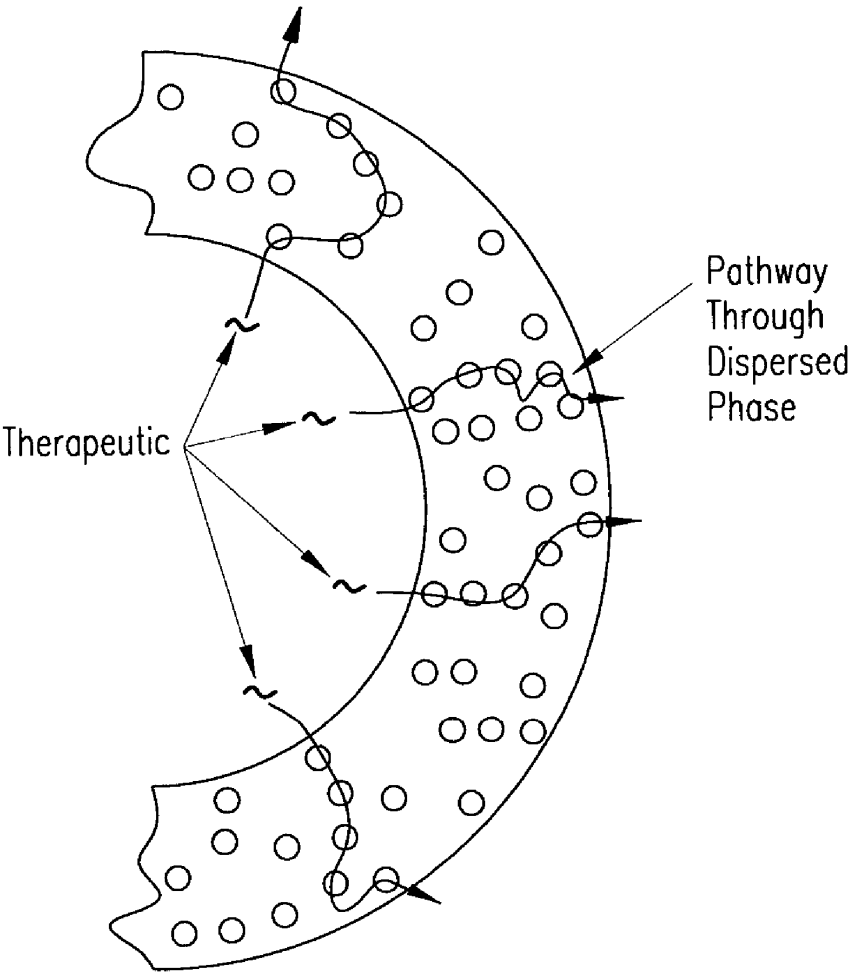


FIG. 11

DRUG RELEASING BIODEGRADABLE FIBER FOR DELIVERY OF THERAPEUTICS

CROSS REFERENCES TO RELATED APPLICATIONS

This application is a continuation-in-part of application Ser. No. 09/632,457, filed Aug. 4, 2000 now U.S. Pat. No. 6,596,296, which claims the benefit of U.S. Provisional Application No. 60/147,827, filed Aug. 6, 1999.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to the field of medicine and tissue engineering, and in particular to drug releasing biodegradable fibers used in the delivery of therapeutics.

2. Description of Related Art

Tissue engineering is a discipline wherein living cells are used to replace cells lost as a result of injury, disease, or birth defect in an animal or human. These replacement cells can be autologous, allogenic, or xenogenic. The field of tissue engineering is a new area of medicine and optimal procedures have yet to be elucidated.

At present, there are several avenues for engineering tissues. One avenue is to harvest cells from a healthy donor, preferably from the same individual, or at least from an appropriate donor of the same species, and grow those cells on a scaffold in vitro. This scaffold is typically a three-dimensional polymer network, often composed of biodegradable fibers. Cells adherent to the polymer network can then typically be induced to multiply. This cell filled scaffold can be implanted into the impaired host with the goal that the cells will perform their physiological function and avoid destruction by the host immune system. To this end, it is important that purified cell lines are used, as the introduction of non-self immune cells can up-regulate a strong host immune attack. The difficulty with this approach is the scaffolding must be small, as no cell can survive more than a couple millimeters away from a source of oxygen and nutrients. Therefore, large scaffolds cannot be used, as the scaffold will not vascularize adequately in time to save the cells in the interior regions.

In another approach, an empty three-dimensional, biodegradable polymer scaffold is directly implanted in the patient, with the goal of inducing the correct type of cells from the host's body to migrate into the polymer scaffold. The benefit is that vascularization can happen simultaneously with migration of cells into the matrix. A major problem is that there is currently no way to ensure that the appropriate cell types will migrate into the scaffold, and that the mechanical and biological properties will be maintained to provide the patient's physiological need.

In both of the above approaches, the scaffold may be biodegradable, meaning that over time it will break down both chemically and mechanically. As this break down occurs, the cells secrete their own extracellular matrix, which plays a critical role in cell survival and function. In normal tissue, there is an active and dynamic reciprocal exchange between the constitutive cells of the tissue and the surrounding extracellular matrix. The extracellular matrix provides chemical signals that regulate the morphological properties and phenotypic traits of cells and may induce division, differentiation or even cell death. In addition, the cells are also constantly rearranging the extracellular matrix. Cells both degrade and rebuild the extracellular matrix and secrete chemicals into the matrix to be used later by themselves or other cells that may migrate into the area. It has also been discovered that the extracellular matrix is one of the most important components in embryological development. Pioneering cells secrete chemical signals that help following cells differentiate into the appropriate final phenotype. For example, such chemical signals cause the differentiation of neural crest cells into axons, smooth muscle cells or neurons.

The integrated relationship between extracellular matrix and tissue cells establishes the extracellular matrix as an important parameter in tissue engineering. If cells are desired to behave in a specific manner, then the extracellular matrix must provide the appropriate environment and appropriate chemical/biological signals to induce that behavior for that cell type. Currently it is not possible to faithfully reproduce a biologically active extracellular matrix. Consequently, some investigators use a biodegradable matrix that enables the cells to create their own extracellular matrix as the exogenous matrix degrades.

In the above-described approaches to tissue engineering, a polymer scaffold provides not only the mechanical support, but also the three-dimensional shape that is desired for the new tissue or organ. Because cells must be close to a source of oxygen and nutrients in order to survive and function, a major current limitation is that of blood supply. Most current methodologies provide no specific means of actively assisting the incorporation of blood vessels into and throughout the polymer matrix. This places limitations on the physical size and shape of the polymer matrix. The only current tissue-engineering device that has made it into widespread clinical use is artificial skin, which by definition is of limited thickness. The present invention provides compositions and methods that promote the directed migration of appropriate cell types into the engineered extracellular matrix. By directing specific three-dimensional cell migration and functional patterns, directed vascularization can be induced, which overcomes the current limitations on the shape and size of polymer implants. It also ensures that appropriate cell types will be physically located in specific locations within the matrix. Compositions and methods are provided to modulate phenotypic expression as a function of both time and space.

Most of the drug delivery from polymeric drug-loaded vehicles is based on the following formats: microspheres, nano-particles, foams, films, liposomes, polymeric micelles, or viral packages. There are a number of inherent disadvantages with respect to the above mentioned formats. Several of the above mentioned drug delivery formats do not remain in place after they have been implanted. As a result retrieval of the implant is not possible in the case of an adverse reaction to the implant. Additionally, these formats display high surface area per unit volume, which leads to quick drug release times, a feature that is antithetical to the goal of drug delivery. Furthermore, the amount of drug that can be loaded into the above mentioned formats is somewhat limited. Some of these formats cannot be used in conditions which in addition to drug delivery, also require mechanical support.

The present invention provides a fiber composition that does not possess the disadvantages of the drug delivery formats known in the prior art.

SUMMARY OF THE INVENTION

The present invention relates to fiber compositions comprising gels or hydrogels. The invention further relates to the composition of a gel or hydrogel loaded biodegradable fiber and methods of fabricating such fibers. The present inven-

tion further provides tissue engineering and drug-delivery compositions and methods wherein three-dimensional matrices for growing cells are prepared for in vitro and in vivo use. The invention also relates to methods of manipulating the rate of therapeutic agent release by changing both the biodegradable polymer properties as well as altering the properties of the incorporated gel or hydrogel.

An embodiment of the invention provides a drug delivery composition comprising at least one fiber, wherein said fiber comprises a first component and a second component, and wherein said first component is a biodegradable polymer and said second component is selected from the group consisting of a gel and a hydrogel. Another embodiment of the invention provides a drug delivery composition comprising a fiber, wherein said fiber comprises a first component and a second component, and wherein said first component is a biodegradable polymer and said second component is water, and further wherein said water is present as an inner core. A further embodiment of the invention provides a drug delivery composition comprising a fiber, wherein said fiber comprises an emulsion consisting essentially of a gel or hydrogel. An embodiment of the invention provides drug delivery composition comprising a fiber, wherein said fiber comprises a first component, and wherein said first component is a gel or hydrogel and further wherein said fiber comprises a hollow bore. An embodiment of the invention provides a scaffold composition comprising one or more fibers, wherein said fibers comprise a first component and a second component, and wherein said first component is a biodegradable polymer and said second component is selected from the group consisting of a gel and a hydrogel. Embodiments of the invention also provide methods of manufacturing the fibers of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein. The drawings are not intended to limit the scope of the invention.

FIG. **1**A depicts a bicomponent fiber with a water bore (**10**) and a wall comprising a hydrophobic polymer (**20**).

FIG. **1**B depicts a bicomponent fiber with a water bore (**10**), a wall comprising a hydrophobic polymer (**20**) and a water emulsion (**30**).

FIG. **1**C depicts a bicomponent fiber with a water bore (**10**), a wall comprising a hydrophobic polymer (**20**), and a gel or hydrogel emulsion (**40**).

FIG. **1**D depicts a bicomponent fiber with a water bore (**10**), a wall comprising a hydrophobic polymer (**20**), and both water and gel or hydrogel emulsions (**50**).

FIG. **2**A depicts a bicomponent fiber with a gel or hydrogel bore (**60**) and a wall comprising a hydrophobic polymer (**20**).

FIG. **2**B depicts a bicomponent fiber with a gel or hydrogel bore (**60**), a wall comprising a hydrophobic polymer (**20**), and a water emulsion (**30**).

FIG. **2**C depicts a bicomponent fiber with a gel or hydrogel bore (**60**), a wall comprising a hydrophobic polymer (**20**), and a gel or hydrogel emulsion (**40**).

FIG. **2**D depicts a bicomponent fiber with a gel or hydrogel bore (**60**), a wall comprising a hydrophobic polymer (**20**) and both water emulsions and gel or hydrogel emulsions (**50**).

FIG. **3**A depicts a bicomponent fiber with a gel or hydrogel bore (**60**) and a wall comprising a hydrophobic polymer (**20**) that comprises a drug (**70**).

FIG. **3**B depicts a bicomponent fiber with a polymer bore (**80**) surrounded by a gel or hydrogel wall (**90**).

FIG. **3**C depicts a bicomponent fiber with a polymer bore (**80**) comprising a water emulsion (**30**) that is surrounded by a gel or hydrogel wall (**90**).

FIG. **3**D depicts a bicomponent fiber with a polymer bore (**80**) comprising a gel or hydrogel emulsion (**40**) that is surrounded by a gel or hydrogel wall (**90**).

FIG. **4**A depicts a bicomponent fiber with a polymer bore (**80**) comprising a water emulsion and a gel or hydrogel emulsion (**50**) that is surrounded by a gel or hydrogel wall (**90**).

FIG. **4**B depicts a multicomponent fiber with a gel or hydrogel bore (**60**) surrounded by two hydrophobic polymer walls (**20** and **100**), with the outer polymer wall comprising a water emulsion (**30**) and the inner polymer wall comprising a gel or hydrogel emulsion (**40**).

FIG. **4**C depicts a monofilament fiber comprising a hydrophobic polymer (**100**) and a gel or hydrogel emulsion (**40**).

FIG. **4**D depicts a monofilament fiber comprising a hydrophobic polymer (**100**) and a water emulsion and a gel or hydrogel emulsion (**50**).

FIG. **5**A depicts a bicomponent fiber with a hydrophobic polymer bore (**90**), and a wall comprising a hydrophobic polymer (**20**) that comprises a gel or hydrogel emulsion (**40**).

FIG. **5**B depicts a bicomponent fiber with a hydrophobic polymer bore (**90**) and a wall comprising a hydrophobic polymer (**20**) comprising a water emulsion and a gel or hydrogel emulsion (**50**).

FIG. **5**C depicts a bicomponent fiber with a hydrophobic polymer bore (**90**) comprising a water emulsion (**30**) and a wall comprising a hydrophobic polymer (**20**) that comprises a gel or hydrogel emulsion (**40**).

FIG. **5**D depicts a bicomponent fiber with a hydrophobic polymer bore (**90**) comprising a gel or hydrogel emulsion (**40**) and a wall comprising a hydrophobic polymer (**20**) that comprises a gel or hydrogel emulsion (**40**).

FIG. **6**A depicts a bicomponent fiber with a hydrophobic polymer bore (**90**) comprising a water emulsion and a gel or hydrogel emulsion (**50**) and a wall comprising a hydrophobic polymer (**20**) that comprises a gel or hydrogel emulsion (**40**).

FIG. **6**B depicts a bicomponent fiber with a hydrophobic polymer bore (**90**) comprising a water emulsion (**30**) and a wall comprising a hydrophobic polymer (**20**) that comprises a water emulsion and a gel, or hydrogel emulsion (**50**).

FIG. **6**C depicts a bicomponent fiber with a hydrophobic polymer bore (**90**) comprising a gel or hydrogel emulsion (**40**) and a wall comprising a hydrophobic polymer (**20**) comprises a water emulsion and a gel or hydrogel emulsion (**50**).

FIG. **6**D depicts a bicomponent fiber with a hydrophobic polymer bore (**90**) comprising both water and gel or hydrogel emulsions (**50**) and a wall comprising a hydrophobic polymer (**20**) comprising both water and gel or hydrogel emulsions (**50**).

FIG. **7** depicts a wet extrusion apparatus used to extrude fibers of the invention.

FIG. **8** depicts a spinneret used in the present invention.

FIG. **9** depicts a triple apparatus used in the extrusion of fibers of the invention.

FIG. **10** depicts a triple spinneret used in the manufacture of multicomponent fibers.

FIG. **11** depicts the flow of a therpeutic through the walls of an emulsion-loaded fiber.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

An embodiment of the invention provides a drug delivery composition comprising at least one fiber, wherein said fiber comprises a first component and a second component, and wherein said first component is a biodegradable polymer and said second component is selected from the group consisting of a gel and a hydrogel. Another embodiment of the invention provides a drug delivery composition comprising a fiber, wherein said fiber comprises a first component and a second component, and wherein said first component is a biodegradable polymer and said second component is water, and further wherein said water is present as an inner core. A further embodiment of the invention provides a drug delivery composition comprising a fiber, wherein said fiber comprises an emulsion consisting essentially of a gel or hydrogel. An embodiment of the invention provides drug delivery composition comprising a fiber, wherein said fiber comprises a first component, and wherein said first component is a gel or hydrogel and further wherein said fiber comprises a hollow bore. An embodiment of the invention provides a scaffold composition comprising one or more fibers, wherein said fibers comprise a first component and a second component, and wherein said first component is a biodegradable polymer and said second component is selected from the group consisting of a gel and a hydrogel. Embodiments of the invention also provide methods of manufacturing the fibers of the present invention.

An embodiment of the invention provides a bi-component fiber where the inner bore of the fiber, i.e., inside diameter of the fiber, comprises a gel or hydrogel and the outer wall of the fiber comprises a biodegradable polymer. As used herein, the term "gel" refers to a colloidal system with at least two phases, one of which forms a continuous three-dimensional network that acts as an elastic solid. As used herein, the term "hydrogel" refers to a colloid in which a dispersed phase (colloid) is combined with a continuous phase (water) to produce a viscous jellylike product.

An alternate embodiment of the invention provides the inverse of the above, i.e. where the outer wall comprises a gel or hydrogel and the inner bore comprises a biodegradable polymer fiber.

Another embodiment of the invention provides a monofilament fiber where a hydrogel or gel is dispersed randomly throughout the biodegradable polymer layer(s). This configuration results in distinct phase separation where the biodegradable polymer fiber constitutes a continuous phase and the gel or hydrogel constitutes a disperse phase. As used herein, a "continuous phase" refers to the liquid in a disperse system in which solids are suspended or droplets of another liquid are dispersed. As used herein, a "disperse phase" refers to the phase of a disperse system consisting of particles or droplets of one system dispersed through another system.

In certain embodiments, where the gel or hydrogel concentration is zero, a water-bored fiber is provided i.e., a fiber in which water is present within the inside diameter of the fiber. In this case, water, optionally in combination with other materials, comprises the inner core of the fiber and the biodegradable polymer fiber comprises the surrounding sheath of the fiber. In an alternate embodiment, the biodegradable polymer fiber sheath comprises a dispersion of gel or hydrogel. In another embodiment, the biodegradable polymer fiber sheath comprises a dispersion of water in place of a dispersion of gel or hydrogel. In other embodiments, the biodegradable polymer fiber sheath comprises a dispersion of water together with a dispersion of gel and hydrogel.

In an embodiment of the invention, the above described fibers are combined with fibers of similar composition. In other embodiments, fibers of dissimilar type and composition are combined.

In an embodiment, a therapeutic agent is incorporated into one or more of the above described fibers, present individually or in combination. In other embodiments, a drug is incorporated into one or more of the above described fibers, present individually or in combination.

In certain embodiments of the invention, a layer of a fiber circumscribes a layer of an adjacent inner fiber. The inner fiber is approximately centered within the outer fiber. In certain embodiments, one or more of the layers of the circumscribed fibers comprise a hydrogel or a gel in the wall of the fiber or in the bore of the fiber. In additional embodiments, a gel or a hydrogel is incorporated as a dispersed phase within the biodegradable polymer of one or more layers of the fibers. Additional embodiments of the invention provide multi-layered fibers, where each layer comprises varying compositions of gels, hydrogels and therapeutic agents. Certain embodiments of the invention provide fibers comprising more than one kind of therapeutic agent within its one or more layers.

The invention further relates to methods of manipulating the rate of therapeutic agent release by changing both the biodegradable polymer properties as well as altering the properties of the incorporated gel or hydrogel. A therapeutic agent-loaded fiber is suitable for implantation in animals, or more preferably in humans as either single strands for use as a therapeutic agent delivery vehicles, or together with other fibers (of either similar or different type) for the formation of a fiber-based scaffold for use in tissue engineering, wound healing, regenerative medicine, or other medically related applications. These fibers may also be used outside the body to create scaffolds for cell culture, tissue culture, or in vitro organogenesis, wherein specific three-dimensional structures of these fibers may be woven, knitted, braided, used as a non-woven mesh, or maintained as parallel, non-parallel, twisted or random arrays for the creation of complex three-dimensional scaffolds. As each fiber within said fiber scaffold might be loaded with different therapeutic agents, and each with a different release kinetics profile, it may be possible to induce specific cell growth into specific regions of the scaffold. This provides the ability to create complicated three-dimensional biological architecture by deliberate placement of specific fibers at specific locations within the fiber scaffold. These three dimensional biological structures may or may not be biomemetic in their design. By the same means, it is possible to release different therapeutic agents to one section of the cell culture, tissue culture, or organoid than to another within the same sample.

This type of complex three-dimensional fiber scaffold may also be implanted into an animal, or a human to induce specific biological responses at different locations within said fiber scaffold. This is accomplished by designing the fiber scaffold such that fibers with specific therapeutic agents and specific release profiles are placed at specific locations within the scaffold. This enables the control of both temporal and spatial therapeutic agent delivery from the fiber scaffold.

"Defined nonhomogeneous pattern" in the context of the current application means the incorporation of specific fibers into a scaffold matrix such that a desired three-dimensional

distribution of one or more therapeutic agents within the scaffold matrix is achieved. The distribution of therapeutic agents within the fibers, and possibly within their centers, controls the subsequent spatial distribution within the interstitial medium of the matrix scaffold following release of the agents from the polymer fibers. In this way, the spatial contours of desired concentration gradients can be created within the three dimensional scaffold structure and in the immediate surroundings of the scaffold matrix. Temporal distribution is controlled by the polymer composition and gel or hydrogel composition of the fiber and by the use of multi-layers within a fiber.

One aspect of the present invention is a biocompatible implant composition comprising a scaffold of biodegradable polymer fibers. In various embodiments of the present invention, the distance between the fibers may be about 20 microns, about 70 microns, about 90 microns, about 100 microns, about 120 microns, about 140 microns, about 160 microns, about 180 microns, about 200 microns, about 220 microns, about 240 microns, about 260 microns, about 280 microns, about 300 microns, about 320 microns, about 340 microns, about 360 microns, about 380 microns, about 400 microns, about 450 microns or about 500 microns. In various embodiments the distance between the fibers may be less than 50 microns or greater than 500 microns.

Additionally, it is envisioned that in various embodiments of the invention, the fibers will have a diameter of about 20 microns, about 40 microns, about 60 microns, about 80 microns, about 100 microns, about 120 microns, about 140 microns, about 160 microns, about 180 microns, about 200 microns, about 220 microns, about 240 microns, about 260 microns, about 280 microns, about 300 microns, about 320 microns, about 340 microns, about 360 microns, about 380 microns, about 400 microns, about 450 microns or about 500 microns (including intermediate lengths). In various embodiments the diameter of the fibers may be less than about 20 microns or greater than about 500 microns. Additionally, large fibers with diameters up to 3.5 cm are envisioned for certain embodiments. Preferably, the diameter of the fibers will be from about 60 microns to about 500 microns.

In another embodiment of the present invention, the fibers or a subset of fibers, contain one or more therapeutic agents such that the concentration of the therapeutic agent or agents varies along the longitudinal axis of the fibers or subset of fibers. The concentration of the active agent or agents may vary linearly, exponentially or in any desired fashion, as a function of distance along the longitudinal axis of a fiber. The variation may be monodirectional, that is, the content of one or more therapeutic agents decreases from the first end of the fibers or subset of the fibers to the second end of the fibers or subset of the fibers. The content may also vary in a bidirection fashion, that is, the content of the therapeutic agent or agents increases from the first ends of the fibers or subset of the fibers to a maximum and then decreases towards the second ends of the fibers or subset of the fibers.

In certain embodiments of the present invention, a subset of fibers comprising the scaffold may contain no therapeutic agent. For fibers that contain one or more therapeutic agents, the agent or agents may include: a growth factor, an immunodulator, a compound that promotes angiogenesis, a compound that inhibits angiogenesis, an anti-inflammatory compound, an antibiotic, a cytokine, an anti-coagulation agent, a procoagulation agent, a chemotactic agent, agents that promotes apoptosis, an agent that inhibits apoptosis, a mitogenic agent, a radioactive agent, a contrast agent for imaging studies, a viral vector, a polynucleotide, therapeutic genes, DNA, RNA, a polypeptide, a glycosaminoglycan, a carbohydrate, a glycoprotein. The therapeutic agents may also include those drugs that are to be administered for long-term maintenance to patients such as cardiovascular drugs, including blood pressure, pacing, anti-arrhythmia, beta-blocking drugs, and calcium channel based drugs. Therapeutic agents of the present invention also include anti-tremor and other drugs for epilepsy or other movement disorders. These agents may also include long-term medications such as contraceptives and fertility drugs. They could comprise neurologic agents such as dopamine and related drugs as well as psychological or other behavioral drugs. The therapeutic agents may also include chemical scavengers such as chelators, antioxidants and nutritional agents. Wherein the therapeutic agent promotes angiogenesis, that agent may be vascular endothelial growth factor. The therapeutic agents may be synthetic or natural drugs, proteins, DNA, RNA, or cells (genetically altered or not). As used in the specification and claims, following long-standing patent law practice, the terms "a" and "an," when used in conjunction with the word "comprising" or "including" means one or more.

In general, the present invention contemplates the use of any drug incorporated in the biodegradable polymer fibers of the invention. The word "drug" as used herein is defined as a chemical capable of administration to an organism, which modifies or alters the organism's physiology. More preferably the word "drug" as used herein is defined as any substance intended for use in the treatment or prevention of disease. Drug includes synthetic and naturally occurring toxins and bioaffecting substances as well as recognized pharmaceuticals, such as those listed in "The Physicians Desk Reference," 471st edition, pages 101–321; "Goodman and Gilman's The Pharmacological Basis of Therapeutics" 8th Edition (1990), pages 84–1614 and 1655–1715; and "The United States Pharmacopela, The National Formulary", USP XXII NF XVII (1990), the compounds of these references being herein incorporated by reference. The term "drug" also includes compounds that have the indicated properties that are not yet discovered or available in the U.S. The term "drug" includes pro-active, activated, and metabolized forms of drugs. Tissue stimulating factors are also included such as: dimers of Platelet Derived Growth Factor (PDGF), insulin-like growth factor-1 (IGF-1), IGF-2, basic Fibroblast Growth Factor (bFGF), acidic FGF, Vascular Endothelial Cell Growth Factor (VEGF), Nerve Growth Factor (NGF), Neurotrophic Factor 3 (NT-3), Neurotrophic Factor 4 (NT-4), Brain Derived Neurotrophic Factor (BDNF), Endothelial Growth Factor (EGF), Insulin, Interleukin 1 (II-1), Tumor Necrosis Factor alpha (TNFα.), Connective Tissue Growth Factor (CTGF), Transforming Growth Factor alpha (TGFα), and all other growth factors and cytokines, as well as para-thyroid hormone (PTH), prostaglandin such as Prostaglandin E-1 and Prostaglandin E-2, Macrophage Colony Stimulating Factor (MCSF), and corticosteroids such as dexamethasone, prednisolone, and corticosterone.

The present invention also contemplates the use of hydrogel forming material within the core of the fibers. Hydrogels are structurally stable, synthetic polymer or biopolymer matrices that are highly hydrated. These materials may absorb up to thousands of times their weight in water, (Hoffman, A. S., Advanced Drug delivery Reviews, 43 (2000), 3–12). Hydrogels can be classified into two broad categories: reversible or physical and irreversible or chemical. The networks in physical gels are held together by molecular entanglements and/or secondary forces including

ionic, H-bonding or hydrophobic forces. Physical hydrogels are characterized by significant changes in the rheological properties as a function of temperature, ionic concentration, and dilution. Chemical gels, also called permanent gels, are characterized by chemically crosslinked networks. When crosslinked, these gels reach an equilibrium swelling level in aqueous solutions which depends mainly on the crosslink density.

The preparation of hydrogels can be achieved by a variety of methods well known to those of ordinary skill in the art. Physical gels can be formed by: heating or cooling certain polymer solutions (cool agarose, for example), using freeze-thaw cycles to form polymer microcrystals, reducing the solution pH to form a H-bonded gel between two different polymers in the same aqueous solution, mixing solutions of a polyanion and a polycation to form a complex coacervate gel, gelling a polyelectrolyte solution with a multivalent ion of opposite charge, reticulation of linear polymers, grafting of synthetic polymers onto naturally occurring macromolecules, and chelation of polycations (Hoffman, A. S., Advanced Drug delivery Reviews, 43 (2000), 3–12). Chemical gels can be created by crosslinking polymers in the solid state or in solution with radiation, chemical crosslinkers like glutaraldehyde, or multifunctional reactive compounds. They can also be made by copolymerizing a monomer and a crosslinker in solution, copolymerizing a monomer and a multifunctional macromer, polymerizing a monomer within a different solid polymer to form an IPN gel, or chemically converting a hydrophobic polymer to a hydrogel (Hoffman, A. S., Advanced Drug delivery Reviews, 43 (2000), 3–12); Hennick, W. F. and van Nostrum, C. F., Advanced Drug Delivery Reviews, 54 (2002), 13–26.

The present invention contemplates the use of hydrogel precursor materials and non-gelling proteins and polysaccharides within the bore of the fibers. Hydrogel precursor materials are the same materials as those that form hydrogels, but they are not exposed to the agents or conditions that normally gel the materials, or can be other proteins and polysaccharides that form gels but not hydrogels. For example, alginate salts, such as sodium alginate, are gelled in the presence of divalent cations, such as calcium, while other materials create hydrogels via a change in pH or temperature. Certain embodiments of the invention comprise the use of precursor materials that are never gelled. Other embodiments of the invention comprise the use of precursor materials in the fabrication process that later may form gels or hydrogels. The formation of gels or hydrogels in the fiber layer may take place as a part of the fiber fabrication process, after the fiber has been fabricated, or after the application of an appropriate type of external stimuli, including placing the fiber in vitro or in vivo. The terms "gel" or "hydrogel" as used herein is intended to include the formed gel or hydrogel as well as the appropriate precursor molecules involved in the formation of gels and hydrogels.

The biodegradable polymer used for fiber construction may be a single polymer or a co-polymer or blend of polymers and may comprise poly(L-lactic acid), poly(DL-lactic acid), polycaprolactone, poly(glycolic acid), polyanhydride, or natural polymers or polypeptides, such as reconstituted collagen or spider silk and polysaccharides.

The fibers of the claimed invention are manufactured using wet or dry/wet (dry jet wet) spinning. Each method affects the final properties of the fiber being constructed. Wet spinning is a process in which a polymeric material is extruded into a liquid bath containing a coagulant. The coagulant is typically comprised of a non-solvent for the polymer that is miscible with the solvent in the polymer solution, but it can also contain a solvent/non-solvent mixture. In dry jet wet spinning, the polymer solution is first exposed to an air gap before entering the coagulation bath.

In an embodiment of the invention, the fiber comprises a plurality of co-axial layers of biodegradable polymers. The drug delivery fiber of the present invention may be implanted into many sites in the body including dermal tissues, cardiac tissue, soft tissues, nerves, bones, and the eye. Ocular implantation has particular use for treatment of cataracts, diabetically induced proliferative retinopathy and non-proliferative retinopathy, glaucoma, and macular degeneration.

A further aspect of the present invention is a method of producing a fiber-scaffold for preparing an implant capable of controlling the spatial and temporal concentration of one or more therapeutic agents. This method generally comprises forming biodegradable polymer fibers into a three dimensional fiber-scaffold. The biodegradable polymer fibers contain one or more therapeutic agents. The therapeutic agent or agents are distributed in the fiber-scaffold in a defined nonhomogeneous pattern.

In certain embodiments of the invention, gels and hydrogels comprised in the fiber layers may exist at infinitely dilute concentrations, i.e., the concentration of gel or hydrogel is zero, and water is used with or without other substances and/or active agents, including therapeutic agents, in place of the gel or hydrogel.

In one embodiment of this invention, the preferred material for the hydrogel contained in the bore of the fiber will be alginate or modified alginate material. Alginate molecules are comprised of (1–4)-linked β-D-mannuronic acid (M units) and (α-L-guluronic acid (G units) monomers, which vary in proportion and sequential distribution along the polymer chain. Alginate polysaccharides are polyelectrolyte systems that have a strong affinity for divalent cations (e.g. Ca^{2+}, Sr^{2+}, Ba^{2+}) and form stable hydrogels when exposed to these molecules. The biodegradable polymer is poly(L-lactic acid) (PLLA). In an embodiment, the alginate is contained as the inner core and the PLLA is the outer sheath. The concentration of alginate is in the range of 0.25 w/v % to 100 w/v % (i.e., g/100 ml water), preferably in the range of 0.75 w/v % to 20 w/v %, and most preferably at a concentration of 1 w/v %. The source and composition of alginate directly affects its usable concentration.

In another embodiment of this invention, the PLLA sheath surrounding the inner gel or hydrogel core comprises a cocktail of PLLA polymers of different molecular weights as a means of increasing the degradation rate. The proportions of the PLLA polymers and the range of the polymer molecular weights can vary. In an exemplary embodiment, the polymer cocktail comprises 80% by weight of a PLLA polymer of Mw=100,000 Daltons; 15% by weight of a polymer of Mw=2,000 Daltons; and 5% by weight of a polymer Mw=300,000 Daltons.

In another embodiment of the invention, the PLLA sheath surrounding the inner gel or hydrogel core is comprised of two phases, a continuous phase comprising a biodegradable polymer and a dispersed phase comprising an aqueous phase stabilized by a surfactant. The aqueous phase may optionally comprise therapeutic agents. The amount of the dispersed phase ranges from about 0% to about 85% by weight relative to the weight of the fiber. In a preferred embodiment the amount of the dispersed phase ranges from about 33% to about 50% by weight relative to the weight of the fiber. As the ratio of the dispersed phase increases, so does the rate of

degradation of the polymer. This leads to increased release rates of loaded therapeutic agents.

In an embodiment of this invention, agents that are designed to degrade the gel or hydrogel are loaded into the dispersed aqueous phase of the biodegradable polymer component of the fiber (as described above). This agent is released into the gel or hydrogel slowly over time to break down the gel or hydrogel. This increases therapeutic agent release rates. In addition, many of the potential gels and hydrogels are not directly biodegradable within animals, or more especially humans. Therefore, this planned degradation helps the body to eliminate the gels or hydrogels when they are no longer needed.

In an embodiment, the alginate is gelled internally by the addition of gelling agents added directly to the alginate solution. Typical gelling agents include calcium chloride, calcium carbonate, calcium-EDTA (Ethylene Diamine Tetracetic Acid), or other compounds containing bivalent cations that are well known to those skilled in the art. The concentration of the gelation agent ranges from about 5 mM to about 100 mM, more preferably from about 12 mM to about 50 mM, and most preferably from about 15 mM to 30 mM. The range chosen is determined by desired hydrogel properties. If not readily soluble at neutral pH, the gelling agent is typically activated by a drop in pH of the solution. This acidification can be achieved through a number of acids or lactones. This list includes, but is not limited to, citric acid, hydrochloric acid, D-glucono-delta-lactone, and glacial acetic acid.

In another embodiment, the gel or hydrogel is gelled externally by incorporating the gelling agent source into the biodegradable fiber. Alternately, the gelling agent source is added to a water phase that is loaded into one or more layers of the biodegradable polymer. In this way, the gelling agent is slowly released into the gel or hydrogel as the fiber degrades. In certain embodiments, as the fiber degrades and becomes weaker and more porous, the gel becomes more tightly cross-linked. In this way, it may be possible to continuously alter the release rate as the fiber degrades. Release rates tend to increase as the polymer becomes more porous, in this case, this trend would be offset by the gel becoming more tightly cross-linked, hence retarding release rates through the gel or hydrogel as the fiber degrades.

In another embodiment, the gelling agent is soluble in the polymer solvent and is mixed with the polymer solution at the time of fiber fabrication. In this embodiment, rather than the gelling agent being maintained in an aqueous phase, it is molecularly mixed with the polymer. The same net effect of releasing the gelling agent into the gel or hydrogel slowly as the fiber degrades. This embodiment allows the use of organically soluble sources of gelling agents.

In another embodiment, the gelation agents are carried within the alginate solution that are activated over time, such as within lipospheres, microspheres, nanoparticles or other encapsulants that are activated later. These may be slowly activated over time, or purposefully activated by some external event. This will result in the gel either being strengthened, or maintained over time.

In another embodiment of the invention, the gel or hydrogel is the exterior sheath and the biodegradable polymer is the interior core. In this embodiment the gelling agent is in the coagulating bath, which would be an external gelation.

The present invention provides compositions and methods to create single, drug releasing fibers as well as the composition and methods to create a heterogeneous, woven, knitted, braided, non-woven, twisted, parallel array or random three-dimensional fiber scaffold for growing cells in tissue engineering applications. These scaffolds can be used in vitro and in vivo, and due to their heterogeneity can create both spatial and temporal distributions of therapeutic agents. In this invention, therapeutic agents may include drugs, proteins, peptides, mono- and di-saccharides, polysaccharides, glycoproteins, DNA, RNA, viruses, or other biological molecules of interest. The term therapeutic agent in this invention also includes radioactive materials used to help destroy harmful tissues such as tumors in the local area, or to inhibit growth of healthy tissues, such as in current stent applications; or markers to be used in imaging studies.

A. Three Dimensional Fiber Scaffolds

To create the heterogeneous scaffolds of the present invention, the therapeutic agents are encapsulated into individual fibers of the matrix by methods to be described herein. The therapeutic agents are released from each individual fiber slowly, and in a controlled manner. The fiber format has many advantages as a drug delivery platform over other slow drug-releasing agents known to those familiar in the art such as microspheres, porous plugs or patches. The primary advantage of fibers is that they can provide complex three-dimensional woven, or non-woven scaffolding, with or without patterning, to allow cells to attach, spread, differentiate, and mature into appropriately functioning cells. Because they can form patterns, a "smart scaffold" can be produced to induce cells of specific types to migrate to specific regions of the scaffold due to specific chemotactic factors being released. This scaffold mimics the function of the extracellular matrix material both during embryological development and in post-embryological tissues. Additionally, filaments could be formed into a unique scaffold that provides a growth substrate for tissue repair or reconstruction that is not reminiscent of a natural like structure.

Because of the ability to weave patterns to induce appropriate cell types into specific regions, it is possible to incorporate strands that will induce the formation of blood vessels into the fabric. This may be accomplished by providing fibers that release growth factors such as vascular endothelial growth factor (VEGF). By appropriate spacing of VEGF containing-fibers into the weave pattern, large tissues may be engineered, and the cells in such tissues can be provided with a sufficient blood supply and thereby receive oxygen and nutrients and enable the removal of waste products.

Fibers also have the advantage of providing the body with short term mechanical support in such applications as stents, wherein the polymer fiber can maintain the lumen of any tubular body, such as arteries, veins, ducts (e.g. bile duct, ureter, urethra, trachea, etc.), organs of the digestive track such as esophagus, intestine, colon, and connective tissue such as tendons, ligaments, muscle and bone. The fibers provide a useful structure to support mechanical strength or tension during the healing process. Fibers may also be useful to promote neural regeneration or reconstruction of nerves or spinal cord.

B. Fiber Formats

There are a large number of combinations and variations within the scope of this invention. This invention covers gel or hydrogel combinations with a biodegradable polymer fiber in a multi-layer, multi-component format, where each layer is fully contained within the next outer layer, and the inner layer is generally centered within the outer layer. These layers can be comprised of different gels or hydrogels, or different biodegradable polymers.

This invention also includes the use of gels or hydrogels as a dispersed phase within biodegradable polymer layer, wherein the continuous phase is the biodegradable polymer

phase. The dispersed phase may be stabilized by either an internal or external surfactant.

In the case of the dispersed gel or hydrogel within the biodegradable polymer layer, and in the case of the gel or hydrogel layer being interior to a biodegradable polymer layer, an allowable special case is that the concentration of the hydrogel is zero. This means that water may be used (with or without the inclusion of other substances) in the place of the gel or hydrogel.

As an additional special case, it may be possible for the polymer concentration in the innermost core to be zero, in which case the solvent normally used with the polymer is replaced by a non-solvent. In this case, the non-solvent core acts as an internal coagulating bath. The result is that a hollow fiber is created. This special case can occur with or without a gel or hydrogel exterior to the biodegradable polymer layer(s) and with or without a dispersed gel, hydrogel or water phase within the biodegradable polymer layer(s).

This leads to a large number of potential combinations. The basic types are external biodegradable polymer with internal gel or hydrogel, and the inverse design, i.e. gel or hydrogel external with the biodegradable polymer as the internal core. In each of these combinations, the biodegradable polymer layer may or may not have a dispersed water, gel or hydrogel phase. Another case is a monofilament fiber with a gel or hydrogel dispersed phase.

C. Release Kinetics of Individual Fibers

Further, there are various means for controlling the release kinetics of the therapeutic agent, thus temporally controlling the release of the therapeutic agent. The following discussion will pertain only to the fiber format wherein the polymer sheath surrounds an inner core of gel or hydrogel. The first point of control for the polymer is to mix low molecular weight polymer in with the higher molecular weight, fiber forming polymers. In this way, the lower molecular weight component is able to rapidly degrade and diffuse from the fiber, making the fiber more porous. This makes the interior therapeutic agents within the gel or hydrogel more accessible. A second means of accelerating the release rate of the fiber is to create a bi-phasic fiber, wherein the continuous phase is the biodegradable polymer, and the dispersed phase is aqueous pockets that are stabilized by a surfactant. As the concentration of the dispersed phase increases, a pathway is created from the outside to the inner gel or hydrogel where the only polymer that must be degraded is between the various pockets of the dispersed aqueous phase. This has the effect of leaving much less polymer to degrade to connect the gel or hydrogel to the outside world, thus accelerating the release of the therapeutic agent. It is also possible for this dispersed aqueous phase to contain the same or a different drug or therapeutic agent. In this case, the drug or therapeutic agent in the dispersed aqueous phase will be released first, followed by the release of the therapeutic agent in the gel or hydrogel. To alter the release kinetics of the drug or therapeutic agent in the polymer fiber wall, it is possible to slightly adapt the above description such that the dispersed phase is now a gel or hydrogel as opposed to being aqueous. In this case, the fluid pathway shortening exists as in the case of an aqueous dispersed phase; however, the connecting pathway must now go through pockets of gel or hydrogel, wherein the diffusion of the therapeutic agent is retarded compared to a purely aqueous pathway. The degree to which the diffusion is retarded is a function of the type of gel or hydrogel, the type and degree of cross-linking, and the concentration of the gel or hydrogel. All of these parameters are within the control of the entity forming the fiber. It is also possible to control the concentration of the dispersed aqueous or gel phase within the biodegradable polymer as a function of distance along the long axis of the fiber. By this means, it is possible to have different release kinetics at one end of the fiber than at the other, with a defined gradient of release kinetics down the length of the fiber. This change in release kinetics may or may not be combined with a gradient of therapeutic agent concentration. By the same means, it is possible to have the content of the disperse phase vary as a function of distance down the polymer fiber such that at one end the dispersed phase would be for example purely aqueous and at the second end of the fiber, the dispersed phase could be a gel or hydrogel. Other gradients are also possible including varying concentrations of the gel within the disperse phase. Thus a great deal of control is available on the release kinetics of the fiber. Aside from these changes in the polymer wall of the fiber, it is also possible to control the release kinetics from this fiber by altering the type, concentration, and degree of cross-linking within the gel or hydrogel in the core of the fiber, which contains a therapeutic agent.

The ability to dynamically change the release kinetics of the gel or hydrogel being loaded into the core or as a dispersed phase within a biodegradable polymer fiber over the course of the drug delivery period constitutes an important aspect of the invention. This affords unique opportunities that are not possible to be present in other forms of drug delivery from gels or hydrogels. The first means of control available because of the gel being loaded into a biodegradable polymer fiber is the ability of this fiber to release agents known to cross link the gel. In this way, over time, the cross-linking density of the gel actually increases, which will retard the release of the therapeutic agent. This release of the cross linking agent from the biodegradable polymer fiber sheath is itself controllable by means outlined above, i.e. using a cocktail of molecular weights, or changing the concentration of the dispersed aqueous phase. As a special case of the biodegradable polymer fiber sheath is a multi-layer, and multi-component biodegradable polymer sheath. This allows the creation of directional specificity, as well as changes in the release kinetics from each layer of the biodegradable polymer fiber sheath. For example, consider the case of two layers of biodegradable polymer fiber in the sheath. The innermost layer could contain agents that act to cross link the gel or hydrogel core of the fiber, and this layer could be composed of a biodegradable polymer that has a rapid degradation rate. Further, this layer could contain a high degree of dispersed aqueous phase. In this same example, the outermost layer may be composed of a different biodegradable polymer with a different degradation rate, and a different concentration of dispersed aqueous (or gel or hydrogel) dispersed phase, including zero. This example would create a situation where the cross-linking agent would be delivered inwardly to the gel or hydrogel in the core of the fiber over time, thus creating a situation wherein the diffusion coefficient of the therapeutic agent loaded into the gel or hydrogel in the core of the fiber decreases over time.

Another special case is where the polymer fiber contains agents that degrade the gel or hydrogel in the core of the fiber. Using the same logic as explained above, this too creates a situation where the diffusion coefficient of the therapeutic agent in the gel or hydrogel in the core or dispersed within the fiber changes continuously over time. In this case, however, the diffusion rate increases over time. This particular case also has the advantage that the body of the animal or preferably the human into which the fiber is

implanted may not have the specific enzymes or other chemical conditions required to degrade the gel or hydrogel. In this case, loading appropriate degradation agents into the wall of the fiber allows the degradation of the gel or hydrogel, and thus aids the clearance of the gel or hydrogel from the host. Again, as described above, the release of the degradation agents is largely controllable by changing properties of the biodegradable polymer layers in the sheath of the fiber.

By these methods, it is seen that the release kinetics of the therapeutic agent from a gel or hydrogel core or dispersed in a sheath of biodegradable polymer fiber is alterable by virtue of the presence of biodegradable polymer sheath.

In the case where the gel or hydrogel is the exterior layer and the biodegradable polymer is the core of the fiber. In this case the biodegradable polymer core may consist of one or more multi-component layers as described above, and again each layer may contain a different concentration of dispersed aqueous or gel or hydrogel phase, which may or may not themselves carry therapeutic agents. The overall release of therapeutic agent(s) from the fiber is controlled by the location of the therapeutic agents, either in the gel or hydrogel exterior, or within the biodegradable polymer core or both. By the same means as described above, the exterior gel or hydrogel release kinetics may be altered by the release of cross-linking, or degrading agents from the biodegradable polymer fiber core. As these agents are released from the biodegradable polymer fiber core, they will alter the properties of the exterior gel or hydrogel, thus decreasing or increasing the diffusion of the therapeutic agent from the exterior gel or hydrogel. For any therapeutic agent(s) within the biodegradable polymer core, the release of these agents is controlled on two levels. First, as explained above the type and molecular weight distribution of the polymer itself changes the release kinetics, as well known to those skilled in the art. In addition to this, the concentration of any dispersed aqueous or gel or hydrogel phase will alter the release from the biodegradable polymer. However, as the gel or hydrogel is surrounding the biodegradable fiber, all therapeutic agents within the biodegradable polymer must diffuse through the gel or hydrogel. Therefore, any changes to the diffusion of the therapeutic agent(s) through the gel or hydrogel also directly affect the release of any therapeutic agents within the core of the fiber. Therefore, in this case, one can change the release kinetics of the fiber by altering both the gel and the biodegradable polymer segments.

If the dispersed phase is a gel or hydrogel that also contains the therapeutic agent, then the release of that therapeutic agent is controllable by the same means of choice of biodegradable polymer, molecular weight distribution, and concentration of the dispersed phase. In addition, the properties of the gel or hydrogel also alter the release of the therapeutic agent from the dispersed phase within the monofilament fiber.

D. Biodegradable Polymers

Preferred polymers for use in the present invention include single polymer, co-polymer or a blend of polymers of poly(L-lactic acid), poly(DL-lactic acid), polycaprolactone, poly(glycolic acid) or polyanhydride. Naturally occurring polymers may also be used such as reconstituted collagen or natural silks. Those of skill in the art will understand that these polymers are just examples of a class of biodegradable polymer matrices that may be used in this invention. Further biodegradable matrices include polyanhydrides, polyorthoesters, and poly(amino acids) (Peppas and Langer, 1994). Any such matrix may be utilized to fabricate a biodegradable polymer matrix with controlled properties for use in this invention. A non-exhaustive list of biodegradable polymers that produce non-toxic degradation products are listed in Table 1.

TABLE 1

Biodegradable polymers
Synthetic
Polypeptides
Polydepsipeptides
Nylon-2/nylon-6 copolyamides
Aliphatic polyesters
Poly(glycolic acid) (PGA) and copolymers
Poly(lactic acid) (PLA) and copolymer
Poly(alkylene succinates)
Poly(hydroxy butyrate) (PHB)
Poly(butylene diglycolate)
Poly(ϵ-caprolactone) and copolymers
Polydihydropyrans
Polyphosphazenes
Poly(ortho ester)
Poly(cyano acrylates)
Natural
Modified polysaccharides
cellulose, starch, chitin
Modified proteins
collagen, fibrin

Adapted from Wong and Mooney, 1997.

E. Types of Gels and Hydrogels

In simple terms, a gel is a liquid system that acts like a solid. More technically defined, a gel is a colloidal system with at least two phases, one of which forms a continuous three-dimensional network that acts as an elastic solid. Gel formation through physical, molecular, or chemical association results in an infinite molecular weight for the system. The viscoelastic material formed has a storage modulus, G', that is greater than the loss modulus, G", and both G' and G" are almost independent of frequency. [E. R. Morris, Polysaccharide solution properties: origin, rheological characterization and implications for food systems, Frontiers in Carbohydrate Research 1: Food Applications (R. P. Millane, J. N. BeMiller, and R. Chandrasekaran, eds.), Elsevier, London, 1989, p. 132.] The storage modulus characterizes the rigidity of the sample, while the loss modulus characterizes the resistance of the sample to flow. [Damodaran, Srinivasan, Food Proteins and Their Applications, Food Science and Technology (Marcel Dekker, Inc.); New York Marcel Dekker, Inc., 1997.] Examples are polymer solutions, micellar solutions, microemulsions and, in more recent years, the field has been extended with the large number of organic solvents that are gelled by the presence of small organic molecules at very low concentrations.

A hydrogel is defined as a colloid in which the disperse phase (the colloid) has combined with the continuous phase (water) to produce a viscous jellylike product. [Dictionary of Chemical Terms, 4th Ed., McGraw Hill (1989)]. Hydrogels are able to swell rapidly in excess water and retain large volumes of water in their swollen structures. The polymeric material comprising the hydrogel can absorb more than 20% of its weight in water, though formed hydrogels are insoluble in water and they maintain three-dimensional networks. [Amidon, Gordon L., Transport Processes in Pharmaceutical Systems, Drugs and the Pharmaceutical Sciences; v. 102 New York Marcel Dekker, Inc., 2000]. They are usually made of hydrophilic polymer molecules crosslinked either

by chemical bonds or by other cohesion forces such as ionic interaction, hydrogen bonding, or hydrophobic interaction. [J. I. Kroschwitz, Concise Encyclopedia of Polymer Science and Engineering, New York, Wiley, XXIX, p 1341, 1990.]

Hydrogels are -elastic solids in the sense that there exists a remembered reference configuration to which the system returns even after being deformed for a very long time.

An organogel is defined as an organic phase with an interlaced polymeric component. Preferred solvents include non-toxic organic solvents including, but not limited to, dimethyl sulfoxide (DMSO), mineral oils and vegetable oils. The term "organogel" was initially used to describe a specific concept of gelation, by a gelatin solution, of a water-in-oil inverse microemulsion (see Luisi et al. Colloid & Polymer Science, 1990, vol. 268, p. 356–374). The term has recently been extended to gelled systems comprising two immiscible phases (water in oil) stabilized in lecithin enriched with phosphatidylcholine and usually hydrogenated (see Williman et al. Journal of Pharmaceutical Sciences, 1992, vol. 81, p. 871–874, and Schchipunov et al., Colloid Journal, 1995, vol. 57, p. 556–560). These emulsions have a lamellar phase and are in the form of gels even in the absence of gelling agents, hence the name organogels, which denotes this type of emulsion irrespective of the orientation of the emulsion (Water-in-Oil or Oil-in-Water).

The types of gel materials used in the present invention include polysaccharides, including but not be limited to, amylose, amylopectin, glycogen, cellulose, hyaluronate, chondroitin, heparin, dextrin, inulin, mannan, chitin, galactose, guar gum, carrageenan, agar, furcellaran, xanthan gum, other hydrocolloid gums, pectin, locust bean gum, acacia, ghatti gum, pentosan, arabinogalactan, synthetic derivatives thereof, and mixtures thereof

Examples of materials which can form hydrogels include natural and synthetic polysaccharides and other natural and synthetic polymers and their derivatives, and combinations of these. Suitable polysaccharides and polymers include but are not limited to: amylose, amylopectin, glycogen, cellulose, hyaluronic acid, chondroitin sulfate, heparin, dextrin, inulin, mannan, chitin, galactose, guar gum, carrageenan, agar, furcellaran, xanthan gum, other hydrocolloid gums, pectic acid and pectin, locust bean gum, acacia, ghatti gum, pentosan, arabinogalactan, alginates and alginate derivatives, gellan, gellan gum, glucose, collagen (and gelatin), cellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, methylcellulose, and methoxycellulose, fibrin, xanthan and xanthan gum, agarose, chitosan (polycationic polysaccharide polymers), albumin, human gamma globulin, pullulan, carrageenan (polyanionic polysaccharide polymers), dextrin, dextran, dextran sulfate, keratin, inulin, dextrose, amylose, glycogen, amylopectin, polylysine and other polyamino acids, polyesters such as polyhydroxybutyrate and polyphosphazines, poly(vinyl alcohols), poly(alkylene oxides) particularly poly(ethylene oxides), polyethylene glycol (including PEO-PPO-PEO and the like block copolymers like Pluronics®), poly(allylamines) (PAM), poly(acrylates), modified styrene polymers, pluronic polyols, polyoxamers, polypropylenes, polyurethanes, poly(uronic acids), polyvinyl chloride, poly (vinylpyrrolidone) and copolymers, graft copolymers, synthetic derivatives, blends and other mixtures of the above. Polysaccharides are the preferred polymers for this invention. Alginate, for example, is biocompatible, non-cytotoxic, non-carcinogenic, non-inflammatory, and non-immunogenic, and, therefore, a good candidate for use.

F. Types of Polymeric Materials

Exemplary natural polymers include naturally occurring polysaccharides, such as, for example, arabinans, fructans, fucans, galactans, galacturonans, glucans, mannans, xylans (such as, for example, inulin), levan, fucoidan, carrageenan, galatocarolose, pectic acid, pectins, including amylose, pullulan, glycogen, amylopectin, cellulose, dextran, dextrin, dextrose, glucose, polyglucose, polydextrose, pustulan, chitin, agarose, keratin, chondroitin, dermatan, hyaluronic acid, alginic acid, xanthan gum, starch and various other natural homopolymer or heteropolymers, such as those containing one or more of the following aldoses, ketoses, acids or amines: erythrose, threose, ribose, arabinose, xylose, lyxose, allose, altrose, glucose, dextrose, mannose, gulose, idose, galactose, talose, erythrulose, ribulose, xylulose, psicose, fructose, sorbose, tagatose, mannitol, sorbitol, lactose, sucrose, trehalose, maltose, cellobiose, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, glucuronic acid, gluconic acid, glucaric acid, galacturonic acid, mannuronic acid, glucosamine, galactosamine, and neuraminic acid, and naturally occurring derivatives thereof Accordingly, suitable polymers include, for example, proteins, such as albumin.

Exemplary semi-synthetic polymers include carboxymethylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, methylcellulose, and methoxycellulose. Exemplary synthetic polymers include polyphosphazenes, polyethylenes (such as, for example, polyethylene glycol (including the class of compounds referred to as Pluronics®, commercially available from BASF, Parsippany, N.J.), polyoxyethylene, and polyethylene terephthlate), polypropylenes (such as, for example, polypropylene glycol), polyurethanes, polyvinyl alcohol (PVA), polyvinyl chloride and polyvinylpyrrolidone, polyamides including nylon, polystyrene, polylactic acids, fluorinated hydrocarbon polymers, fluorinated carbon polymers (such as, for example, polytetrafluoroethylene), acrylate, methacrylate, and polymethylmethacrylate, and derivatives thereof.

The polymeric materials are selected from those materials which can be polymerized or their viscosity altered in vivo by application of exogenous means, for example, by application of light, ultrasound, radiation, or chelation, alone or in the presence of added catalyst, or by endogenous means, for example, a change to physiological pH, diffusion of calcium ions (alginate) or borate ions (polyvinyl alcohol) into the polymer, or change in temperature to body temperature (37° C.).

G. Agents that Promote Angiogenesis

One class of therapeutic agents to be encapsulated by the polymer fibers of the present invention are therapeutic agents that promote angiogenesis. The successful engineering of new tissue requires the establishment of a vascular network. The induction of angiogenesis is mediated by a variety of factors, any of which may be used in conjunction with the present invention (Folkman and Klagsbrun, 1987, and references cited therein, each incorporated herein in their entirety by reference). Examples of angiogenic factors includes, but is not limited to: vascular endothelial growth factor (VEGF) or vascular permeability factor (VPF); members of the fibroblast growth factor family, including acidic fibroblast growth factor (aFGF) and basic fibroblast growth factor (bFGF); interleukin-8 (IL-8); epidermal growth factor (EGF); platelet-derived growth factor (PDGF) or platelet-derived endothelial cell growth factor (PD-ECGF); transforming growth factors alpha and beta (TGF-α, TGF-β); tumor necrosis factor alpha (TNF-α); hepatocyte growth

factor (HGF); granulocyte-macrophage colony stimulating factor (GM-CSF); insulin growth factor-1 (IGF-1); angiogenin; angiotropin; angiotensin; fibrin and nicotinamide (Folkman, 1986, 1995; Auerbach and Auerbach, 1994; Fidler and Ellis, 1994; Folkman and Klagsbrun, 1987; Nagy et al., 1995).

H. Cytokines

In certain embodiments the use of particular cytokines incorporated in the polymer fibers of the present invention is contemplated. Table 2 below is an exemplary, but not limiting, list of cytokines and related factors contemplated for use in the present invention.

TABLE 2

Cytokine	Reference
Human IL-1	March et al., Nature, 315: 641, 1985
Murine IL-1	Lomedico et al., Nature, 312: 458, 1984
Human IL-1	March et al., Nature, 315: 641, 1985; Auron et al., Proc. Natl. Acad. Sci. U.S.A., 81: 7907, 1984
Murine IL-1	Gray, J. Immunol., 137: 3644, 1986; Telford, NAR, 14: 9955, 1986
Human IL-1ra	Eisenberg et al., Nature, 343: 341, 1990
Human IL-2	Taniguchi et al., Nature, 302: 305, 1983; Maeda et al., Biochem. Biophys. Res. Commun., 115: 1040, 1983
Human IL-2	Taniguchi et al., Nature, 302: 305, 1983
Human IL-3	Yang et al., Cell, 47: 3, 1986
Murine IL-3	Yokota et al., Proc. Natl. Acad. Sci. U.S.A., 81: 1070, 1984; Fung et al., Nature, 307: 233, 1984; Miyatake et al., Proc. Natl. Acad. Sci. U.S.A., 82: 316, 1985
Human IL-4	Yokota et al., Proc. Natl. Acad. Sci. U.S.A., 83: 5894, 1986
Murine IL-4	Norma et al., Nature, 319: 640, 1986; Lee et al., Proc. Natl. Acad. Sci. U.S.A., 83: 2061, 1986
Human IL-5	Azuma et al., Nuc. Acids Res., 14: 9149, 1986
Murine IL-5	Kinashi et al., Nature, 324: 70, 1986; Mizuta et al., Growth Factors, 1: 51, 1988
Human IL-6	Hirano et al., Nature, 324: 73, 1986
Murine IL-6	Van Snick et al., Eur. J. Immunol., 18: 193, 1988
Human IL-7	Goodwin et al., Proc. Natl. Acad. Sci. U.S.A., 86: 302, 1989
Murine IL-7	Namen et al., Nature, 333: 571, 1988
Human IL-8	Schmid et al., J. Immunol., 139: 250, 1987; Matsushima et al., J. Exp. Med. 167: 1883, 1988; Lindley et al., Proc. Natl. Acad. Sci. U.S.A., 85: 9199, 1988
Human IL-9	Renauld et al., J. Immunol., 144: 4235, 1990
Murine IL-9	Renauld et al., J. Immunol., 144: 4235, 1990
Human Angiogenin	Kurachi et al., Biochemistry, 24: 5494, 1985
Human GRO	Richmond et al., EMBO J., 7: 2025, 1988
Murine MIP-1	Davatelis et al., J. Exp. Med., 167: 1939, 1988
Murine MIP-1	Sherry et al., J. Exp. Med., 168: 2251, 1988
Human MIF	Weiser et al., Proc. Natl. Acad. Sci. U.S.A., 86: 7522, 1989
Human G-CSF	Nagata et al., Nature, 319: 415, 1986; Souza et al., Science, 232: 61, 1986
Human GM-CSF	Cantrell et al., Proc. Natl. Acad. Sci. U.S.A., 82: 6250, 1985; Lee et al., Proc. Natl. Acad. Sci. U.S.A., 82: 4360, 1985; Wong et al., Science, 228: 810, 1985
Murine GM-CSF	Gough et al., EMBO J., 4: 645, 1985
Human M-CSF	Wong, Science, 235: 1504, 1987; Kawasaki, Science, 230; 291, 1985; Ladner, EMBO J., 6: 2693, 1987
Human EGF	Smith et al., Nuc. Acids Res., 10: 4467, 1982; Bell et al., NAR, 14: 8427, 1986
Human TGF-	Derynck et al., Cell, 38: 287, 1984
Human FGF acidic	Jaye et al., Science, 233: 541, 1986; Gimenez-Gallego et al., Biochem. Biophys. Res. Commun., 138: 611, 1986; Harper et al., Biochem., 25: 4097, 1986
Human-ECGF	Jaye et al., Science, 233: 541, 1986
Human FGF basic	Abraham et al., EMBO J., 5: 2523, 1986; Sommer et al., Biochem. Biophys. Res. Comm., 144: 543, 1987
Murine IFN-	Higashi et al., J. Biol. Chem., 258: 9522, 1983; Kuga, NAR, 17: 3291, 1989
Human IFN-	Gray et al., Nature, 295: 503, 1982; Devos et al., NAR, 10: 2487, 1982; Rinderknecht, J. Biol. Chem., 259: 6790, 1984
Human IGF-I	Jansen et al., Nature, 306: 609, 1983; Rotwein et al., J. Biol. Chem., 261: 4828, 1986
Human IGF-II	Bell et al., Nature, 310: 775, 1984
Human-NGF chain	Ullrich et al., Nature, 303: 821, 1983
Human NT-3	Huang EJ. Et al., Development. 126(10): 2191–203, 1999 May.
Human PDGF A chain	Betsholtz et al., Nature, 320: 695, 1986
Human PDGF B chain	Johnsson et al., EMBO J., 3: 921, 1984; Collins et al., Nature, 316: 748, 1985
Human TGF-1	Derynck et al., Nature, 316: 701, 1985
Human TNF-	Pennica et al., Nature, 312: 724, 1984; Fransen et al., Nuc. Acids Res., 13: 4417, 1985
Human TNF-	Gray et al., Nature, 312: 721, 1984
Murine TNF-	Gray et al., Nucl. Acids Res., 15: 3937, 1987
Human E-Selectin	Bevilacqua el al., Science, 243: 1160, 1989; Hensley et al., J. Biol. Chem., 269: 23949, 1994
Human ICAM-1	Simmons et al., Nature, 331: 624, 1988
Human PECAM	Simmons et al., J. Exp. Med., 171: 2147, 1990
Human VCAM-1	Hession et al., J. Biol. Chem., 266: 6682; Osborn et al., Cell, 59: 1203, 1989
Human L-Selectin (membrane bound)	Ord et al., J. Biol. Chem., 265: 7760, 1990; Tedder et al., J. Exp. Med., 170: 123, 1989
Human L-Selectin (soluble form)	Ord et al., J. Biol. Chem., 265: 7760, 1990; Tedder et al., J. Exp. Med., 170: 123, 1989
Human Calcitonin	Le Moullec et al., FEBS Lett., 167: 93, 1984
Human Hirudin (*E. coli* optimized)	Dodt et al., FEBS Lett., 165: 180, 1984

G. Polynucelotides

The polynucleotides to be incorporated within the polymer fibers of the present invention extend to the full variety of nucleic acid molecules. The nucleic acids thus include genomic DNA, cDNAs, single stranded DNA, double stranded DNA, triple stranded DNA, oligonucleotides, Z-DNA, mRNA, tRNA and other RNAs. DNA molecules are generally preferred, even where the DNA is used to express a therapeutic RNA, such as a ribozyme or antisense RNA.

A "gene" or DNA segment encoding a selected protein or RNA, generally refers to a DNA segment that contains sequences encoding the selected protein or RNA, but is isolated away from, or purified free from, total genomic DNA of the species from which the DNA is obtained. Included within the terms "gene" and "DNA segment", are DNA segments and smaller fragments of such segments, and also recombinant vectors, including, for example, plasmids, cosmids, phage, retroviruses, adenoviruses, and the like.

The term "gene" is used for simplicity to refer to a functional protein or peptide encoding unit. As will be understood by those in the art, this functional term includes both genomic sequences and cDNA sequences. "Isolated substantially away from other coding sequences" means that the gene of interest forms the significant part of the coding region of the DNA segment, and that the DNA segment does not contain large portions of naturally-occurring coding DNA, such as large chromosomal fragments or other functional genes or cDNA coding regions. Of course, this refers to the DNA segment as originally isolated, and does not exclude genes or coding regions, such as sequences encoding leader peptides or targeting sequences, later added to the segment by the hand of man.

The present invention does not require that highly purified DNA or vectors be used, so long as any coding segment employed encodes a selected protein or RNA and does not include any coding or regulatory sequences that would have a significant adverse effect on the target cells. Therefore, it will also be understood that useful nucleic acid sequences may include additional residues, such as additional non-coding sequences flanking either of the 5' or 3' portions of the coding region or may include various internal sequences, i.e., introns, that are known to occur within genes.

Many suitable DNA segments may be obtained from existing, including commercial sources. One may also obtain a new DNA segment encoding a protein of interest using any one or more of a variety of molecular biological techniques generally known to those skilled in the art. For example, cDNA or genomic libraries may be screened using primers or probes with designed sequences. Polymerase chain reaction (PCR) may also be used to generate a DNA fragment encoding a protein of interest.

After identifying an appropriate selected gene or DNA molecule, it may be inserted into any one of the many vectors currently known in the art, so that it will direct the expression and production of the selected protein when incorporated into a target cell. In a recombinant expression vector, the coding portion of the DNA segment is positioned under the control of a promoter/enhancer element. The promoter may be in the form of the promoter that is naturally associated with a selected gene, as may be obtained by isolating the 5' non-coding sequences located upstream of the coding segment or exon, for example, using recombinant cloning and/or PCR technology.

In other embodiments, it is contemplated that certain advantages will be gained by positioning the coding DNA segment under the control of a recombinant, or heterologous, promoter. As used herein, a recombinant or heterologous promoter is intended to refer to a promoter that is not normally associated with a selected gene in its natural environment. Such promoters may include those normally associated with other selected genes, and/or promoters isolated from any other bacterial, viral, eukaryotic, or mammalian cell. Naturally, it will be important to employ a promoter that effectively directs the expression of the DNA segment in the chosen target cells.

The use of recombinant promoters to achieve protein expression is generally known to those of skill in the art of molecular biology, for example, see Sambrook et al (1989; incorporated herein by reference). The promoters employed may be constitutive, or inducible, and can be used under the appropriate conditions to direct high level or regulated expression of the introduced DNA segment. Expression of genes under the control of constitutive promoters does not require the presence of a specific substrate to induce gene expression and will occur under all conditions of cell growth. In contrast, expression of genes controlled by inducible promoters is responsive to the presence or absence of an inducing agent.

Promoters isolated from the genome of viruses that grow in mammalian cells, e.g., RSV, vaccinia virus 7.5K, SV40, HSV, adenoviruses MLP, MMTV LTR and CMV promoters, may be used herewith, as well as promoters produced by recombinant DNA or synthetic techniques. Currently preferred promoters are those such as CMV, RSV LTR, the SV40 promoter alone, and the SV40 promoter in combination with the SV40 enhancer.

Exemplary tissue specific promoter/enhancer elements and transcriptional control regions that exhibit tissue specificity include, but are not limited to: the elastase I gene control region that is active in pancreatic acinar cells; the insulin gene control region that is active in pancreatic cells; the immunoglobulin gene control region that is active in lymphoid cells; the albumin, 1-antitrypsin and -fetoprotein gene control regions that are active in liver; the -globin gene control region that is active in myeloid cells; the myelin basic protein gene control region that is active in oligodendrocyte cells in the brain; the myosin light chain-2 gene control region that is active in skeletal muscle; and the gonadotropic releasing hormone gene control region that is active in the hypothalamus.

Specific initiation signals may also be required for sufficient translation of inserted protein coding sequences. These signals include the ATG initiation codon and adjacent sequences. In cases where the entire coding sequence, including the initiation codon and adjacent sequences are inserted into the appropriate expression vectors, no additional translational control signals may be needed. However, in cases where only a portion of the coding sequence is inserted, exogenous translational control signals, including the ATG initiation codon should be provided. The initiation codon must be in phase with the reading frame of the protein coding sequences to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency and control of expression may be enhanced by the inclusion of transcription attenuation sequences, enhancer elements, etc.

A variety of vectors may be used including, but not limited to, those derived from recombinant bacteriophage DNA, plasmid DNA or cosmid DNA. For example, plasmid vectors such as pBR322, pUC 19/18, pUC 118, 119 and the M13 mp series of vectors may be used. Bacteriophage vectors may include gt10, gt11, gt18–23, ZAP/R and the EMBL series of bacteriophage vectors. Cosmid vectors that may be utilized include, but are not limited to, pJB8, pCV 103, pCV 107, pCV 108, pTM, pMCS, pNNL, pHSG274, COS202, COS203, pWE15, pWE16 and the charomid 9 series of vectors. Vectors that allow for the in vitro transcription of RNA, such as SP6 vectors, may also be used to produce large quantities of RNA that may be incorporated into matrices.

The selected genes and DNA segments may also be in the form of a DNA insert located within the genome of a recombinant virus, such as, for example a recombinant herpes virus, retroviruses, vaccinia viruses, adenoviruses, adeno-associated viruses or bovine papilloma virus. While integrating vectors may be used, non-integrating systems, which do not transmit the gene product to daughter cells for many generations will often be preferred. In this way, the gene product is expressed during a defined biological process, e.g., a wound healing process, and as the gene is diluted out in progeny generations, the amount of expressed gene product is diminished.

In such embodiments, to place the gene in contact with a target cell, one would prepare the recombinant viral particles, the genome of which includes the gene insert, and contact the target cells or tissues via release from the polymer fiber of the present invention, whereby the virus infects the cells and transfers the genetic material.

Genes with sequences that vary from those described in the literature are also contemplated for use in the invention, so long as the altered or modified gene still encodes a protein that functions to effect the target cells in the desired (direct or indirect) manner. These sequences include those caused by point mutations, those due to the degeneracies of the genetic code or naturally occurring allelic variants, and

further modifications that have been introduced by genetic engineering, i.e., by the hand of man.

Techniques for introducing changes in nucleotide sequences that are designed to alter the functional properties of the encoded proteins or polypeptides are well known in the art. Such modifications include the deletion, insertion or substitution of bases, and thus, changes in the amino acid sequence. Changes may be made to increase the activity of a protein, to increase its biological stability or half-life, to change its glycosylation pattern, confer temperature sensitivity or to alter the expression pattern of the protein, and the like. All such modifications to the nucleotide sequences are encompassed by this invention.

It is an advantage of the present invention that one or more than one selected gene may be used in the gene transfer methods and compositions. The nucleic acid delivery methods may thus entail the administration of one, two, three, or more, selected genes. The maximum number of genes that may be applied is limited only by practical considerations, such as the effort involved in simultaneously preparing a large number of gene constructs or even the possibility of eliciting an adverse cytotoxic effect. The particular combination of genes may be chosen to alter the same, or different, biochemical pathways. For example, a growth factor gene may be combined with a hormone gene; or a first hormone and/or growth factor gene may be combined with a gene encoding a cell surface receptor capable of interacting with the polypeptide product of the first gene.

In using multiple genes, they may be combined on a single genetic construct under control of one or more promoters, or they may be prepared as separate constructs of the same of different types. Thus, an almost endless combination of different genes and genetic constructs may be employed. Certain gene combinations may be designed to, or their use may otherwise result in, achieving synergistic effects on cell stimulation and tissue growth, any and all such combinations are intended to fall within the scope of the present invention. Indeed, many synergistic effects have been described in the scientific literature, so that one of ordinary skill in the art would readily be able to identify likely synergistic gene combinations, or even gene-protein combinations.

It will also be understood that, if desired, the nucleic segment or gene could be administered in combination with further agents, such as, e.g. proteins or polypeptides or various pharmaceutically active agents. So long as genetic material forms part of the composition, there is virtually no limit to other components which may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or tissues. The nucleic acids may thus be delivered along with various other agents, for example, in certain embodiments one may wish to administer an angiogenic factor as disclosed in U.S. Pat. No. 5,270,300 and incorporated herein by reference.

As the chemical nature of genes, i.e., as a string of nucleotides, is essentially invariant, and as the process of gene transfer and expression are fundamentally the same, it will be understood that the type of genes transferred by the fiber matrices of the present invention is virtually limitless. This extends from the transfer of a mixture of genetic material expressing antigenic or immunogenic fragments for use in DNA vaccination; to the stimulation of cell function, as in wound-healing; to aspects of cell killing, such as in transferring tumor suppressor genes, antisense oncogenes or apoptosis-inducing genes to cancer cells.

By way of example only, genes to be supplied by the invention include, but are not limited to, those encoding and expressing: hormones, growth factors, growth factor receptors, interferons, interleukins, chemokines, cytokines, colony stimulating factors and chemotactic factors; transcription and elongation factors, cell cycle control proteins, including kinases and phosphatases, DNA repair proteins, apoptosis-inducing genes; apoptosis-inhibiting genes, oncogenes, antisense oncogenes, tumor suppressor genes; angiogenic and anti-angiogenic proteins; immune response stimulating and modulating proteins; cell surface receptors, accessory signaling molecules and transport proteins; enzymes; and anti-bacterial and anti-viral proteins.

H. Kits

All the essential materials and reagents required for the various aspects of the present invention may be assembled together in a kit. The kits of the present invention also will typically include a means for containing the vials comprising the desired components in close confinement for commercial sale such as, e.g., injection or blow-molded plastic containers into which the desired vials are retained. Irrespective of the number or type of containers, the kits of the invention are typically packaged with instructions for use of the kit components.

WORKING EXAMPLES

The following examples are included to demonstrate preferred embodiments of the invention and are not intended to limit the scope of the invention in any way. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Example 1

Extrusion of Gel or Hydrogel Bored Fibers

In one embodiment of the present invention, the following procedure is used to create gel or hydrogel bored drug-releasing fibers. The apparatus used is depicted in FIG. 7, which details a fiber spinneret in which a coagulant bore fluid is fed through a small diameter hypodermic tube, which is centered in a blunt-end hypodermic needle. However, any similar configuration including scaled-up versions and specifically built apparatus' are included within the scope of the invention. This configuration allows for an annulus of polymer to flow through the spinneret, bored by a water-based gel or hydrogel. First, a biodegradable polymer such as poly(L-lactic acid) (PLLA), poly(DL-lactic acid), polycaprolactone, poly(glycolic acid), polyanhydride, or copolymers or blends of these or other biodegradable polymers is dissolved in some appropriate solvent (A) at concentrations ranging from 5 to 30 wt % depending on the type of polymer, 10 wt % being preferred for PLLA at 200 kD molecular weight. In this embodiment, solvent (A) has low miscibility with water, and is very miscible with the coagulation bath solvent (B), but not with the water in the gel or hydrogel in the bore. The water does not function as a solvent or non-solvent in this application. Preferred choices of solvent (A) include chloroform and methylene chloride. Once the polymer is dissolved in the chosen solvent, a non-solvent (solvent C) is typically added to the polymer solution in an

appropriate concentration to reduce the solvation power of the solvent system, yet not bring the solution to its cloud point. This non-solvent is highly miscible with solvent (A), and with solvent (B), and in some cases may be the same as solvent (B). Typical choices include iso-octane, cyclohexane, and hexane. This non-solvent brings the polymer in the solution close to its cloud point, so that the solution will more quickly precipitate to form a fiber when extruded into the coagulant bath, solvent (B).

The gel or hydrogel is prepared using standard procedures known to those who practice the art. As an example, for an internally gelled alginate bore fluid, sodium alginate powder is first dissolved in distilled-deionized water to yield a concentration in the range of 0.5 to 50 wt %, with 1 wt % being desired for this-example. Once dissolved, the solution is sterile filtered to provide an appropriate stock for the gel extrusion process. To promote internal gelation of the alginate, an appropriate quantity of calcium carbonate, $CaCO_3$, is added to the solution and mixed thoroughly by vortexing, sonicating, or homogenizing. Calcium carbonate is not soluble in water at neutral pH, so the powder ultimately is suspended in the alginate solution. To this solution, an appropriate quantity of D-Glucono-delta-Lactone (GDL) is added to slowly drop the solution pH, which initiates liberation of free Ca^{++} from the $CaCO_3$ to cross-link the guluronic acid residues in the alginate, thus forming a hydrogel. The rate of gelation and the properties of the gel can be controlled through the concentration of $CaCO_3$ and the ration of GDL to $CaCO_3$ used in the solution.

The prepared gel solution and the polymer solution are then immediately extruded into the coagulating bath containing solvent (B), through the spinneret device depicted in FIG. **8**, such that the polymer flows around a center tube containing the gel or hydrogel and, if desired, a drug of choice either dissolved in the gel, or encapsulated in nanospheres or liposomes and suspended in the gel. The polymer solution and gel or hydrogel core are extruded into the coagulation bath through a spinneret according to the size of the desired fiber, as these fibers are not typically drawn, the final fiber size is close to the spinneret size. The optimum ration of outer annulus to inner gel or hydrogel diameter needs to be experimentally determined. For example, to obtain fibers whose outer diameter are approximately 500 μm, the inventor's laboratory has used an outer lumen of 18 gage with a 24 or 25 gage inner lumen for the bore fluid. Any water-based gel, precursor hydrogel component, or hydrogel can be delivered through the center tube. Frequently, the inner gel or hydrogel is carrying a drug that is incompatible with organic solvents, or the gel or hydrogel does not tolerate the presence of organic solvents. Therefore, it is generally preferred that the solvent for the gel or hydrogel (generally water) is immiscible with solvents (A), (B) and (C). Solvent (B) must be highly miscible with solvents (A) and (C), immiscible with the water component of the bore fluid, and must be a non-solvent for the polymer; hexane and pentane are the most typical choices, but any solvent that meets the above criteria and quickly draws the solvent from the polymer solution will theoretically work. Wherefore, chloroform and pentane make a good solvent and coagulating bath combination with iso-octane as the added non-solvent. Because solvent (A) is highly miscible with coagulating bath solvent (B), it freely diffuses from the polymer solution stream into the coagulating bath, reducing the solvent power of the polymer solution below the cloud point, which causes the polymer to begin to precipitate to form a solid polymer sheath. Occasionally, the polymer sheath must begin to precipitate and form before it is subjected to the stress of being exposed to the gel or hydrogel flowing in the inner lumen. This requires that the axial positions of the inner lumen protrude below the outlet of the outer annulus (0–2 mm typical in inventor's laboratory) to ensure that the polymer solution is exposed to the coagulant bath just prior to the gel or hydrogel bore fluid contacting the polymer. The non-solvent (C), incorporated into the polymer solution accelerates the precipitation process. As neither solvent (A) nor (B) freely diffuse into the bore fluid, only a single coagulant front is created as the polymer exits the spinneret, thereby encapsulating the bore gel or hydrogel. The distance the fiber drops into the coagulating bath is important to the formation of the fiber and its ultimate properties, and is typically 10–30 cm. In the inventor's laboratory, the fiber has been allowed to freely Call and collect at the bottom of the coagulating bath container; however, other designs including drawing the fiber out of the coagulating bat are included as part of this invention. The extruded fiber may be post-processed and stored in a number of ways including freeze-dried, frozen, or oven dried and placed in a desecrator or freezer, depending upon recommended storage conditions of the loaded biomolecules and the properties of the gel or hydrogel.

Example 2

Extrusion of a Gel Coated Polymer Fiber

In another embodiment of the present invention, a PLLA or other biodegradable polymer fiber coated with a hydrogel is created. The extrusion process is similar to that described, except the coagulant bath used contains a coagulant or crosslinker for the hydrogel. The polymer and hydrogel are extruded through a spinneret similar to that previously described, with the polymer solution (possibly containing a drug in a dispersed aqueous or gel phase) extruded through the inner bore of the spinneret and the gel or hydrogel (possibly containing a drug) solution extruded through the outer annulus of the spinneret. The solutions are prepared as described or as otherwise known to those who practice the art, and are extruded at the same time through the spinneret. In the case of a dual lumen spinneret, the polymer solution is extruded without direct exposure to a coagulant. In this case, the polymer solvent must be removed by a post-processing step, or if there are no reasons to the contrary, the coagulating bath may contain a mixture of solvents, at least one of which miscible with both water and the polymer solvent; examples of which include isopropyl alcohol, acetone etc. This will allow the polymer solvent (typically chloroform or methylene chloride) to leave through the gel or hydrogel exterior layer being carried by the water miscible solvent. The coagulant bath also contains a solution known to those who practice the art that crosslinks or otherwise forms the gel or hydrogel. In the case of alginate hydrogel, the coagulant bath can be an appropriate concentration solution of $CaCl_2$ in water. As the polymer solution, and alginate solution flow from the spinneret, the alginate solution (which could contain $CaCO_3$ and GDL as noted above) contacts the coagulant and is crosslinked by calcium ions in the solution. If a polymer coagulant is used, solvent in the polymer/emulsion will diffuse into the coagulant and the polymer will form a fiber. If no coagulant is used, the polymer solution will be encapsulated by the rapidly crosslinking alginate solution such that an alginate shelled fiber will form. The residual solvent within the polymer can be removed by appropriate post-processing techniques.

Example 3

Extrusion of Gel or Hydrogel Exterior Hollow Fibers Using a Coagulant Bore Fluid

In one embodiment of the present invention, the following procedure is used to create gel or hydrogel exterior, hollow fibers. The apparatus includes a triple lumen spinneret, which also implies three pumps. The coagulant bath consists of a glass tube mounted vertically with one end immersed into reservoir of coagulant bath consists of a glass tube mounted vertically with one end immersed into a reservoir of coagulant fluid, and the other end sealed with a septum. Coagulant is drawn into the tube from the reservoir by piercing the septum with a needle and extracting the air in the tube with a large volume syringe. When filled, the syringe needle is removed and the septum seals the tube. As in example 2, the coagulant must include a means of gelling the exterior layer of gel or hydrogel. Again, in the case of alginate for example, a solution of calcium chloride may be appropriate. The gel or hydrogel solution flows through the outermost lumen, the biodegradable polymer through the inner lumen, and a coagulant for the polymer as defined above, flows through the innermost lumen. The fiber is drawn from the coagulation bath at a determined rate. In the laboratory, the inventors have used a cylinder attached to a modified variable-speed lathe that can accurately maintain its angular velocity. The drawn and extruded fiber is then removed from the cylinder and coagulant in the center of the fiber without collapsing the fiber. Residual coagulant and water are removed by freeze-drying, freezing or oven drying the fiber and placing it into a desecrator or freezer, depending upon recommended storage conditions.

Example 4

Extrusion of Hollow Fibers Using Water as a Bore Fluid (Water Bore Fiber)

In one embodiment of the present invention, the following procedure is used to create water-bored drug-released fibers. The apparatus is similar to that used in Example 1. This configuration allows for an annulus of polymer to flow through the spinneret, bored by a water-based fluid. First, a biodegradable polymer such as poly(L-lactic acid) (PLLA), poly(DL-lactic acid), polycaprolactone, poly(glycolic acid), polyanhydride, or copolymers or blends of these or other biodegradable polymers is dissolved in some appropriate solvent (A) at concentrations ranging from 5 to 30 wt % depending on the type of polymer, 10 wt % being preferred for PLLA at 200 kD molecular weight. In this embodiment, solvent (A) has low miscibility with water, and is very miscible with the coagulation bath solvent (B), but not with the water in the bore. The water does not function as a solvent or non-solvent in this application. Preferred choices of solvent (A) include chloroform and methylene chloride. Once the polymer is dissolved in the chosen solvent, a non-solvent is added to the polymer solution in an appropriate concentration to reduce the solvating power of the solvent system of the polymer, yet not bring the solution to its cloud point. This non-solvent (solvent C) is highly miscible with solvent (A), and with solvent (B). Typical choices include iso-octane, cyclohexane, and hexane. This non-solvent brings the polymer in the solution close to its point of coagulation, so that the solution will more quickly form a fiber when extruded into the coagulant bath.

The polymer solution is then extruded into a coagulating bath containing solvent (B), though a spinneret device such that the polymer flows around a center tube containing water and, if desired, a drug of choice either dissolved in the water, or encapsulated in nanospheres or liposomes and suspended in the water. The polymer solution is extruded into the coagulation bath through a dispensing tip ranging in size from 16 gage down to 27 gage, with the hypodermic tubing containing the water bore fluid appropriately sized to fit within the chosen dispensing tip. Any water-based fluid can be delivered through the center tube, provided this solution is immiscible with solvent (A). Solvent (B) must be highly miscible with solvents (A) and (C), and must be a non-solvent for the polymer; hexane and pentane are the most typical choices, but any solvent that is a non-solvent for the polymer and highly miscible with solvents (A) and (C) will work for this application, provided it quickly draws the solvent from the polymer solution. For example pentane is very miscible with chloroform and iso-octane, yet is a non-solvent for the polymer. Therefore, chloroform, iso-octane and pentane make a good solvent, non-solvent, and coagulating bath combination. Because solvent (A) is highly miscible with coagulating bath solvent (B), it freely diffuses from the polymer solution stream into the coagulating bath. The relative axial positions of the inner hypodermic tubing and the dispensing tip are adjusted to assure the annulus of polymer solution is exposed to the coagulant bath prior to the water bore contacting the polymer. The non-solvent incorporated into the polymer solution accelerates the precipitation process, such that a shell is formed in the polymer that entraps the bore solution. Neither solvent (A) nor (C) freely diffuse into the bore fluid, so only a single coagulant front is created as the polymer exits the spinneret. Additionally, the immiscibility of the solvents with the bore protects it and its contents. The coagulant bath used for this application consists of a 250 ml or greater flask into which the fiber is allowed to drop and spool as it coagulates. The height of the drop is important to the formation of the fiber, and is typically 10–30 cm. The extruded fiber is removed from the flask and either freeze-dried, frozen, or oven dried and placed in a desecrator or freezer, depending upon recommended storage conditions.

Example 5

Alternate Fabrication Technique for Example 1, for Hydrophilic Fiber

The only difference is to use as a coagulating bath a molecule such as poly(ethylene glycol) (PEG) of low molecular weight (in the range of 200 to 600 Daltons is typical). This polymer is miscible with chloroform and methylene chloride, yet a non-solvent for the polymer, such as PLLA. Therefore, it qualifies as a coagulation bath, however, this unique coagulating bath creates an interpenetrating network of PEG in the wall of the fiber, making them hydrophilic upon exposure to an aqueous environment. This can have interesting implications for implantation and may alter cellular response to the fibers.

Example 6

Neural Tissue Engineering

In this aspect of the present invention, parallel arrays of fibers are packed into tubes and loaded with neurotrophins for axonal growth. The tube may be a very large version of

a fiber of composition claimed in this invention, wherein the gel or hydrogel core may have a concentration of zero, or alternatively, be designed with an outer sheath of gel or hydrogel, with a multi-component inner core of gel or hydrogel with an intermediate layer consisting of biodegradable polymer. The innermost gel or hydrogel may have a concentration of zero, and the biodegradable polymer layer may be loaded with therapeutic agents either in a dispersed phase or directly mixed with the polymer. The exterior gel or hydrogel may also contain therapeutic agents as may the interior gel or hydrogel. Within the tube is a parallel array of fibers, whose composition may or may not be described by this invention or our prior invention. For this example, at least one component, either the tube, or at least one fiber must be of a composition as described in this invention. This array of fibers inside the tube is placed in severed peripheral or central nerves. The therapeutic agents may be loaded in a linear or some other appropriate gradient in every element of the device in which they are loaded (the exterior gel or hydrogel of the tube, the intermediate biodegradable polymer layer, or the innermost core of the tube, as well as the individual fibers within the tube in any and all possible constituents as described herein), but the gradient can differ in every occurrence within the device as desired. This device is implanted bridging the gap between the ends of the nerve stumps. As the device releases its therapeutic agents, which may consist of neurotrophins, anti-inflammatory agents, angiogenic factors, specific chemotactic or chemorepulsive agents etc., axons, vasculature, and other supporting cells and tissues begin to migrate across the lesion. Once the axons reach the distal end, guidance cues are provided by existing Schwann or glial cells and reconnections can then be made. It has been previously found that axons receive contact guidance by these fiber bundles and are able to traverse at least 1.8 cm in a rat sciatic nerve resection using non-loaded fibers. The optimal density of unloaded fibers in the tube is approximately 32 fibers in a 1.5 mm diameter tube for rat sciatic nerve growth.

Example 7

Preparation and use of Polymer Fiber Stents

In another embodiment, fibers can be loaded with a drug of interest and used in stents or other medical devices where mechanical strength is required. The stents can be woven in such a manner as to have loaded fibers intermingled with unloaded fibers if needed for mechanical properties.

Fibers can also be used in conjunction with commercially available stents to deliver drugs at the placement site. In this case, the fibers would not provide any mechanical support, but would only serve as a drug delivery reservoir.

Example 8

Preparation and use of Wound Dressings

In another embodiment, a gauze or dressing can be made from these fibers. This dressing can have two sides, an upper surface that will release molecules for re-epithelialization and provide a substrate for these cells. The bottom surface will promote regeneration of dermal tissue. This dressing is designed for dermal wound healing, including burns, full thickness dermal wounds and chronic or non-healing wounds and sores. Each fiber can have multi-component, multi-layer configuration to provide temporal release of drugs or factors that roughly correspond to the three phases of dermal wound healing.

As one example, in the case of a dressing designed for trauma patients, the first chemical to be released could be a pro-coagulant to help stop the bleeding. The next layer could then release cytokines to help recruit neutrophils and macrophages for the next phase of wound healing. Finally, a release of factors to help with reducing excessive scar tissue and to inhibit contractions, which are particularly disabling to burn patients.

Example 9

Fabrication of Artificial Arteries

It may be possible to construct an artificial artery using techniques described herein. A series of hollow, concentric cylindrical sections can be knitted, woven, braided or fabricated using non-woven technology with fibers loaded with various biological agents. The innermost cylinder is preferably tightly woven and contains drugs or agents to promote migrating, spreading and functioning of an intact endothelial cell layer. The next cylinder is composed of a woven or knitted architecture with fibers predominately circumferentially wound around the inner cylinder. This layer will induce the migration and proliferation of smooth muscle fibers, and promote the expression of elastin to create the internal elastic media. The next cylinder is composed of knitted or non-woven fibers and will contain drugs to promote the ingrowth of fibroblasts, macrophages and the creation of extracellular matrix. The last layer will compose longitudinal fibers that will promote the vascularization of the arterial cells via an artificial vasa vasorum, created by VEGF releasing fibers, or other promoters of angiogenesis.

Example 10

Drug Delivery Scaffold

In another application embodiment, these fibers can be used for drug delivery scaffolds in places where a fiber format is appropriate. For example, inside the eye, where microspheres or other formats may be more likely to interfere with the subject's vision, a fiber could be tacked down and not float into the field of view. Fibers may be able to stay in place better than microspheres or other formats such as nanoparticles, hydrogels, etc.

Example 11

Directed in situ Angiogenesis

In this embodiment, one or more fibers containing one or more of the family of angiogenic factors such as VEGF, bFGF, angiotensin or others known to induce angiogenesis are placed into the body along the path where the directed angiogenesis is desired. As the fiber begins to release the angiogenic factors endothelial cells from the surrounding vasculature will be induced to migrate out towards the fiber(s) following a process similar to normal angiogenesis. The fiber(s) used may have one or more of the compositions described in this invention, or it may be a tube with VEGF or similar growth factor that is chemotactic for endothelial cells on the inside, and a different factor for smooth muscles on the outside. In this way, the size of the created vessel may be determined. In this application, cells are guided into initially cell-free scaffoldings by cell-specific growth factors.

Example 12

Bone Fracture Healing

In another wound healing embodiment, proteins known to enhance bone fracture healing are loaded into a fiber. This fiber can then be wrapped around the bone at the site of the fracture, releasing the growth factors and enhancing the rate of fracture repair.

These fibers can either be in a helical structure (single or multiple helix), or they may be woven into a loose, open weave. Either in the helical or in the woven format, the fibers are placed around the bone fragments, holding them in place while releasing their growth factors.

In the case of a non-healing fracture that is due to lost or poor blood supply to the fracture site, a fiber or set of fibers containing VEGF or its equivalent may be used to enhance blood supply to the fractured area.

In this embodiment, bone fractures may be healed at accelerated rates compared to non-treated fractures, and non-unions may be healed in certain cases.

In yet a third bone healing application, fibers releasing pain relieving drugs may be used in the local area of the fracture. In this case, the fiber may be used in cases where plates, screws or other orthopedic devices are implanted or other surgical manipulations of the bone are performed. The local pain relief may lead the patient to apply load to the fracture sooner and may lead to a stronger and more rapid mend, as well as making life more comfortable for the patient.

Example 13

Skin Ulcer Healing

Similar to example 8 which described one form of dermal wound healing, another important example of this technology is the potential of healing chronic skin ulcers of various origins, such as diabetic foot ulcers, venous ulcers and general pressure sores. These conditions, and potentially other similar conditions may be healed based on creating a non-woven mesh of fibers that release factors known to accelerate dermal wound healing, for example, platelet derived growth factor (PDGF), transforming growth factor-beta (TGF-beta), and VEGF or similar protein. This non-woven mesh can be inserted or packed directly into the ulcer or wound, where these growth factors can help accelerate the wound-healing process. These dressings can be designed for healing dermal sores and ulcers. In this case, there is little need to reduce bleeding; rather one of the biggest needs of these patients, particularly those with diabetic ulcers is lack of blood supply to the wound site. Therefore, factors that induce angiogenesis may be able to increase circulation and help to rejuvenate the tissue at the site of the sore or ulcer.

Each dressing can be designed for the particular needs of the various types of wounds or sores by altering the biomolecules that are released, and the kinetics at which they are released.

Example 14

Muscle Grafts

In another embodiment, parallel arrays of fibers may be loaded with muscle stem cells. These stem cells can be of cardiac, smooth or skeletal muscle origin. Once these muscle stem cells are seeded onto the fiber array, the fibers can be mechanically stretched in vitro to help these cells align and differentiate properly. Alignment may also-be achieved by using fibers of very small diameter. Our experience with axons indicates that with fibers on the order of 50 μm diameter tend to help cells align parallel to the axis of the fibers. Other fibers in this bundle can release angiogenic factors to create a vascular supply for the muscle cells. In the case of skeletal or smooth muscle tissue, fibers for nerve growth can also be included to induce the formation of neuromuscular junctions. Various experimental conditions used to harvest, isolate, reproduce and differentiate these stem cells are known to those skilled in the art, and is not a part of this patent.

Example 15

Treatment of Glaucoma

Similar to drug delivery in the eye, described in example 10, and the neural stent described briefly in example 6, glaucoma may be treated by combining an intraocular drug delivery with a neural treatment applied to the optic nerve. Retinal ganglion cells undergo apoptosis leading to death of the axons of the optic nerve. It is hypothesized that if the cells could be supported both within the eye as well as along the path of the optic nerve, the cells may be able to survive. A fiber bundle that releases growth factors such as NT-4, BDNF, CNTF, may be applied topically to the exterior of the optic nerve. Simultaneously, fibers that release apoptosis inhibitors, or factors to support the retinal ganglion cells are implanted within the eye. This combined effort may prolong or save the sight of those suffering from glaucoma.

As is seen from the preceding examples, other tissues, organs, or structures are possible to weave once the basic physiologic structure is understood. This can be extended to organs of the digestive system, musculoskeletal system, urological system, circulatory system, and nervous system.

Example 16

Creation of a Gel or Hydrogel Core in a Biodegradable Polymer Sheath that Contains a Dispersed Aqueous Phase

In another embodiment of the invention, gel bored fibers may also contain therapeutic agents in a dispersed aqueous, gel or hydrogel phase within the biodegradable polymer fiber wall. The apparatus and extrusion conditions are similar to example 1 except as noted here.

Once the polymer is dissolved in solvent (A), an aqueous solution or a gel or a hydrogel (including precursors) containing both the biomolecules(s) of interest and a surfactant is added to the polymer solution. Additionally, a surfactant can be added to solvent (A). The concentration of the aqueous phase is typically in the range of 1 to 70% v/v of the polymer solution, 4–20% being most typical for gel or hydrogel filled PLLA fibers. The surfactant can be one or a combination of substances familiar to those skilled in the art, such as bovine serum albumin (BSA), poly(vinyl alcohol), pluronics, or biological surfactants such as the family of phospholipids. Other surfactants not specifically mentioned here, but known to those skilled in the art are included by extension. In a typical use, BSA is used as the surfactant at concentrations ranging from about 10 fold to 100 fold higher than the biological molecule of interest, with typical concentrations ranging from 2 wt % to 50 wt % of the aqueous phase. Note that the inventors experience has demonstrated

that high protein concentrations are difficult in the case of a gel or hydrogel, and therefore, the surfactant of choice may depend on the type of the dispersed phase.

Using some form of mechanical energy such as sonication, vortexing, or shear forces generated by forcing the liquid through a small orifice, a water-in-oil type emulsion is formed between the aqueous and organic phases. Depending on the volume of aqueous solution relative to the polymer solution, emulsification can be accomplished in stages, using partial additions of the aqueous phase until the total volume is incorporated into the polymer solution. This emulsion must be stable for periods far in excess of time required for extrusion to insure homogeneity of the emulsion throughout the extrusion process. The size of the dispersed aqueous phase droplets is primarily dependent on the quality of the surfactant, and the total amount of mechanical energy imparted to the system in forming the emulsion. The aqueous phase size is an important variable in both release kinetics and mechanical properties of the fiber. This emulsion is then used as the polymer solution, and all other details are the same as explained in example 1.

Example 17

Creation of a Gel or Hydrogel Exterior Fiber with a Biodegradable Polymer Fiber Core Containing a Dispersed Aqueous, Gel, or Hydrogel Phase Within the Fiber Wall

This example is similar to example 2 in all details except that a dispersed phase is added to the polymer solution as described in example 16.

Example 18

Creation of a Gel or Hydrogel Exterior Hollow Fiber with a Dispersed Gel or Hydrogel Phase Within the Fiber Wall

This example is similar to example 3 in all details except that a dispersed phase is added to the polymer solution as described in example 16.

Example 19

Creation of a Water-bore Fiber with a Dispersed Aqueous, Gel or Hydrogel Phase Within the Wall of the Fiber

This example is similar to example 4 in all details except that a dispersed phase is added to the polymer solution as described in example 16.

All of the compositions and methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

REFERENCES

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

Aigner, Tegeler, Hutzler, Campoccia, Pavesio, Hammer, Kastenbauer, Naumann, "Cartilage tissue engineering with novel nonwoven structured biomaterial based on hyaluronic acid benzyl ester," *J. of Biomed. Materials Res.*, 42(2): 172–81, 1998.

Auerbach and Auerbach, "Angiogenesis inhibition: a review," *Pharmac. Ther.*, 63:265, 1994.

Breitbart, Grande, Kessler, Ryaby, Fitzsimmons, Grant, "Tissue engineered bone repair of calvarial defects using cultured periosteal cells," *Plastic & Reconstructive Surgery*, 101(3):567–74, 1998.

Cao, Rodriguez, Vacanti, Ibarra, Arevalo, Vacanti, "Comparative study of the use of poly(glycolic acid), calcium alginate and pluronics in the engineering of autologous porcine cartilage," *J. of Biomaterials Sci., Polymer Edition*, 9(5):475–87, 1998.

Dillon, Yu, Sridharan, Ranieri, Bellamkonda, "The influence of physical structure and charge on neurite extension in a 3D hydrogel scaffold," *J. of Biomaterials Sci., Polymer Ed.*, 9(10):1049–69, 1998.

Elcin, Dixit, Lewin, Gitnick, "Xenotransplantation of fetal porcine hepatocytes in rats using a tissue engineering approach," *Artificial Organs*, 23(2):146–52, 1999.

Fauza, Fishman, Mehegan, Atala, "Videofetoscopically assisted fetal tissue engineering: skin replacement," *J. of Pediatric Surgery*, 33(2):357–61, 1998.

Fidler and Ellis, "The implications of angiogenesis for the biology and therapy of cancer metastasis," *Cell*, 79:185, 1994.

Folkman and Klagsbrun, "Angiogenic factors," *Science*, 235:442–447, 1987.

Folkman, "How is blood vessel growth regulated in normal and neoplastic tissue," *Cancer Res.*, 46:467, 1986.

Folkman, J., "Angiogenesis in cancer, vascular, rheumatoid and other disease," *Nature Med.*, 1:27, 1995.

Grande, Halberstadt, Naughton, Schwartz, Manji, "Evaluation of matrix scaffolds for tissue engineering of articular cartilage grafts," *J. of Biomed. Mat. Res.*, 34(2):211–20, 1997.

Gutsche, Lo, Zurlo, Yager, Leong, "Engineering of a sugar-derivatized porous network for hepatocyte culture," *Biomaterials*, 17(3):387–93, 1996.

Hoerstrup, Zund, Lachat, Schoeberlein, Uhlschmid, Vogt, Turina, "Tissue engineering: a new approach in cardiovascular surgery-seeding of human fibroblasts on resorbable mesh," *Swiss Surgery*, (Suppl.), 2:23–5, 1998.

Hoerstrup, Zund, Schoeberlein, Ye, Vogt, Turina, "Fluorescence activated cell sorting: a reliable method in tissue engineering of a bioprosthetic heart valve," *Annals of Thoracic Surgery*, 665(5):1653–7, 1998.

Isogai, Landis, Kim, Gerstenfeld, Upton, Vacanti, "Formation of phalanges and small joints by tissue-engineering," *J. of Bone & Joint Surgery, American Vol.*, 81(3):306–16, 1999.

Martin, Padera, Vunjak-Novakovic, Freed, "In vitro differentiation of chick embryo bone marrow stromal cells into cartilaginous and bone-like tissues," *J. of Orthopaedic Res.*, 16(2):181–9, 1998.

Nagy et al., "Pathogenesis of ascites tumor growth: vascular permeability factor, vascular hyperpermeability, and ascites fluid accumulation," *Cancer Res*., 55:360, 1995.

Peppas and Langer, "New challenges in biomaterials," Science, 263:1715–1720, 1994.

Peter, Miller, Yasko, Yaszemski, Mikos, "Polymer concepts in tissue engineering," *J. of Biomed. Materials Res*., 43(4):422–7, 1998.

Sacks, Chuong, Petroll, Kwan, Halberstadt, "Collagen fiber architecture of a cultured dermal tissue," *J. of Biomed. Engineering*, 119(1):124–7, 1997.

Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989.

Shinoka, Shum-Tim, Ma, Tanel, Isogai, Langer, Vacanti, Mayer, "Creation of viable pulmonary artery autografts through tissue engineering," *J. of Thoracic & Cardiovascular Surgery*, 115(3):536–45, 1998.

Sims, Butler, Cao, Casanova, Randolph, Black, Vacanti, Yaremchuk, "Tissue engineered neocartilage using plasma derived polymer substrates and chondrocytes," *Plastic & Reconstructive Surgery*, 101(6):1580–5, 1998.

Vunjak-Novakovic, Obradovic, Martin, Bursac, Langer, Freed, "Dynamic cell seeding of polymer scaffolds for cartilage tissue engineering," *Biotechnology Progress*, 14(2):193–202, 1998.

Whang, Tsai, Nam, Aitken, Sprague, Patel, Healy, "Ectopic bone formation via rhBMP-2 delivery from porous bioabsorbably polymer scaffolds," *J. of Biomed. Materials Res*., 42(4):491–9, 1998.

Wong and Mooney, "Synthesis and properties of biodegradable polymers used in tissue engineering," *In: Synthetic Biodegradable Polymer Scaffolds*, (Atala and Mooney, eds.), Birkhauser Press, Boston, Mass., pp. 51–82, 1997.

Yoo and Atala, "A novel gene delivery system using urothelial tissue engineered neoorgans," *J. of Urology*, 158(3 Pt 2):1066–70, 1997.

What is claimed is:

1. A drug delivery composition comprising at least one fiber having a bore and a wall, wherein said fiber comprises a first component and a second component, and wherein said first component is a biodegradable polymer and said second component is selected from the group consisting of a gel and a hydrogel.

2. The composition of claim **1** wherein said first component is present in the fiber bore and said second component is present in the fiber wall.

3. The composition of claim **1** wherein said second component is present in the fiber bore and said first component is present in the fiber wall.

4. The composition of claim **1** further comprising at least one additional fiber, wherein said additional fiber circumscribes an adjacent inner fiber.

5. The composition of claim **4** wherein said adjacent inner fiber is approximately centered within the outer fiber.

6. The composition of claim **1**, wherein a therapeutic agent is loaded into the gel or hydrogel.

7. The composition of claim **6**, wherein the therapeutic agent is a growth factor.

8. The composition of claim **7**, wherein said growth factor is a promoter of angiogenesis.

9. The composition of claim **7**, wherein said growth factor promotes nerve regeneration.

10. The composition of claim **6**, wherein the therapeutic agent is a virus.

11. The composition of claim **6**, wherein the therapeutic agent is selected from the group consisting of protein, enzymes, transcription factors, signaling molecules, internal messengers, second messengers, kinases, proteases, cytokines, chemokines, structural proteins, interleukins, hormones, anti-coagulants, pro-coagulants, anti-inflammatory agents, antibiotics, agents that promote angiogenesis, agents that inhibit angiogenesis, growth factors, immunomodulators, chemotactic agents, agents that promote apoptosis, agents that inhibit apoptosis, and mitogenic agents.

12. The composition of claim **1**, wherein said gel or hydrogel is a precursor gel or precursor hydrogel.

13. The composition of claim **1**, wherein said biodegradable polymer fiber comprises a hydrophobic drug.

14. The composition of claim **1**, wherein said gel or hydrogel comprises a radioactive material.

15. A drug delivery composition comprising a fiber, wherein said fiber comprises a first component and a second component, and wherein said first component is a biodegradable polymer and said second component is water, and further wherein said water is present as an inner core.

16. The composition of claim **15** Anther comprising at least one additional fiber, wherein said additional fiber circumscribes an adjacent inner fiber.

17. The composition of claim **16** wherein said adjacent inner fiber is approximately centered within the outer fiber.

18. The composition of claim **15**, wherein said biodegradable polymer fiber comprises a hydrophobic drug.

19. A drug delivery composition comprising a fiber, wherein said fiber comprises an emulsion consisting essentially of a gel or hydrogel.

20. A drug delivery composition comprising a fiber, wherein said fiber comprises a first component, and wherein said first component is a gel or hydrogel and further wherein said fiber comprises a hollow bore.

21. A scaffold composition comprising one or more fibers, wherein said fibers comprise a first component and a second component and wherein said first component is a biodegradable polymer and said second component is selected from the group consisting of a gel and a hydrogel.

22. The composition of claim **21** wherein said first component is present in the fiber bore and said second component is present in the fiber wall.

23. The composition of claim **21** wherein said second component is present in the fiber bore and said first component is present in the fiber wall.

24. The composition of claim **21** further comprising at least one additional fiber, wherein said additional fiber circumscribes an adjacent inner fiber.

25. The composition of claim **24** wherein said adjacent inner fiber is approximately centered within the outer fiber.

26. The composition of claim **21**, wherein therapeutic agent is loaded into the gel or hydrogel.

27. The composition of claim **26**, wherein the therapeutic agent is a growth factor.

28. The composition of claim **27**, wherein said growth factor is a promoter of angiogenesis.

29. The composition of claim **27**, wherein said growth factor promotes nerve regeneration.

30. The composition of claim **26**, wherein the therapeutic agent is a virus.

31. The composition of claim **26**, wherein the therapeutic agent is selected from the group consisting of protein, enzymes, transcription factors, signaling molecules, internal

messengers, second messengers, kinases, proteases, cytokines, chemokines, structural proteins, interleukins, hormones, anti-coagulants, pro-coagulant, anti-inflammatory agents, antibiotics, agents that promote angiogenesis, agents that inhibit angiogenesis, growth factors, immunomodulators, chemotactic agents, agents that promote apoptosis, agents that inhibit apoptosis, and mitogenic agents.

32. The composition of claim **21**, wherein said gel or hydrogel is a precursor gel or precursor hydrogel.

33. The composition of claim **21**, wherein said biodegradable polymer fiber comprises a hydrophobic drug.

34. The composition of claim **21**, wherein said gel or hydrogel comprises a radioactive material.

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APPEAL,CLOSED,PATENT/TRADEMARK

U.S. District Court [LIVE]
Western District of Texas (Austin)
CIVIL DOCKET FOR CASE #: 1:17-cv-01103-LY

Board of Regents, The University of Texas System et al v. Boston Scientific Corporation
Assigned to: Judge Lee Yeakel
Case in other court: USCA for the Federal Circuit, 18-01700
Cause: 35:271 Patent Infringement

Date Filed: 11/20/2017
Date Terminated: 03/12/2018
Jury Demand: Plaintiff
Nature of Suit: 830 Patent
Jurisdiction: Federal Question

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Date Filed	#	Docket Text
11/20/2017	1	COMPLAINT *Plaintiffs' Original Complaint for Patent Infringement* (Filing fee $ 400 receipt number 0542-10198934). No Summons requested at this time, filed by Board of Regents, The University of Texas System, TissueGen, Inc.. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Civil Cover Sheet)(Chan, Alfonso) (Entered: 11/20/2017)
11/20/2017		Case assigned to Judge Lee Yeakel. CM WILL NOW REFLECT THE JUDGE INITIALS AS PART OF THE CASE NUMBER. PLEASE APPEND THESE JUDGE INITIALS TO THE CASE NUMBER ON EACH DOCUMENT THAT YOU FILE IN THIS CASE. (afd) (Entered: 11/21/2017)
11/20/2017		DEMAND for Trial by Jury by Board of Regents, The University of Texas System, TissueGen, Inc.. (afd) (Entered: 11/21/2017)
11/21/2017	2	Report on Patent/Trademark sent to U.S. Patent and Trademark Office with copy of Complaint. (afd) (Entered: 11/21/2017)
12/08/2017	3	REQUEST FOR ISSUANCE OF SUMMONS by Board of Regents, The University of Texas System, TissueGen, Inc.. *for Boston Scientific Corp.* (Chan, Alfonso) (Entered: 12/08/2017)
12/11/2017	4	Summons Issued as to Boston Scientific Corporation. (klw) (Entered: 12/11/2017)
12/21/2017	5	NOTICE of Attorney Appearance by Christopher M. Odell on behalf of Boston Scientific Corporation. Attorney Christopher M. Odell added to party Boston Scientific Corporation(pty:dft) (Odell, Christopher) (Entered: 12/21/2017)
12/21/2017	6	Unopposed MOTION for Extension of Time to File Answer re 1 Complaint, by Boston Scientific Corporation. (Attachments: # 1 Proposed Order)(Odell, Christopher) (Entered: 12/21/2017)
12/26/2017	7	ORDER GRANTING 6 Motion for Extension of Time to Answer re 1 Complaint. Boston

		Scientific Corporation answer due 2/1/2018. Signed by Judge Lee Yeakel. (klw) (Entered: 12/26/2017)
12/27/2017	8	MOTION to Appear Pro Hac Vice by Christopher M. Odell *for John E. Nilsson* (Filing fee $ 100 receipt number 0542-10306586) by on behalf of Boston Scientific Corporation. (Attachments: # 1 Proposed Order)(Odell, Christopher) (Entered: 12/27/2017)
12/28/2017	9	ORDER GRANTING 8 Motion for John Nilsson to Appear Pro Hac Vice on behalf of Defendant. Pursuant to our Administrative Policies and Procedures for Electronic Filing, the attorney hereby granted to practice pro hac vice in this case must register for electronic filing with our court within 10 days of this order. Signed by Judge Lee Yeakel. (klw) (Entered: 01/02/2018)
01/05/2018	10	SUMMONS Returned Executed by Board of Regents, The University of Texas System, TissueGen, Inc. Boston Scientific Corporation served on 12/11/2017, answer due 1/2/2018. (Chan, Alfonso) Modified on 1/5/2018 to correct text and answer deadline (klw). (Entered: 01/05/2018)
01/05/2018		Reset Deadlines: Boston Scientific Corporation answer due 1/2/2018. (klw) (Entered: 01/05/2018)
01/05/2018		Notice of Correction: re 10 Summons Returned Executed. **Docket text and answer deadline corrected.** (klw) (Entered: 01/05/2018)
02/01/2018	11	MOTION to Dismiss *Under Fed. R. Civ. P. 12(B)(3)* by Boston Scientific Corporation. (Attachments: # 1 Proposed Order, # 2 Declaration of Paul Donhauser)(Odell, Christopher) (Entered: 02/01/2018)
02/07/2018	12	ORDER setting Initial Pretrial Conference for 2/14/2018 09:30 AM before Judge Lee Yeakel and Staying Action. Signed by Judge Lee Yeakel. (td) (Entered: 02/07/2018)
02/12/2018	13	ORDER resetting Initial Pretrial Conference for 3/13/2018 09:30 AM before Judge Lee Yeakel. Signed by Judge Lee Yeakel. (klw) (Entered: 02/12/2018)
02/15/2018	14	Response in Opposition to Motion, filed by Board of Regents, The University of Texas System, TissueGen, Inc., re 11 MOTION to Dismiss *Under Fed. R. Civ. P. 12(B)(3)* filed by Defendant Boston Scientific Corporation (Shore, Michael) (Entered: 02/15/2018)
02/16/2018	15	Letters to Christopher Evans, Ari Rafilson and Paul Beeler re: non-admitted status. (klw) (Entered: 02/16/2018)
02/22/2018	16	REPLY to Response to Motion, filed by Boston Scientific Corporation, re 11 MOTION to Dismiss *Under Fed. R. Civ. P. 12(B)(3)* filed by Defendant Boston Scientific Corporation (Odell, Christopher) (Entered: 02/22/2018)
02/26/2018	17	MOTION to Appear Pro Hac Vice by Alfonso Garcia Chan *For Christopher L. Evans* (Filing fee $ 100 receipt number 0542-10499964) by on behalf of Board of Regents, The University of Texas System, TissueGen, Inc.. (Attachments: # 1 Proposed Order Pro Hac Vice)(Chan, Alfonso) (Entered: 02/26/2018)
02/26/2018	18	*(Counsel advised wrong name is on the motion - 20 Corrected motion filed.)* MOTION to Appear Pro Hac Vice by Alfonso Garcia Chan *for Paul T. Beeler* (Filing fee $ 100 receipt number 0542-10499979) by on behalf of Board of Regents, The University of Texas System, TissueGen, Inc.. (Attachments: # 1 Proposed Order Pro Hac Vice)(Chan, Alfonso) Modified on 2/27/2018 (klw). (Entered: 02/26/2018)
02/26/2018	19	MOTION to Appear Pro Hac Vice by Alfonso Garcia Chan *for Paul T. Beeler* (Filing fee $ 100 receipt number 0542-10499988) by on behalf of Board of Regents, The University

		of Texas System, TissueGen, Inc.. (Attachments: # 1 Proposed Order Pro Hac Vice)(Chan, Alfonso) (Entered: 02/26/2018)
02/26/2018	20	CORRECTED MOTION to Appear Pro Hac Vice by Alfonso Garcia Chan *for Ari B. Rafilson* (Filing fee $ 100 receipt number 0542-10499979 paid w/ original 18 Motion to Appear Pro Hac Vice) by Board of Regents, The University of Texas System, TissueGen, Inc. (Attachments: # 1 Proposed Order Pro Hac Vice)(Chan, Alfonso) Modified on 2/27/2018 to clarify text (klw). (Entered: 02/26/2018)
02/28/2018	21	ORDER GRANTING 19 Motion for Paul Beeler to Appear Pro Hac Vice on behalf of Plaintiffs. Pursuant to our Administrative Policies and Procedures for Electronic Filing, the attorney hereby granted to practice pro hac vice in this case must register for electronic filing with our court within 10 days of this order. Signed by Judge Lee Yeakel. (klw) (Entered: 02/28/2018)
02/28/2018	22	ORDER GRANTING 20 Motion for Ari Rafilson to Appear Pro Hac Vice on behalf of Plaintiffs. Pursuant to our Administrative Policies and Procedures for Electronic Filing, the attorney hereby granted to practice pro hac vice in this case must register for electronic filing with our court within 10 days of this order. Signed by Judge Lee Yeakel. (klw) (Entered: 02/28/2018)
02/28/2018	23	ORDER GRANTING 17 Motion for Christopher Evans to Appear Pro Hac Vice on behalf of Plaintiffs. Pursuant to our Administrative Policies and Procedures for Electronic Filing, the attorney hereby granted to practice pro hac vice in this case must register for electronic filing with our court within 10 days of this order. Signed by Judge Lee Yeakel. (klw) (Entered: 02/28/2018)
03/08/2018	24	MOTION to Appear Pro Hac Vice by Christopher M. Odell *for Hannah DeMarco Sibiski* (Filing fee $ 100 receipt number 0542-10544371) by on behalf of Boston Scientific Corporation. (Attachments: # 1 Proposed Order)(Odell, Christopher) (Entered: 03/08/2018)
03/09/2018	25	RULE 7 DISCLOSURE STATEMENT filed by Board of Regents, The University of Texas System, TissueGen, Inc.. (Offor, Chijioke) (Entered: 03/09/2018)
03/12/2018	26	ORDER GRANTING 24 Motion for Hannah DeMarco Sibiski to Appear Pro Hac Vice on behalf of Boston Scientific Corp. Pursuant to our Administrative Policies and Procedures for Electronic Filing, the attorney hereby granted to practice pro hac vice in this case must register for electronic filing with our court within 10 days of this order. Signed by Judge Lee Yeakel. (klw) (Entered: 03/12/2018)
03/12/2018	27	ORDER GRANTING to an EXTENT Defendant's 11 Motion to Dismiss Plaintiff's Complaint. IT IS ORDERED that this action is TRANSFERRED to the United States District Court of Delaware. Signed by Judge Lee Yeakel. (klw) (Entered: 03/12/2018)
03/13/2018		Case transferred from TXWD has been received and opened in Delaware District as case number 1:18-cv-392. (klw) (Entered: 03/13/2018)
03/13/2018	28	Report on Patent/Trademark sent to U.S. Patent and Trademark Office. (klw) (Entered: 03/13/2018)
03/13/2018	29	Appeal of Order entered by District Judge 27 by Board of Regents, The University of Texas System, TissueGen, Inc.. No filing fee submitted (Shore, Michael) (Entered: 03/13/2018)
03/13/2018		Notice of Appeal to the Federal Circuit by Board of Regents, The University of Texas System, TissueGen, Inc. Filing fee $ 505 DUE. (klw) Modified on 3/19/2018 to correct appeal fee amount (klw). (Entered: 03/13/2018)

03/19/2018	30	Transmittal of Notice of Appeal to the U.S. Court of Appeals for the Federal Circuit. (Attachments: # 1 Information Sheet)(klw) (Entered: 03/19/2018)
03/21/2018	31	Appeal Filing fee received in the amount of $505, receipt number 100032691. (klw) (Entered: 03/22/2018)

PACER Service Center			
Transaction Receipt			
05/01/2018 10:24:35			
PACER Login:	sd1430:2971176:0	**Client Code:**	UT/TissueGen
Description:	Docket Report	**Search Criteria:**	1:17-cv-01103-LY
Billable Pages:	5	**Cost:**	0.50

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF TEXAS
AUSTIN DIVISION

BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM; and TISSUEGEN, INC., *Plaintiffs,* *v.* BOSTON SCIENTIFIC CORP., *Defendant.*	CASE NO. 1:17-cv-01103 JURY TRIAL DEMANDED

PLAINTIFFS' ORIGINAL COMPLAINT FOR PATENT INFRINGEMENT

1. Plaintiffs BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM ("UT") and TISSUEGEN, INC. ("TissueGen") (collectively, "Plaintiffs"), by and through their undersigned counsel, file this Original Complaint against Defendant BOSTON SCIENTIFIC CORPORATION ("Boston Scientific" or "Defendant") as follows:

I. THE PARTIES

2. UT is an agency of the State of Texas and is the assignee and owner of patents relating to drug-releasing biodegradable fibers used in the delivery of therapeutics, including U.S. Patent Nos. 6,596,296 (the "'296 Patent") and 7,033,603 (the "'603 Patent"). UT has its principal place of business at 201 West 7th Street, Austin, Texas 78701. For the avoidance of doubt, UT neither waives its sovereign immunity nor consents to any suit or proceeding filed separate from this action, including but not limited to any declaratory judgment action or *inter partes* review.

3. TissueGen is the developer of ELUTE® fiber and the exclusive licensee of the

'296 Patent and '603 Patent. ELUTE® fiber is a groundbreaking biodegradable fiber format for advanced drug delivery, nerve regeneration, and tissue engineering. TissueGen was established in 2000 by Dr. Kevin Nelson, while still faculty in Biomedical Engineering at The University of Texas at Arlington, following his research with Dr. George Smith at UT Southwestern Medical Center at Dallas. TissueGen is a Delaware corporation with a principal place of business at 2110 Research Row, Suite 330, Dallas, Texas 75235.

4. Defendant BOSTON SCIENTIFIC CORPORATION ("Boston Scientific") is a Delaware corporation with a principal place of business at 300 Boston Scientific Way, Marlborough, Massachusetts 01752 and may be served through its registered agent, Corporation Service Company, 211 E. 7th Street, Suite 620, Austin, Texas 78701, or wherever else it may be found.

II. JURISDICTION AND VENUE

5. This action arises under the patent laws of the United States, 35 U.S.C. § 1 *et seq.* This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a).

6. UT is an arm of the State of Texas, and has sovereign immunity. *See* TEX. EDUC. CODE § 61.003; TEX. GOV'T CODE § 441.101(3); *Tegic Comm'ns, Corp. v. Board of Regents of Univ. of Tex. Sys.*, 458 F.3d 1335, 1344-45 (Fed. Cir. 2006); *Xechem Int'l, Inc. v. Univ. of Tex. M.D. Anderson Cancer Ctr.*, 382 F.3d 1324, 1327-28 (Fed. Cir. 2004); *Northern Ins. Co. of N.Y. v. Chatham Cty., Ga.*, 547 U.S. 189, 193 (2006).

7. Venue is proper in the Western District of Texas because UT has sovereign immunity and this Court has personal jurisdiction over Defendant.

8. This Court has personal jurisdiction over Boston Scientific. Defendant has conducted and does conduct business within the State of Texas and the Western District of

Texas. Defendant is registered to conduct business in Texas with the Texas Secretary of State. Defendant has purposefully and voluntarily availed itself of the privileges of conducting business in the United States, the State of Texas, and the Western District of Texas by continuously and systematically placing goods into the stream of commerce through an established distribution channel with the expectation that they will be purchased by consumers in Texas and this District. Upon information and belief, Boston Scientific employs sales representatives in this District and/or has an agency relationship with sales representatives to promote sales of its products in this District.

9. Plaintiffs' causes of action arise directly from Defendant's business contacts and other activities in the State of Texas and this District. Upon information and belief, Defendant has committed acts of infringement in this District giving rise to this action and does business in this District, making sales and/or providing service and support for its customers, in this District. Defendant purposefully and voluntarily sold one or more of its infringing products with the expectation that they would be purchased by consumers in this District. These infringing products have been and continue to be purchased by consumers in this District. Defendant has committed acts of patent infringement within the United States, the State of Texas, and the Western District of Texas.

10. Venue is proper in the Western District of Texas because UT is an arm of the State of Texas, has the same sovereign immunity as the State of Texas, it would offend the dignity of the State to require it to pursue persons who have harmed the State outside the territory of Texas, and the State of Texas cannot be compelled to respond to any counterclaims, whether compulsory or not, outside its territory due to the Eleventh Amendment.

III. TISSUEGEN'S FOUNDATION

11. In the late 1990s, TissueGen's founder Dr. Kevin D. Nelson, while still faculty in Biomedical Engineering at The University of Texas at Arlington, was inspired to investigate delivering drugs directly from an extruded fiber while working to develop biodegradable vascular stents and microspheres for delivering non-toxic drugs to the inner ear.

12. Dr. Nelson's early work was followed by collaborations with Dr. George Smith at UT Southwestern Medical Center at Dallas, a leading researcher working on peripheral nerve regeneration, as well as Dr. Nadir Alikacem at the Callier Center, Texas Woman's University.

13. Working in peripheral nerve regeneration, Dr. Nelson and Dr. Smith showed fascicle formation in regenerated nerves with the aid of fibers, convincing Dr. Nelson that the fiber-based drug delivery technology had commercial viability.

14. The peripheral nerve regeneration work was the culmination of a long line of extremely successful experiments that demonstrated the benefit of drug delivery fibers in numerous applications.

15. With Dr. Alikacem, for example, Dr. Nelson demonstrated the ability to load a small pharmaceutical agent into a fiber to help stem the blindness that results from diabetes.

16. In 2000, Dr. Nelson embarked upon the path to commercialization by founding TissueGen, Inc. Dr. Nelson's work led to several issued patents, ultimately assigned to UT and licensed exclusively to TissueGen, including the '296 Patent and the '603 Patent.

17. Following relentless development efforts spanning more than a decade,

TissueGen has brought the scientific promise of implantable drug delivery via biodegradable fibers to commercial reality.

18. In 2013, TissueGen commercially released ELUTE® fiber, a groundbreaking biodegradable fiber format for advanced drug delivery, nerve regeneration, and tissue engineering.

19. ELUTE® fiber may directly replace standard fibers used in medical devices, including, but not limited to, biodegradable textiles currently on the market, and provide significantly improved clinical outcomes by delivering therapeutic agents directly at the site of the implant.

20. By delivering therapeutic agents including, but not limited to, pharmaceuticals and growth factors at the topical application or implant site, ELUTE® fiber may enable medical devices, including but not limited to cardiovascular stents, to aid the body's healing and regenerative processes.

IV. COUNT I: INFRINGEMENT OF U.S. PATENT NO. 6,596,296 B1

21. Plaintiffs repeat and re-allege every allegation of the prior paragraphs as though set forth fully herein.

22. On July 22, 2003, U.S. Patent No. 6,596,296 B1 (the "'296 Patent")—titled "Drug Releasing Biodegradable Fiber Implant"—was duly and legally issued by the United States Patent and Trademark Office to Board of Regents, The University of Texas System, as assignee of named inventors Kevin D. Nelson, Andres A. Romero-Sanchez, George M. Smith, Nadir Alikacem, Delia Radulescu, Paula Waggoner, and Zhibing Hu. A true and correct copy of the '296 Patent is attached hereto as **Exhibit A**.

23. UT is the owner of all right, title, and interest in and to the '296 Patent and has granted TissueGen an exclusive license "to manufacture, have manufactured, use, have

used, and/or Sell or have Sold" products including inventions and discoveries covered by the '296 Patent and "to otherwise exploit" UT's rights in information or discoveries covered by the '296 Patent.

24. The '296 Patent is directed to useful and novel compositions that provide for three-dimensional matrices for in vitro and in vivo use comprised of biodegradable polymer fibers capable of the controlled delivery of therapeutic agents.

25. Each claim of the '296 Patent is valid and enforceable and enjoys a statutory presumption of validity separate, apart, and in addition to the statutory presumption of validity enjoyed by every other of its claims. 35 U.S.C. § 282.

26. Upon information and belief, Defendant has been, and is currently, directly and/or indirectly infringing one or more claims of the '296 Patent in violation of 35 U.S.C. § 271, including as stated below.

27. Upon information and belief, Defendant has directly infringed, literally and/or under the doctrine of equivalents, and will continue to directly infringe claims of the '296 Patent by making, using, selling, offering to sell, and/or importing into the United States products that embody or practice the apparatus and/or method covered by one or more claims of the '296 Patent, including but not limited to the following products: Defendant's SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (Monorail™ Catheter), including the following products: H7493926008220, H7493926012220, H7493926016220, H7493926020220, H7493926024220, H7493926028220, H7493926032220, H7493926038220, H7493926008250, H7493926012250, H7493926016250, H7493926020250, H7493926024250, H7493926028250, H7493926032250, H7493926038250, H7493926008270,

H7493926012270, H7493926016270, H7493926020270, H7493926024270, H7493926028270, H7493926032270, H7493926038270, H7493926008300, H7493926012300, H7493926016300, H7493926020300, H7493926024300, H7493926028300, H7493926032300, H7493926038300, H7493926008350, H7493926012350, H7493926016350, H7493926020350, H7493926024350, H7493926028350, H7493926032350, H7493926038350, H7493926008400, H7493926012400, H7493926016400, H7493926020400, H7493926024400, H7493926028400, H7493926032400, H7493926038400 and any other products offered and/or sold under the SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (Monorail™ Catheter) name (the "Monorail™ Catheter Products"); Defendant's SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (Over-The-Wire), including the following products: H7493926108220, H7493926112220, H7493926116220, H7493926120220, H7493926124220, H7493926128220, H7493926132220, H7493926138220, H7493926108250, H7493926112250, H7493926116250, H7493926120250, H7493926124250, H7493926128250, H7493926132250, H7493926138250, H7493926108270, H7493926112270, H7493926116270, H7493926120270, H7493926124270, H7493926128270, H7493926132270, H7493926138270, H7493926108300, H7493926112300, H7493926116300, H7493926120300, H7493926124300, H7493926128300, H7493926132300, H7493926138300, H7493926108350, H7493926112350, H7493926116350, H7493926120350, H7493926124350, H7493926128350, H7493926132350, H7493926138350, H7493926108400, H7493926112400, H7493926116400, H7493926120400, H7493926124400,

H7493926128400, H7493926132400, H7493926138400 and any other products offered and/or sold under the SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (Over-the-Wire Catheter) name (the "SYNERGY™ Over-The-Wire Products"); and Defendant's products within the scope of FDA PMA Number P150003 (the "P150003 Products") (collectively, the "'296 Accused Products").

28. On information and belief, Defendant indirectly infringes the '296 Patent by inducing others to infringe one or more claims of the '296 Patent through sale and/or use of the '296 Accused Products. On information and belief, at least as a result of the filing of this action, Defendant is aware of the '296 Patent; is aware that its actions with regards to distributors, resellers, and/or end users of the '296 Accused Products would induce infringement; and despite such awareness will continue to take active steps—such as creating and disseminating the '296 Accused Products and product manuals, instructions, promotional and marketing materials, and/or technical materials to distributors, resellers, and end users—encouraging others to infringe the '296 Patent with the specific intent to induce such infringement.

29. Plaintiffs adopt, and incorporate by reference, as if fully stated herein, the attached claim chart for claim 1 of the '296 Patent, which is attached hereto as **Exhibit B**. The claim chart describes and demonstrates how Defendant infringes the '296 Patent. In addition, Plaintiffs allege that Defendant infringes one or more additional claims of the '296 Patent in a similar manner.

A. MONORAIL™ CATHETER PRODUCTS

30. At least one of the Monorail™ Catheter Products includes a biodegradable polymer fiber. For example, at least one of the Monorail™ Catheter Products is composed of bioabsorbable polymer.

31. The biodegradable polymer fiber included in at least one of the Monorail™ Catheter Products comprises a first phase and a second phase. For example, the biodegradable polymer fiber included in at least one of the Monorail™ Catheter Products comprises polymer structure and structure containing pharmacological agents.

32. The first phase and the second phase comprising the biodegradable polymer fiber included in at least one of the Monorail™ Catheter Products are immiscible. For example, the polymer structure and the structure containing pharmacological agents comprising the biodegradable polymer fiber included in at least one of the Monorail™ Catheter Products are immiscible.

33. The second phase comprising the biodegradable polymer fiber included in at least one of the Monorail™ Catheter Products includes at least one therapeutic agent. For example, at least one therapeutic agent (e.g., everolimus) is included in the structure containing pharmacological agents comprising the biodegradable polymer fiber included in at least one of the Monorail™ Catheter Products.

34. The second phase comprising the biodegradable polymer fiber included in at least one of the Monorail™ Catheter Products is derived from an aqueous solution, a hydrogel, or a polymer.

35. The therapeutic agent included in the second phase comprising the biodegradable polymer fiber included in at least one of the Monorail™ Catheter Products is a drug, a protein, an enzyme, a growth factor, an immunomodulator, a compound promoting angiogenesis, a compound inhibiting angiogenesis, an anti-inflammatory compound, an antibiotic, a cytokine, an anti-coagulation agent, a pro-coagulation agent, a chemotactic agent, an agent to promote apoptosis, an agent to inhibit apoptosis, or a

mitogenic agent. For example, one or more antimicrobial agents are included in the structure containing pharmacological agents comprising the biodegradable polymer fiber included in at least one of the Monorail™ Catheter Products.

36. The biodegradable polymer fiber included in at least one of the Monorail™ Catheter Products is a single polymer, a co-polymer, or a mixture of polymers.

37. The biodegradable polymer fiber included in at least one of the Monorail™ Catheter Products is a single polymer, a co-polymer, or a mixture of polymers selected from the group consisting of polypeptides, polydepsipeptides, nylon copolyamides, aliphatic polyesters, polydihydropyrans, polyphosphazenes, poly(ortho ester), poly(cyano acrylates), polyanhydride, modified polysaccharides and modified proteins.

38. The biodegradable polymer fiber included in at least one of the Monorail™ Catheter Products includes aliphatic polyesters selected from the group consisting of poly(glycolic acid), poly(lactic acid), poly(alkylene succinates) poly(hydroxybutyrate), poly(butylene diglycolate), poly(epsilon-caprolactone) and copolymers, blends and mixtures thereof.

39. The therapeutic agent included the biodegradable polymer fiber included in at least one of the Monorail™ Catheter Products is released over time from said fiber.

B. SYNERGY™ OVER-THE-WIRE PRODUCTS

40. At least one of the SYNERGY™ Over-The-Wire Products includes a biodegradable polymer fiber. For example, at least one of the SYNERGY™ Over-The-Wire Products is composed of bioabsorbable polymer.

41. The biodegradable polymer fiber included in at least one of the SYNERGY™ Over-The-Wire Products comprises a first phase and a second phase. For example, the biodegradable polymer fiber included in at least one of the SYNERGY™ Over-The-Wire

Products comprises polymer structure and structure containing pharmacological agents.

42. The first phase and the second phase comprising the biodegradable polymer fiber included in at least one of the SYNERGY™ Over-The-Wire Products are immiscible. For example, the polymer structure and the structure containing pharmacological agents comprising the biodegradable polymer fiber included in at least one of the SYNERGY™ Over-The-Wire Products are immiscible.

43. The second phase comprising the biodegradable polymer fiber included in at least one of the SYNERGY™ Over-The-Wire Products includes at least one therapeutic agent. For example, at least one therapeutic agent (e.g., everolimus) is included in the structure containing pharmacological agents comprising the biodegradable polymer fiber included in at least one of the SYNERGY™ Over-The-Wire Products.

44. The second phase comprising the biodegradable polymer fiber included in at least one of the SYNERGY™ Over-The-Wire Products is derived from an aqueous solution, a hydrogel, or a polymer.

45. The therapeutic agent included in the second phase comprising the biodegradable polymer fiber included in at least one of the SYNERGY™ Over-The-Wire Products is a drug, a protein, an enzyme, a growth factor, an immunomodulator, a compound promoting angiogenesis, a compound inhibiting angiogenesis, an anti-inflammatory compound, an antibiotic, a cytokine, an anti-coagulation agent, a pro-coagulation agent, a chemotactic agent, an agent to promote apoptosis, an agent to inhibit apoptosis, or a mitogenic agent. For example, one or more antimicrobial agents are included in the structure containing pharmacological agents comprising the biodegradable polymer fiber included in at least one of the SYNERGY™ Over-The-Wire Products.

46. The biodegradable polymer fiber included in at least one of the SYNERGY™ Over-The-Wire Products is a single polymer, a co-polymer, or a mixture of polymers.

47. The biodegradable polymer fiber included in at least one of the SYNERGY™ Over-The-Wire Products is a single polymer, a co-polymer, or a mixture of polymers selected from the group consisting of polypeptides, polydepsipeptides, nylon copolyamides, aliphatic polyesters, polydihydropyrans, polyphosphazenes, poly(ortho ester), poly(cyano acrylates), polyanhydride, modified polysaccharides and modified proteins.

48. The biodegradable polymer fiber included in at least one of the SYNERGY™ Over-The-Wire Products includes aliphatic polyesters selected from the group consisting of poly(glycolic acid), poly(lactic acid), poly(alkylene succinates) poly(hydroxybutyrate), poly(butylene diglycolate), poly(epsilon-caprolactone) and copolymers, blends and mixtures thereof.

49. The therapeutic agent included the biodegradable polymer fiber included in at least one of the SYNERGY™ Over-The-Wire Products is released over time from said fiber.

C. P150003 PRODUCTS

50. At least one of the P150003 Products includes a biodegradable polymer fiber. For example, at least one of the P150003 Products is composed of bioabsorbable polymer.

51. The biodegradable polymer fiber included in at least one of the P150003 Products comprises a first phase and a second phase. For example, the biodegradable polymer fiber included in at least one of the P150003 Products comprises polymer structure and structure containing pharmacological agents.

52. The first phase and the second phase comprising the biodegradable polymer fiber included in at least one of the P150003 Products are immiscible. For example, the polymer structure and the structure containing pharmacological agents comprising the

biodegradable polymer fiber included in at least one of the P150003 Products are immiscible.

53. The second phase comprising the biodegradable polymer fiber included in at least one of the P150003 Products includes at least one therapeutic agent. For example, at least one therapeutic agent (e.g., everolimus) is included in the structure containing pharmacological agents comprising the biodegradable polymer fiber included in at least one of the P150003 Products.

54. The second phase comprising the biodegradable polymer fiber included in at least one of the P150003 Products is derived from an aqueous solution, a hydrogel, or a polymer.

55. The therapeutic agent included in the second phase comprising the biodegradable polymer fiber included in at least one of the P150003 Products is a drug, a protein, an enzyme, a growth factor, an immunomodulator, a compound promoting angiogenesis, a compound inhibiting angiogenesis, an anti-inflammatory compound, an antibiotic, a cytokine, an anti-coagulation agent, a pro-coagulation agent, a chemotactic agent, an agent to promote apoptosis, an agent to inhibit apoptosis, or a mitogenic agent. For example, one or more antimicrobial agents are included in the structure containing pharmacological agents comprising the biodegradable polymer fiber included in at least one of the P150003 Products.

56. The biodegradable polymer fiber included in at least one of the P150003 Products is a single polymer, a co-polymer, or a mixture of polymers.

57. The biodegradable polymer fiber included in at least one of the P150003 Products is a single polymer, a co-polymer, or a mixture of polymers selected from the

group consisting of polypeptides, polydepsipeptides, nylon copolyamides, aliphatic polyesters, polydihydropyrans, polyphosphazenes, poly(ortho ester), poly(cyano acrylates), polyanhydride, modified polysaccharides and modified proteins.

58. The biodegradable polymer fiber included in at least one of the P150003 Products includes aliphatic polyesters selected from the group consisting of poly(glycolic acid), poly(lactic acid), poly(alkylene succinates) poly(hydroxybutyrate), poly(butylene diglycolate), poly(epsilon-caprolactone) and copolymers, blends and mixtures thereof.

59. The therapeutic agent included the biodegradable polymer fiber included in at least one of the P150003 Products is released over time from said fiber.

60. Defendant's acts of infringement have caused and will continue to cause substantial and irreparable damage to Plaintiffs.

61. As a result of Defendant's infringement of the '296 Patent, Plaintiffs have been damaged. Plaintiffs are, therefore, entitled to damages pursuant to 35 U.S.C. § 284 in an amount that presently cannot be pled but that will be determined at trial.

V. COUNT II: INFRINGEMENT OF U.S. PATENT NO. 7,033,603 B2

62. Plaintiffs repeat and re-allege each and every allegation of the prior paragraphs as though set forth fully herein.

63. On April 25, 2006, U.S. Patent No. 7,033,603 B2 (the "'603 Patent")—titled "Drug Releasing Biodegradable Fiber for Delivery of Therapeutics"—was duly and legally issued by the United States Patent and Trademark Office on April 25, 2006 to Board of Regents, The University of Texas System, as assignee of named inventors Kevin D. Nelson and Brent B. Crow. A true and correct copy of the '603 Patent is attached hereto as **Exhibit C**.

64. The Board is the owner of all right, title, and interest in and to the '603 Patent

and has granted TissueGen an exclusive license "to manufacture, have manufactured, use, have used, and/or Sell or have Sold" products including inventions and discoveries covered by the '603 Patent and "to otherwise exploit" the Board's rights in information or discoveries covered by the '603 Patent.

65. The '603 Patent is directed to useful and novel compositions that provide for three-dimensional matrices for in vitro and in vivo use comprised of biodegradable polymer fibers capable of the controlled delivery of therapeutic agents.

66. Each and every claim of the '603 Patent is valid and enforceable and enjoys a statutory presumption of validity separate, apart, and in addition to the statutory presumption of validity enjoyed by every other of its claims. 35 U.S.C. § 282.

67. Upon information and belief, Defendant has been, and is currently, directly and/or indirectly infringing one or more claims of the '603 Patent in violation of 35 U.S.C. § 271, including as stated below.

68. Upon information and belief, Defendant has directly infringed, literally and/or under the doctrine of equivalents, and will continue to directly infringe claims of the '603 Patent by making, using, selling, offering to sell, and/or importing into the United States products that embody or practice the apparatus and/or method covered by one or more claims of the '603 Patent, including but not limited to the following products: Defendant's SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (Monorail™ Catheter), including the following products: H7493926008220, H7493926012220, H7493926016220, H7493926020220, H7493926024220, H7493926028220, H7493926032220, H7493926038220, H7493926008250, H7493926012250, H7493926016250, H7493926020250, H7493926024250,

H7493926028250, H7493926032250, H7493926038250, H7493926008270, H7493926012270, H7493926016270, H7493926020270, H7493926024270, H7493926028270, H7493926032270, H7493926038270, H7493926008300, H7493926012300, H7493926016300, H7493926020300, H7493926024300, H7493926028300, H7493926032300, H7493926038300, H7493926008350, H7493926012350, H7493926016350, H7493926020350, H7493926024350, H7493926028350, H7493926032350, H7493926038350, H7493926008400, H7493926012400, H7493926016400, H7493926020400, H7493926024400, H7493926028400, H7493926032400, H7493926038400 and any other products offered and/or sold under the SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (Monorail™ Catheter) name (the "Monorail™ Catheter Products"); Defendant's SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (Over-The-Wire), including the following products: H7493926108220, H7493926112220, H7493926116220, H7493926120220, H7493926124220, H7493926128220, H7493926132220, H7493926138220, H7493926108250, H7493926112250, H7493926116250, H7493926120250, H7493926124250, H7493926128250, H7493926132250, H7493926138250, H7493926108270, H7493926112270, H7493926116270, H7493926120270, H7493926124270, H7493926128270, H7493926132270, H7493926138270, H7493926108300, H7493926112300, H7493926116300, H7493926120300, H7493926124300, H7493926128300, H7493926132300, H7493926138300, H7493926108350, H7493926112350, H7493926116350, H7493926120350, H7493926124350, H7493926128350, H7493926132350, H7493926138350, H7493926108400,

H7493926112400, H7493926116400, H7493926120400, H7493926124400, H7493926128400, H7493926132400, H7493926138400 and any other products offered and/or sold under the SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (Over-the-Wire Catheter) name (the "SYNERGY™ Over-The-Wire Products"); and Defendant's products within the scope of FDA PMA Number P150003 (the "P150003 Products") (collectively, the "'603 Accused Products").

69. On information and belief, Defendant indirectly infringes the '603 Patent by inducing others to infringe one or more claims of the '603 Patent through sale and/or use of the '603 Accused Products. On information and belief, at least as a result of the filing of this action, Defendant is aware of the '603 Patent; is aware that its actions with regards to distributors, resellers, and/or end users of the '603 Accused Products would induce infringement; and despite such awareness will continue to take active steps—such as, creating and disseminating the '603 Accused Products and product manuals, instructions, promotional and marketing materials, and/or technical materials to distributors, resellers, and end users—encouraging others to infringe the '603 Patent with the specific intent to induce such infringement.

70. Plaintiffs adopt, and incorporate by reference, as if fully stated herein, the attached claim chart for claim 19 of the '603 Patent, which is attached hereto as **Exhibit D**. The claim chart describes and demonstrates how Defendant infringes the '603 Patent. In addition, Plaintiffs allege that Defendant infringes one or more additional claims of the '603 Patent in a similar manner.

A. MONORAIL™ CATHETER PRODUCTS

71. At least one of the Monorail™ Catheter Products includes a drug delivery composition.

72. The drug delivery composition included in at least one of the Monorail™ Catheter Products includes at least one fiber.

73. The fiber comprising the drug delivery composition included in at least one of the Monorail™ Catheter Products includes an emulsion consisting of a hydrogel or a colloidal system with at least two phases, one of which phases forms a continuous three-dimensional network that acts as an elastic solid.

B. SYNERGY™ OVER-THE-WIRE PRODUCTS

74. At least one of the SYNERGY™ Over-The-Wire Products includes a drug delivery composition.

75. The drug delivery composition included in at least one of the SYNERGY™ Over-The-Wire Products includes at least one fiber.

76. The fiber comprising the drug delivery composition included in at least one of the SYNERGY™ Over-The-Wire Products includes an emulsion consisting of a hydrogel or a colloidal system with at least two phases, one of which phases forms a continuous three-dimensional network that acts as an elastic solid.

C. P150003 PRODUCTS

77. At least one of the P150003 Products includes a drug delivery composition.

78. The drug delivery composition included in at least one of the P150003 Products includes at least one fiber.

79. The fiber comprising the drug delivery composition included in at least one of the P150003 Products includes an emulsion consisting of a hydrogel or a colloidal system with at least two phases, one of which phases forms a continuous three-dimensional network that acts as an elastic solid.

80. Defendant's acts of infringement have caused and will continue to cause

substantial and irreparable damage to Plaintiffs.

81. As a result of Defendant's infringement of the '603 Patent, Plaintiffs have been damaged. Plaintiffs are, therefore, entitled to damages pursuant to 35 U.S.C. § 284 in an amount that presently cannot be pled but that will be determined at trial.

PRAYER FOR RELIEF

WHEREFORE, PREMISES CONSIDERED, Plaintiffs pray for entry of judgment against Defendant as follows:

A. A judgment that Defendant has infringed and continues to infringe the '296 Patent and the '603 Patent, directly and/or indirectly, as alleged herein;

B. That Defendant provides to Plaintiffs an accounting of all gains, profits, and advantages derived by Defendant's infringement of the '296 Patent and the '603 Patent, and that Plaintiffs be awarded damages adequate to compensate them for the wrongful infringement by Defendant, in accordance with 35 U.S.C. § 284;

C. That Plaintiffs be awarded any other supplemental damages and interest on all damages, including, but not limited to, attorney fees available under 35 U.S.C. § 285;

D. That the Court permanently enjoin Defendant and all those in privity with Defendant from making, having made, selling, offering for sale, distributing, and/or using products that infringe the '296 Patent and the '603 Patent, including the '296 Accused Products and the '603 Accused Products, in the United States; and

E. That Plaintiffs be awarded such other and further relief and all remedies available at law.

DEMAND FOR JURY TRIAL

Pursuant to Federal Rule of Civil Procedure 38(b), Plaintiffs hereby demand a trial by jury on all issues triable to a jury.

Dated: November 20, 2017

Respectfully submitted,

/s/ Alfonso G. Chan

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COUNSEL FOR PLAINTIFFS BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM and TISSUEGEN, INC.

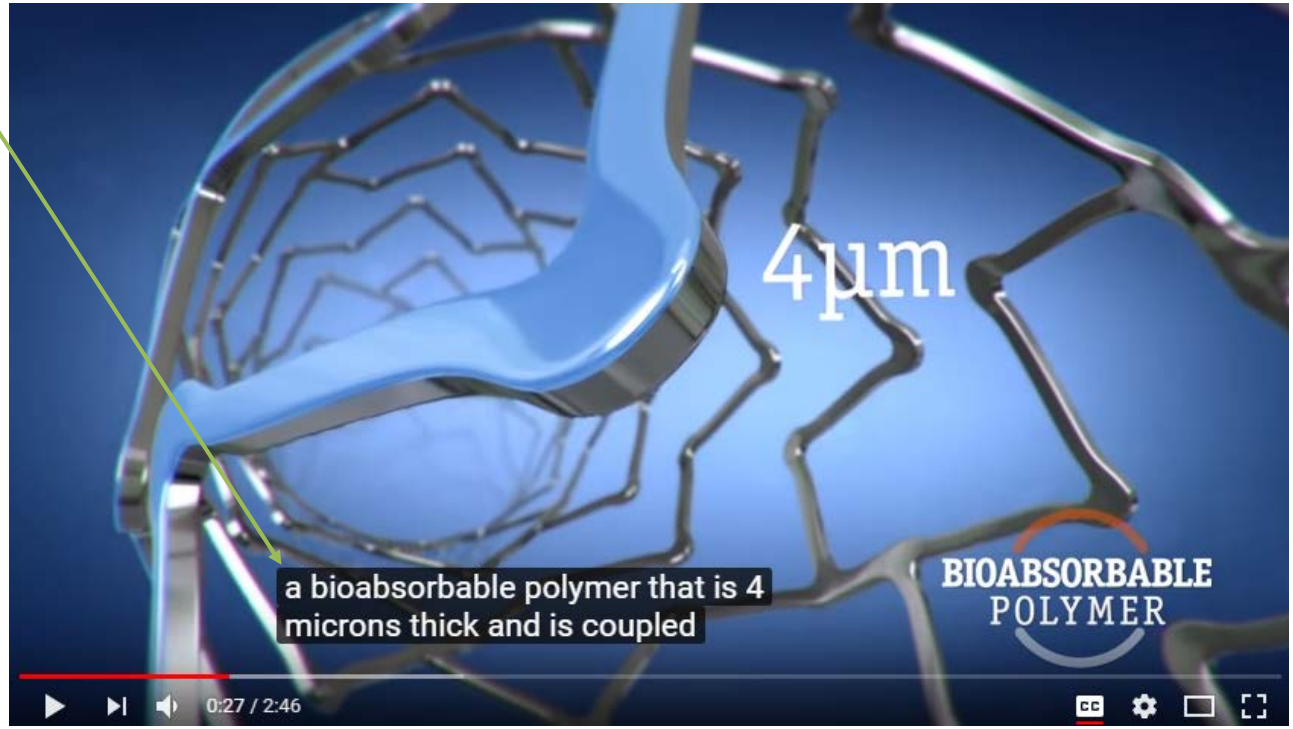
EXHIBIT B

US Patent 6,796,296 Boston Scientific Synergy Everolimus-Eluting Pt-Cr Coronary Stent

Claim 1

A composition comprising at least one **(A) biodegradable polymer fiber**

(A)



Sources: http://www.bostonscientific.com/en-US/products/stents--coronary/bioabsorbable-polymer-stent.html

USP6396296-Boston Scientific Synergy Everolimus-Eluting Pt-Cr Coronary Stent

Claim 1

A composition comprising at least one **(A) biodegradable polymer fiber**

IV. **WARNINGS AND PRECAUTIONS**

The warnings and precautions can be found in the SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System labeling.

V. **DEVICE DESCRIPTION**

The SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY) is a device/drug combination product that provides a mechanical structure for vascular lumen support (primary mode of action) and a pharmacological agent (everolimus) targeted towards reducing the injury response. The System consists of a drug/polymer-coated balloon-expandable stent, pre-mounted on a Monorail™ (MR) or Over-The-Wire (OTW) delivery catheter. The stent is made from a platinum chromium alloy (PtCr). The drug/polymer coating consists of a bioabsorbable polymer, poly (D,L-lactide-co-glycolide) (PLGA), and the active pharmaceutical ingredient, everolimus. The characteristics of the SYNERGY stent system are described in **Table V-T1**.

Table V-T1: SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System Product Description

	SYNERGY Monorail Stent Delivery System	SYNERGY Over-the-Wire Stent Delivery System
Available Stent Lengths (mm)	8, 12, 16, 20, 24, 28, 32, 38	
Available Stent Diameters (mm)	2.25, 2.50, 2.75, 3.00, 3.50, 4.00	
Stent Material	Platinum Chromium Alloy (PtCr)	
Stent Strut Thickness	0.074 mm for diameters 2.25 mm to 2.75 mm 0.079 mm for diameters 3.00mm to 3.50 mm 0.081 mm for diameter of 4.00 mm	
Drug Product	An abluminal (outer surface of the stent) coating of a polymer carrier with approximately 1 µg of everolimus per mm² of total stent surface area with a maximum nominal drug content of 287.2 µg on the largest stent (4.00 x 38 mm).	
Delivery System		
Effective Length	144 cm	
Delivery System Y-Adapter Ports	Single access port to inflation lumen. Guidewire exit port is located approximately 25 cm from tip. Designed for guidewire ≤0.014 inches (0.36 mm)	Y-Connector (Side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen). Designed for guidewire ≤0.014 inches (0.36 mm)
Stent Delivery	A balloon, with two radiopaque balloon markers, nominally placed 0.4 mm (0.016 inches) beyond the stent at each end.	
Balloon Inflation Pressure	Nominal Inflation Pressure: • Diameters 2.25 mm, 2.50 mm, 2.75 mm, 3.00 mm, 3.50 mm, 4.00 mm: 11 atm (1117 kPa) Rated Burst Inflation Pressure: • Diameters 2.25 mm – 2.75 mm: 18 atm (1827 kPa) • Diameters 3.00 mm – 4.00 mm: 16 atm (1620 kPa)	

PMA P150003: FDA Summary of Safety and Effectiveness Data Page 2

DEVICE DESCRIPTION

The SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY) is a device/drug combination product that provides a mechanical structure for vascular lumen support (primary mode of action) and a pharmacological agent (everolimus) targeted towards reducing the injury response. The System consists of a drug/polymer-coated balloon-expandable stent, pre-mounted on a Monorail™ (MR) or Over-The-Wire (OTW) delivery catheter. The stent is made from a platinum chromium alloy (PtCr). The drug/polymer coating consists of a bioabsorbable polymer, poly (D,L-lactide-co-glycolide) (PLGA), and the active pharmaceutical ingredient, everolimus. The characteristics of the SYNERGY stent system are described in **Table V-T1**.

Sources: FDA P150003 PMA, 2015

USP6396296-Boston Scientific Synergy Everolimus-Eluting Pt-Cr Coronary Stent

Claim 1

A composition comprising at least one **(A) biodegradable polymer fiber**

Poly (lactic-co-glycolic acid) (PLGA) copolymers have been broadly used in controlled drug release applications. Because these polymers are biodegradable, they provide an attractive option for drug delivery vehicles. There are a variety of material, processing, and physiological factors that impact the degradation rates of PLGA polymers and concurrent drug release kinetics. This work is intended to provide a comprehensive and collective review of the physicochemical and physiological factors that dictate the degradation behavior of PLGA polymers and drug release from contemporary PLGA-based drug-polymer products. In conjunction with the existing experimental results, analytical and numerical theories developed to predict drug release from PLGA-based polymers are summarized and correlated with the experimental observations.

Sources: Polymer degradation and drug delivery in PLGA-based drug-polymer applications: a review of experiments and theories, PubMed ID: #27098357, 2016

USP6396296-Boston Scientific Synergy Everolimus-Eluting Pt-Cr Coronary Stent

Claim 1

wherein said fiber is composed of a **(B) first phase** and a **(C) second phase**,

IV. **WARNINGS AND PRECAUTIONS**

The warnings and precautions can be found in the SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System labeling.

V. **DEVICE DESCRIPTION**

The SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY) is a device/drug combination product that provides a mechanical structure for vascular lumen support (primary mode of action) and a pharmacological agent (everolimus) targeted towards reducing the injury response. The System consists of a drug/polymer-coated balloon-expandable stent, pre-mounted on a Monorail™ (MR) or Over-The-Wire (OTW) delivery catheter. The stent is made from a platinum chromium alloy (PtCr). The drug/polymer coating consists of a bioabsorbable polymer, poly (D,L-lactide-co-glycolide) (PLGA), and the active pharmaceutical ingredient, everolimus. The characteristics of the SYNERGY stent system are described in **Table V-T1**.

Table V-T1: SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System Product Description

	SYNERGY Monorail Stent Delivery System	SYNERGY Over-the-Wire Stent Delivery System
Available Stent Lengths (mm)	8, 12, 16, 20, 24, 28, 32, 38	
Available Stent Diameters (mm)	2.25, 2.50, 2.75, 3.00, 3.50, 4.00	
Stent Material	Platinum Chromium Alloy (PtCr)	
Stent Strut Thickness	0.074 mm for diameters 2.25 mm to 2.75 mm 0.079 mm for diameters 3.00mm to 3.50 mm 0.081 mm for diameter of 4.00 mm	
Drug Product	An abluminal (outer surface of the stent) coating of a polymer carrier with approximately 1 µg of everolimus per mm² of total stent surface area with a maximum nominal drug content of 287.2 µg on the largest stent (4.00 x 38 mm).	
Delivery System		
Effective Length	144 cm	
Delivery System Y-Adapter Ports	Single access port to inflation lumen. Guidewire exit port is located approximately 25 cm from tip. Designed for guidewire ≤0.014 inches (0.36 mm)	Y-Connector (Side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen). Designed for guidewire ≤0.014 inches (0.36 mm)
Stent Delivery	A balloon, with two radiopaque balloon markers, nominally placed 0.4 mm (0.016 inches) beyond the stent at each end.	
Balloon Inflation Pressure	Nominal Inflation Pressure: • Diameters 2.25 mm, 2.50 mm, 2.75 mm, 3.00 mm, 3.50 mm, 4.00 mm: 11 atm (1117 kPa) Rated Burst Inflation Pressure: • Diameters 2.25 mm – 2.75 mm: 18 atm (1827 kPa) • Diameters 3.00 mm – 4.00 mm: 16 atm (1620 kPa)	

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DEVICE DESCRIPTION

The SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY) is a device/drug combination product that provides a mechanical structure for vascular lumen support (primary mode of action) and a pharmacological agent (everolimus) targeted towards reducing the injury response. The System consists of a drug/polymer-coated balloon-expandable stent, pre-mounted on a Monorail™ (MR) or Over-The-Wire (OTW) delivery catheter. The stent is made from a platinum chromium alloy (PtCr). The drug/polymer coating consists of a bioabsorbable polymer, poly (D,L-lactide-co-glycolide) (PLGA), and the active pharmaceutical ingredient, everolimus. The characteristics of the SYNERGY stent system are described in **Table V-T1**.

(B)

(C)

Sources: FDA P150003 PMA, 2015

USP6396296-Boston Scientific Synergy Everolimus-Eluting Pt-Cr Coronary Stent

Claim 1

the **first** and **second phases** (D) being immiscible,

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System labeling.

V. DEVICE DESCRIPTION

The SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY) is a device/drug combination product that provides a mechanical structure for vascular lumen support (primary mode of action) and a pharmacological agent (everolimus) targeted towards reducing the injury response. The System consists of a drug/polymer-coated balloon-expandable stent, pre-mounted on a Monorail™ (MR) or Over-The-Wire (OTW) delivery catheter. The stent is made from a platinum chromium alloy (PtCr). The drug/polymer coating consists of a bioabsorbable polymer, poly (D,L-lactide-co-glycolide) (PLGA), and the active pharmaceutical ingredient, everolimus. The characteristics of the SYNERGY stent system are described in **Table V-T1**.

Table V-T1: SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System Product Description

	SYNERGY Monorail Stent Delivery System	SYNERGY Over-the-Wire Stent Delivery System
Available Stent Lengths (mm)	8, 12, 16, 20, 24, 28, 32, 38	
Available Stent Diameters (mm)	2.25, 2.50, 2.75, 3.00, 3.50, 4.00	
Stent Material	Platinum Chromium Alloy (PtCr)	
Stent Strut Thickness	0.074 mm for diameters 2.25 mm to 2.75 mm 0.079 mm for diameters 3.00mm to 3.50 mm 0.081 mm for diameter of 4.00 mm	
Drug Product	An abluminal (outer surface of the stent) coating of a polymer carrier with approximately 1 µg of everolimus per mm² of total stent surface area with a maximum nominal drug content of 287.2 µg on the largest stent (4.00 x 38 mm).	
Delivery System		
Effective Length	144 cm	
Delivery System Y-Adapter Ports	Single access port to inflation lumen. Guidewire exit port is located approximately 25 cm from tip. Designed for guidewire ≤0.014 inches (0.36 mm)	Y-Connector (Side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen). Designed for guidewire ≤0.014 inches (0.36 mm)
Stent Delivery	A balloon, with two radiopaque balloon markers, nominally placed 0.4 mm (0.016 inches) beyond the stent at each end.	
Balloon Inflation Pressure	Nominal Inflation Pressure: • Diameters 2.25 mm, 2.50 mm, 2.75 mm, 3.00 mm, 3.50 mm, 4.00 mm: 11 atm (1117 kPa) Rated Burst Inflation Pressure: • Diameters 2.25 mm – 2.75 mm: 18 atm (1827 kPa) • Diameters 3.00 mm – 4.00 mm: 16 atm (1620 kPa)	

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(B)

DEVICE DESCRIPTION

The SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY) is a device/drug combination product that provides a mechanical structure for vascular lumen support (primary mode of action) and a pharmacological agent (everolimus) targeted towards reducing the injury response. The System consists of a drug/polymer-coated balloon-expandable stent, pre-mounted on a Monorail™ (MR) or Over-The-Wire (OTW) delivery catheter. The stent is made from a platinum chromium alloy (PtCr). The drug/polymer coating consists of a bioabsorbable polymer, poly (D,L-lactide-co-glycolide) (PLGA), and the active pharmaceutical ingredient, everolimus. The characteristics of the SYNERGY stent system are described in **Table V-T1**.

(C)

Sources: FDA P150003 PMA, 2015

USP6396296-Boston Scientific Synergy Everolimus-Eluting Pt-Cr Coronary Stent

Claim 1

the **first** and **second phases** (D) being immiscible,

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System labeling.

V. DEVICE DESCRIPTION

The SYNERGY™ Everolimus-Eluting (SYNERGY) is a device/drug combinat for vascular lumen support (primary mc (everolimus) targeted towards reducing drug/polymer-coated balloon-expandable stent, pre-mounted on a Monorail™ (MR) or Over-The-Wire (OTW) delivery catheter. The stent is made from a platinum chromium alloy (PtCr). The drug/polymer coating consists of a bioabsorbable polymer, poly (D,L-lactide-co-glycolide) (PLGA), and the active pharmaceutical ingredient, everolimus. The characteristics of the SYNERGY stent system are described in **Table V-T1**.

(D)

Drug Product	An abluminal (outer surface of the stent) coating of a polymer carrier with approximately 1 µg of everolimus per mm^2 of total stent surface area with a maximum nominal drug content of 287.2 µg on the largest stent (4.00 x 38 mm).

Table V-T1: SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System

Product Description		
	SYNERGY Monorail Stent Delivery System	SYNERGY Over-the-Wire Stent Delivery System
Available Stent Lengths (mm)	8, 12, 16, 20, 24, 28, 32, 38	
Available Stent Diameters (mm)	2.25, 2.50, 2.75, 3.00, 3.50, 4.00	
Stent Material	Platinum Chromium Alloy (PtCr)	
Stent Strut Thickness	0.074 mm for diameters 2.25 mm to 2.75 mm 0.079 mm for diameters 3.00mm to 3.50 mm 0.08 mm for diameter of 4.00 mm	
Drug Product	An abluminal (outer surface of the stent) coating of a polymer carrier with approximately 1 µg of everolimus per mm^2 of total stent surface area with a maximum nominal drug content of 287.2 µg on the largest stent (4.00 x 38 mm).	
Delivery System		
Effective Length	144 cm	
Delivery System Y-Adapter Ports	Single access port to inflation lumen. Guidewire exit port is located approximately 25 cm from tip. Designed for guidewire ≤0.014 inches (0.36 mm)	Y-Connector (Side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen). Designed for guidewire ≤0.014 inches (0.36 mm)
Stent Delivery	A balloon, with two radiopaque balloon markers, nominally placed 0.4 mm (0.016 inches) beyond the stent at each end.	
Balloon Inflation Pressure	Nominal Inflation Pressure: • Diameters 2.25 mm, 2.50 mm, 2.75 mm, 3.00 mm, 3.50 mm, 4.00 mm: 11 atm (1117 kPa) Rated Burst Inflation Pressure: • Diameters 2.25 mm – 2.75 mm: 18 atm (1827 kPa) • Diameters 3.00 mm – 4.00 mm: 16 atm (1620 kPa)	

PMA P150003: FDA Summary of Safety and Effectiveness Data Page 2

Sources: FDA P150003 PMA, 2015

USP6396296-Boston Scientific Synergy Everolimus-Eluting Pt-Cr Coronary Stent

Claim 1

and wherein the **second phase** comprises **(E) one or more therapeutic agents**.

IV. **WARNINGS AND PRECAUTIONS**

The warnings and precautions can be found in the SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System labeling.

V. **DEVICE DESCRIPTION**

The SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY) is a device/drug combination product that provides a mechanical structure for vascular lumen support (primary mode of action) and a pharmacological agent (everolimus) targeted towards reducing the injury response. The System consists of a drug/polymer-coated balloon-expandable stent, pre-mounted on a Monorail™ (MR) or Over-The-Wire (OTW) delivery catheter. The stent is made from a platinum chromium alloy (PtCr). The drug/polymer coating consists of a bioabsorbable polymer, poly (D,L-lactide-co-glycolide) (PLGA), and the active pharmaceutical ingredient, everolimus. The characteristics of the SYNERGY stent system are described in **Table V-T1**.

Table V-T1: SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System Product Description

	SYNERGY Monorail Stent Delivery System	SYNERGY Over-the-Wire Stent Delivery System
Available Stent Lengths (mm)	8, 12, 16, 20, 24, 28, 32, 38	
Available Stent Diameters (mm)	2.25, 2.50, 2.75, 3.00, 3.50, 4.00	
Stent Material	Platinum Chromium Alloy (PtCr)	
Stent Strut Thickness	0.074 mm for diameters 2.25 mm to 2.75 mm 0.079 mm for diameters 3.00mm to 3.50 mm 0.081 mm for diameter of 4.00 mm	
Drug Product	An abluminal (outer surface of the stent) coating of a polymer carrier with approximately 1 µg of everolimus per mm² of total stent surface area with a maximum nominal drug content of 287.2 µg on the largest stent (4.00 x 38 mm).	
Delivery System		
Effective Length	144 cm	
Delivery System Y-Adapter Ports	Single access port to inflation lumen. Guidewire exit port is located approximately 25 cm from tip. Designed for guidewire ≤0.014 inches (0.36 mm)	Y-Connector (Side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen). Designed for guidewire ≤0.014 inches (0.36 mm)
Stent Delivery	A balloon, with two radiopaque balloon markers, nominally placed 0.4 mm (0.016 inches) beyond the stent at each end.	
Balloon Inflation Pressure	Nominal Inflation Pressure: • Diameters 2.25 mm, 2.50 mm, 2.75 mm, 3.00 mm, 3.50 mm, 4.00 mm: 11 atm (1117 kPa)	
	Rated Burst Inflation Pressure: • Diameters 2.25 mm – 2.75 mm: 18 atm (1827 kPa) • Diameters 3.00 mm – 4.00 mm: 16 atm (1620 kPa)	

PMA P150003: FDA Summary of Safety and Effectiveness Data Page 2

DEVICE DESCRIPTION

The SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY) is a device/drug combination product that provides a mechanical structure for vascular lumen support (primary mode of action) and a pharmacological agent (everolimus) targeted towards reducing the injury response. The System consists of a drug/polymer-coated balloon-expandable stent, pre-mounted on a Monorail™ (MR) or Over-The-Wire (OTW) delivery catheter. The stent is made from a platinum chromium alloy (PtCr). The drug/polymer coating consists of a bioabsorbable polymer, poly (D,L-lactide-co-glycolide) (PLGA), and the active pharmaceutical ingredient, everolimus. The characteristics of the SYNERGY stent system are described in **Table V-T1**.

(E)

Sources: FDA P150003 PMA, 2015

EXHIBIT D

USP 7,033,603 Boston Scientific Synergy Everolimus-Eluting Pt-Cr Coronary Stent

Claim 19

A drug delivery composition comprising a fiber,

IV. **WARNINGS AND PRECAUTIONS**

The warnings and precautions can be found in the SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System labeling.

V. **DEVICE DESCRIPTION**

The SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY) is a device/drug combination product that provides a mechanical structure for vascular lumen support (primary mode of action) and a pharmacological agent (everolimus) targeted towards reducing the injury response. The System consists of a drug/polymer-coated balloon-expandable stent, pre-mounted on a Monorail™ (MR) or Over-The-Wire (OTW) delivery catheter. The stent is made from a platinum chromium alloy (PtCr). The drug/polymer coating consists of a bioabsorbable polymer, poly (D,L-lactide-co-glycolide) (PLGA), and the active pharmaceutical ingredient, everolimus. The characteristics of the SYNERGY stent system are described in **Table V-T1**.

Table V-T1: SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System Product Description

	SYNERGY Monorail Stent Delivery System	SYNERGY Over-the-Wire Stent Delivery System
Available Stent Lengths (mm)	8, 12, 16, 20, 24, 28, 32, 38	
Available Stent Diameters (mm)	2.25, 2.50, 2.75, 3.00, 3.50, 4.00	
Stent Material	Platinum Chromium Alloy (PtCr)	
Stent Strut Thickness	0.074 mm for diameters 2.25 mm to 2.75 mm 0.079 mm for diameters 3.00mm to 3.50 mm 0.081 mm for diameter of 4.00 mm	
Drug Product	An abluminal (outer surface of the stent) coating of a polymer carrier with approximately 1 µg of everolimus per mm² of total stent surface area with a maximum nominal drug content of 287.2 µg on the largest stent (4.00 x 38 mm).	
Delivery System		
Effective Length	144 cm	
Delivery System Y-Adapter Ports	Single access port to inflation lumen. Guidewire exit port is located approximately 25 cm from tip. Designed for guidewire ≤0.014 inches (0.36 mm)	Y-Connector (Side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen). Designed for guidewire ≤0.014 inches (0.36 mm)
Stent Delivery	A balloon, with two radiopaque balloon markers, nominally placed 0.4 mm (0.016 inches) beyond the stent at each end.	
Balloon Inflation Pressure	Nominal Inflation Pressure: • Diameters 2.25 mm, 2.50 mm, 2.75 mm, 3.00 mm, 3.50 mm, 4.00 mm: 11 atm (1117 kPa) Rated Burst Inflation Pressure: • Diameters 2.25 mm – 2.75 mm: 18 atm (1827 kPa) • Diameters 3.00 mm – 4.00 mm: 16 atm (1620 kPa)	

PMA P150003: FDA Summary of Safety and Effectiveness Data Page 2

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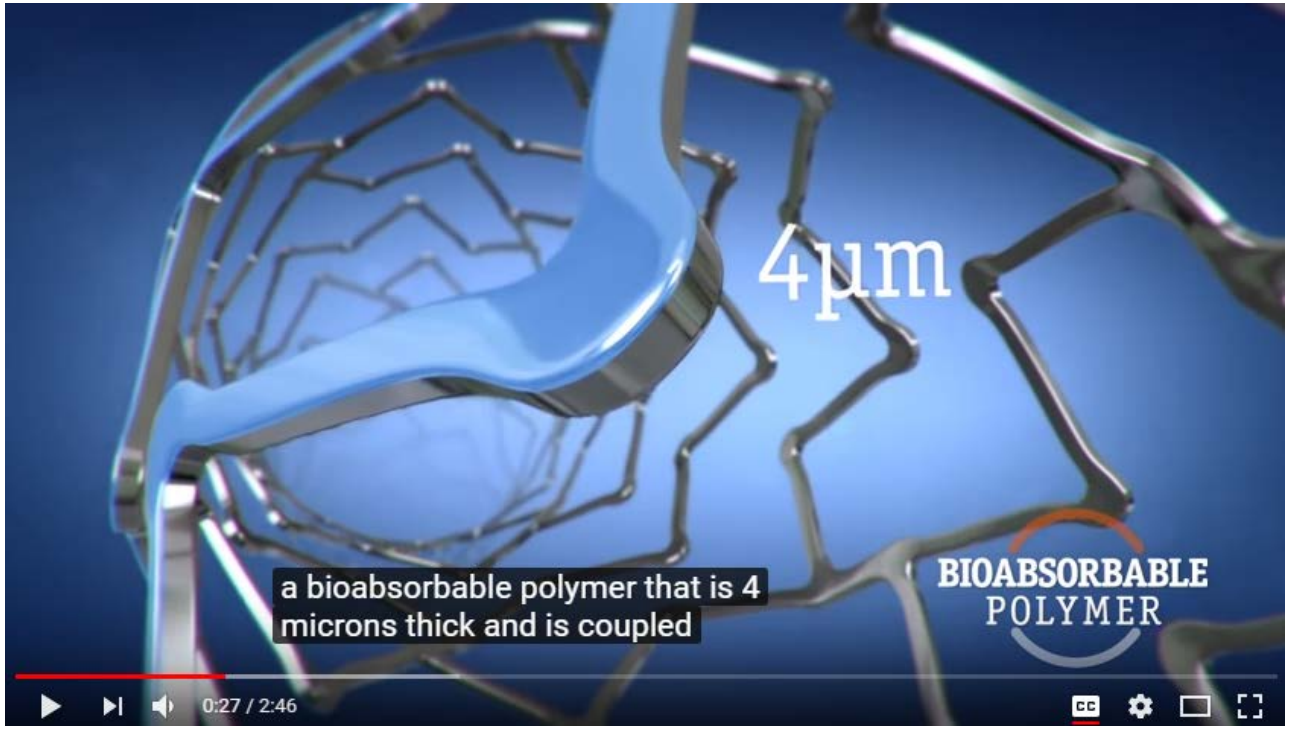
The SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY) is a device/drug combination product that provides a mechanical structure for vascular lumen support (primary mode of action) and a pharmacological agent (everolimus) targeted towards reducing the injury response. The System consists of a drug/polymer-coated balloon-expandable stent, pre-mounted on a Monorail™ (MR) or Over-The-Wire (OTW) delivery catheter. The stent is made from a platinum chromium alloy (PtCr). The drug/polymer coating consists of a bioabsorbable polymer, poly (D,L-lactide-co-glycolide) (PLGA), and the active pharmaceutical ingredient, everolimus. The characteristics of the SYNERGY stent system are described in **Table V-T1**.

Sources: FDA P150003 PMA, 2015

USP 7,033,603 Boston Scientific Synergy Everolimus Eluting Pt-Cr Coronary Stent

Claim 19

A drug delivery composition comprising a fiber,



Sources: http://www.bostonscientific.com/en-US/products/stents--coronary/bioabsorbable-polymer-stent.html

USP 7,036,603-Boston Scientific Synergy Everolimus-Eluting Pt-Cr Coronary Stent

Claim 19

wherein said fiber comprises an **emulsion consisting essentially of a gel** or hydrogel

IV. **WARNINGS AND PRECAUTIONS**

The warnings and precautions can be found in the SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System labeling.

V. **DEVICE DESCRIPTION**

The SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY) is a device/drug combination product that provides a mechanical structure for vascular lumen support (primary mode of action) and a pharmacological agent (everolimus) targeted towards reducing the injury response. The System consists of a drug/polymer-coated balloon-expandable stent, pre-mounted on a Monorail™ (MR) or Over-The-Wire (OTW) delivery catheter. The stent is made from a platinum chromium alloy (PtCr). The drug/polymer coating consists of a bioabsorbable polymer, poly (D,L-lactide-co-glycolide) (PLGA), and the active pharmaceutical ingredient, everolimus. The characteristics of the SYNERGY stent system are described in **Table V-T1**.

Table V-T1: SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System Product Description

	SYNERGY Monorail Stent Delivery System	SYNERGY Over-the-Wire Stent Delivery System
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Delivery System		
Effective Length	144 cm	
Delivery System Y-Adapter Ports	Single access port to inflation lumen. Guidewire exit port is located approximately 25 cm from tip. Designed for guidewire ≤0.014 inches (0.36 mm)	Y-Connector (Side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen). Designed for guidewire ≤0.014 inches (0.36 mm)
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PMA P150003: FDA Summary of Safety and Effectiveness Data Page 2

DEVICE DESCRIPTION

The SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY) is a device/drug combination product that provides a mechanical structure for vascular lumen support (primary mode of action) and a pharmacological agent (everolimus) targeted towards reducing the injury response. The System consists of a drug/polymer-coated balloon-expandable stent, pre-mounted on a Monorail™ (MR) or Over-The-Wire (OTW) delivery catheter. The stent is made from a platinum chromium alloy (PtCr). The drug/polymer coating consists of a bioabsorbable polymer, poly (D,L-lactide-co-glycolide) (PLGA), and the active pharmaceutical ingredient, everolimus. The characteristics of the SYNERGY stent system are described in **Table V-T1**.

An embodiment of the invention provides a bi-component fiber where the inner bore of the fiber, i.e., inside diameter of the fiber, comprises a gel or hydrogel and the outer wall of the fiber comprises a biodegradable polymer. As used herein, the term "gel" refers to a colloidal system with at least two phases, one of which forms a continuous three-dimensional network that acts as an elastic solid. As used herein, the term "hydrogel" refers to a colloid in which a dispersed phase (colloid) is combined with a continuous phase (water) to produce a viscous jellylike product.

Sources: FDA P150003 PMA, 2015, US7036603, Col. 5, lines 33-42

US7036603-Boston Scientific Synergy Everolimus-Eluting Pt-Cr Coronary Stent

Claim 19

wherein said fiber comprises an **emulsion consisting essentially of a gel** or hydrogel

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System labeling.

V. DEVICE DESCRIPTION

The SYNERGY™ Everolimus-Eluting (SYNERGY) is a device/drug combinat for vascular lumen support (primary mc (everolimus) targeted towards reducing drug/polymer-coated balloon-expandable stent, pre-mounted on a Monorail™ (MR) or Over-The-Wire (OTW) delivery catheter. The stent is made from a platinum chromium alloy (PtCr). The drug/polymer coating consists of a bioabsorbable polymer, poly (D,L-lactide-co-glycolide) (PLGA), and the active pharmaceutical ingredient, everolimus. The characteristics of the SYNERGY stent system are described in **Table V-T1**.

Drug Product	An abluminal (outer surface of the stent) coating of a polymer carrier with approximately 1 µg of everolimus per mm^2 of total stent surface area with a maximum nominal drug content of 287.2 µg on the largest stent (4.00 x 38 mm).

Table V-T1: SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System

	SYNERGY Monorail Stent Delivery System	SYNERGY Over-the-Wire Stent Delivery System
Available Stent Lengths (mm)	8, 12, 16, 20, 24, 28, 32, 38	
Available Stent Diameters (mm)	2.25, 2.50, 2.75, 3.00, 3.50, 4.00	
Stent Material	Platinum Chromium Alloy (PtCr)	
Stent Strut Thickness	0.074 mm for diameters 2.25 mm to 2.75 mm 0.079 mm for diameters 3.00mm to 3.50 mm 0.08 mm for diameter of 4.00 mm	
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PMA P150003: FDA Summary of Safety and Effectiveness Data Page 2

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Sources: FDA P150003 PMA, 2015, US7036603, Col. 5, lines 33-42

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF TEXAS
AUSTIN DIVISION

BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM; and TISSUEGEN, INC., Plaintiff, v. BOSTON SCIENTIFIC CORP., Defendant.	CASE NO. 1:17-CV-01103-LY

DEFENDANT BOSTON SCIENTIFIC CORPORATION'S MOTION TO DISMISS PLAINTIFF'S COMPLAINT UNDER FED. R. CIV. P. 12(B)(3)

Defendant Boston Scientific Corporation ("BSC") hereby moves this Court to dismiss this action filed by plaintiffs Board of Regents, the University of Texas System, and Tissuegen, Inc. (collectively, "Plaintiffs") for improper venue pursuant to Federal Rule of Civil Procedure 12(b)(3). In the alternative, BSC requests that the Court transfer this case to the U.S. District Court for the District of Delaware.

I. INTRODUCTION

BSC moves to dismiss this case under Federal Rule of Civil Procedure 12(b)(3) because venue in this jurisdiction is improper. Plaintiffs concede that BSC is not incorporated in this District and is, in fact, a Delaware corporation headquartered in Boston, Massachusetts. Therefore, BSC cannot be said to "reside" in this District under *TC Heartland LLC v. Kraft Foods Group Brands LLC*, 137 S. Ct. 1515, 1517, 1518–19 (2017). Plaintiffs also do not–and cannot–allege that BSC has a regular and established place of business in this District (which would constitute the only other ground for an assertion of proper venue in a patent infringement case such as this). Instead, Plaintiffs assert that the sovereign immunity of the University of Texas is sufficient to establish proper venue under 28 U.S.C. § 1400(b). This assertion, however, is legally incorrect under established precedent. For these reasons, which are explained in more detail below, this action should be dismissed. In the alternative, BSC requests that the Court transfer this action to the U.S. District Court for the District of Delaware.

II. FACTUAL BACKGROUND

On November 20, 2017, Plaintiffs filed a complaint accusing BSC of infringing U.S. Patent Nos. 6,596,296 and 7,033,603 ("the asserted patents"). (Doc. No. 1 at ¶¶ 21–81.) In particular, Plaintiffs contend that BSC has infringed the asserted patents through the manufacture and/or sale of a range of coronary stent systems. *Id.* ¶¶ 27, 68. The Complaint concedes that BSC is incorporated in the State of Delaware and headquartered in Boston, Massachusetts. *Id.* at

¶ 4. The Complaint does not allege that BSC owns or leases any property in the Western District of Texas or that it otherwise maintains a "regular and established" place of business in the District. In point of fact, BSC does not own or lease any property in the Western District of Texas and does not maintain any business address there. (Declaration of Paul Donhauser In Support of Defendant Boston Scientific Corporation's Motion to Dismiss ("Donhauser Decl.") ¶¶ 4-5.) And though BSC employs approximately forty-six employees in this District, these employees maintain home offices and do not work in locations that are owned, leased, or otherwise controlled by BSC. *Id.* Moreover, only seven of these employees are employed in positions related to BSC's interventional cardiology division, which makes and markets the coronary stent systems accused of infringement. *Id.*

III. ARGUMENT

A. Venue In This District Is Improper

Venue in patent cases is governed by 28 U.S.C. § 1400(b), which "constitute[s] the exclusive provision controlling venue in patent infringement proceedings." *TC Heartland*, 137 S. Ct. at 1518 (*quoting Stonite Products Co. v. Melvin Lloyd Co.*, 314 U.S. 561, 563 (1942)). The Plaintiffs bear the burden of establishing that venue in this District is proper under § 1400(b). *See LoganTree LP v. Garmin Int'l, Inc.*, No. SA-17-CA-0098-FB, 2017 WL 2842870, at *1 (W.D. Tex. June 22, 2017) ("Plaintiff has the burden of proving venue is proper in the Western District of Texas now that defendants have filed their motion to dismiss.") (citing *Medical Designs, Inc. v. Orthopedic Technology, Inc.*, 684 F. Supp. 445, 446 (N.D. Tex. 1988)).

Under § 1400(b), venue is proper (1) "where the defendant resides," or (2) "where the defendant has committed acts of infringement and has a regular and established place of business." For purposes of the patent venue statute, "a domestic corporation 'resides' only in its State of incorporation." *TC Heartland*, 137 S. Ct. at 1520-21 17. Ignoring *TC Heartland*,

Plaintiffs contend that venue is proper here because the University of Texas "is an arm of the State of Texas," and – they assert –this Court possesses personal jurisdiction. (Compl. ¶¶ 7, 10.) *TC Heartland* makes clear that this is the improper test for venue. *See TC Heartland*, 137 S. Ct. at 1517-21(rejecting the argument that 28 U.S.C. § 1391(c), which provides that a corporation "resides," for general venue purposes, in any judicial district in which the defendant is subject to the court's personal jurisdiction, modified the meaning of "resides" with respect to the patent venue statute).

If – as is the case here – a defendant does not reside in the district in question, venue is only proper if "'[the] defendant has' a 'place of business' [in the district] that is 'regular' and 'established.'" *In re Cray*, 871 F.3d at 1362. A "place of business" "must be a physical place in the district." *Id.* Plaintiffs do not and cannot allege any facts in the Complaint to establish that BSC has a "regular and established place of business" in this District because BSC does not have *any* place of business in this District. (Donhauser Decl. ¶¶ 4-5.) Although BSC has forty-six employees working in this District, these employees work from home. *Id.* ¶ 6. BSC does not own, lease, or otherwise control its employees' homes. *Id.* Thus, their homes do not constitute a "place" within the meaning of § 1400(b) because. *Cray*, 871 F.3d at 1365 (finding that venue was improper in the district where the Defendant's employees merely worked from home); *see also CAO Lighting, Inc. v. Light Efficient Design & Electrical Wholesale Supply Co., Inc.*, No. 4:16-cv-00482-DCN, 2017 WL 4556717, at *2 (D. Idaho Oct. 11, 2017) (holding that sales representatives working in the district were insufficient for establishing venue where the defendant did not have a regular and established business location in the district). Nor do BSC's

employees in the District keep inventory in their homes. (Donhauser Decl. ¶ 6.)[1] Because BSC does not own or lease a place of business in this District, and because it does not operate or otherwise control its employees' homes there, BSC cannot be said to have does not have a "regular and established place of business" here, and venue thus is improper. *See e.g.*, *LoganTree LP*, 2017 WL 2842870 (W.D. Tex. June 22, 2017) (dismissing for lack of venue because the defendant did not have a physical location in Texas); *Realtime Data LLC v. Acronis, Inc.*, No. 6:17-cv-118 RWS-JDL, 2017 WL 3276385, at *1 (E.D. Tex. July 14, 2017) (dismissing complaint for lack of venue in part because defendant "d[id] not own, lease, or rent any office space in Texas").

B. Plaintiffs' Assertion that the University's "Sovereign Immunity" Can Create Proper Venue Is Wrong as a Matter of Law

Plaintiffs wrongly assert that the sovereign immunity to suit potentially enjoyed by the University of Texas creates proper venue in this District for their patent infringement claims against BSC. Admittedly, a state university may be deemed an arm of its state and thus accorded the same Eleventh Amendment protections as a state. *Tegic Commc'ns Corp. v. Bd. Of Regents of Univ. of Tex. Sys.*, 458 F.3d 1335, 1340 (Fed. Cir. 2006). And such protections typically include the "waivable immunity from suit" in federal court. But while the Eleventh Amendment provides "the waivable immunity from suit" in federal court, such protections do not extend to suits in which the state entity itself is the plaintiff. *See In re Regents of the Univ. of Cal.*, 964 F.2d 1128 (Fed. Cir. 1992) (refusing to deny transfer of venue in an MDL action filed by the Regents of the University of California). As Federal Circuit has explained, "the Eleventh Amendment applies to suits '*against*' a state, not suits *by* a state." *Regents of the University of California v. Eli Lilly & Co*, 119 F.3d 1559, 1564 (Fed. Cir. 1997) (emphasis added). Because

[1] *Cf. Cray* at 1363-64 (noting that it may be pertinent to the venue analysis if the defendant stored inventory in an employee's home in the district or distributed from that place).

the University of Texas is the *plaintiff* in this patent infringement action, not the defendant, its sovereign immunity is irrelevant to the venue analysis.

C. If the Court Does Not Dismiss, This Action Should Be Transferred to the District of Delaware

Under 28 U.S.C. § 1406(a), a district court should "dismiss, or if it be in the interest of justice, transfer such case to any district or division in which it could have been brought," a case that has been brought in a district where venue is "wrong" or "improper." *Atlantic Marine Const. Co., Inc. v. U.S. D. Ct. for the W.D. Of Texas*, 134 S. Ct. 568, 577 (2013). Should the Court decide to transfer rather than dismiss this action, venue is proper in the District of Delaware under the requirements of § 1400(b). As noted above, BSC is incorporated in the District of Delaware and thus indisputably resides there. Moreover, BSC has been a party in no fewer than twenty-two patent infringement suits in the District of Delaware involving coronary stent system technology. That Court thus is well-suited to preside over Plaintiffs' claims of infringement here.

IV. CONCLUSION

For at least the foregoing reasons, BSC neither resides in this District nor maintains a regular and established place of business in this District. No amendment to the Complaint can cure these defects because there are no facts under which Plaintiffs could establish venue. BSC therefore requests that the Court dismiss the Complaint for improper venue without leave to amend. In the alternative, BSC requests that the Court transfer this action to the U.S. District Court for the District of Delaware.

Dated: February 1, 2018

Respectfully submitted,

ARNOLD & PORTER

By: */s/Christopher M. Odell*

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ATTORNEYS FOR DEFENDANT BOSTON SCIENTIFIC CORP.

CERTIFICATE OF SERVICE

The undersigned hereby certifies that all counsel of record who are deemed to have consented to electronic service are being served with a copy of this document via the Court's CM/ECF system on February 1, 2018.

/s/ Christopher M. Odell
Christopher M. Odell

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF TEXAS
AUSTIN DIVISION

BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM; and TISSUEGEN, INC., Plaintiff, v. BOSTON SCIENTIFIC CORP., Defendant.	CASE NO. 1:17-CV-01103-LY

PROPOSED ORDER

Upon consideration of the Motion to Dismiss the Complaint (the "Motion to Dismiss") by Boston Scientific Corporation and for good cause shown, it is hereby:

ORDERED that the Motion to Dismiss is GRANTED and the Complaint is DISMISSED WITH PREJUDICE.

SIGNED ON THIS ____ day of _____, 2018.

_____
LEE YEAKEL
UNITED STATES DISTRICT JUDGE

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF TEXAS
AUSTIN DIVISION

BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM; and TISSUEGEN, INC., Plaintiff, v. BOSTON SCIENTIFIC CORP., Defendant.	NO. 1:17-CV-01103 Date: [Date] Time: [Time]

DECLARATION OF PAUL DONHAUSER IN SUPPORT OF DEFENDANT'S MOTION TO DISMISS UNDER FED. R. CIV. P. 12(B)(3)

I, Paul Donhauser, declare and state the following:

1. I am the Vice President of Global Facilities at Boston Scientific Corporation ("BSC").

2. I am over the age of eighteen and if called to testify to the truth of the matters stated herein, could and would do so competently.

3. As the Vice President of Global Facilities, I have access to information concerning facilities maintained by BSC in the United States and abroad. This includes information regarding the locations of real estate owned or leased by BSC. Unless otherwise indicated below, the statements in this declaration are based upon my personal knowledge, my review of corporate records maintained by BSC in the ordinary course of business, and/or information provided to me in my role as Vice President of Global Facilities.

4. I am informed that the following counties constitute the Western District of Texas: Andrews, Atascosa, Bandera, Bastrop, Bell, Bexar, Blanco, Bosque, Brewster, Burleson, Burnet, Caldwell, Comal, Coryell, Crane, Culberson, Dimmit, Ector, Edwards, El Paso, Falls, Freestone, Frio, Gillespie, Gonzales, Guadalupe, Hamilton, Hays, Hill, Hudspeth, Jeff Davis, Karnes,

Kendall, Kerr, Kimble, Kinney, Lampasas, Lee, Leon, Limestone, Llano, Loving, Martin, Mason, Maverick, McCulloch, McLennan, Medina, Midland, Milam, Pecos, Presidio, Real, Reeves, Robertson, San Saba, Somervell, Terrell, Travis, Upton, Uvalde, Val Verde, Ward, Washington, Williamson, Wilson, Winkler, and Zavalla. BSC does not own or lease any real estate in the Western District of Texas.

5. BSC also does not maintain a business address at any location in the Western District of Texas.

6. BSC employs approximately forty-six sales personnel who reside in the Western District of Texas, but they work out of their homes. BSC does not own, lease of otherwise control these employees' homes. Nor does it store inventory there. And only seven of these employees are employed in positions related to BSC's interventional cardiology division.

I declare under the penalty of perjury under the laws of the United States that the foregoing is true and correct.

Executed on January [25], 2018 at [11:02].

Paul Donhauser

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF TEXAS

BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM and TISSUEGEN, INC., **Plaintiffs,** **v.** **BOSTON SCIENTIFIC CORP.,** **Defendant.**	**CASE NO. A-17-CV-1103-LY** **JURY TRIAL DEMANDED**

PLAINTIFFS' RESPONSE IN OPPOSITION TO MOTION TO DISMISS

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TABLE OF AUTHORITIES

CASES:

STATUTES:

RULES:

Plaintiffs BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM ("The Board of Regents") and TISSUEGEN, INC. ("TissueGen") ask the Court to deny Defendant Boston Scientific Corporation's ("Boston Scientific") motion to dismiss for improper venue and allow The Board of Regents to seek redress for Boston Scientific's patent infringement within the Western District of Texas. As a sovereign, The Board of Regents is empowered to choose the forum in which it litigates its property rights, including the rights embodied in a United States patent. Because this court has personal jurisdiction over Boston Scientific, venue considerations related to convenience or other factors cannot overcome The Board of Regents' sovereign right to control the forum for this dispute. It would be unconstitutional to force The Board of Regents to waive its sovereign immunity in a different forum as a condition for engaging in lawful patent enforcement activities. Thus, Boston Scientific's motion must be denied.

I. BACKGROUND

On November 20, 2017, The Board of Regents and TissueGen jointly sued Boston Scientific in the Western District of Texas for infringement of two patents assigned to The Board of Regents, U.S. Patent Nos. 6,596,296 (the "'296 patent") and 7,033,603 (the "'703 patent").[1] *See* Dkt. 1. The '296 and '703 patents relate to drug-releasing biodegradable polymers used in the delivery of therapeutics and were developed out of research performed at the University of Texas at Arlington. *See Id*. ¶¶ 2, 5. In its complaint, The Board of Regents asserts that venue is proper in this District because, among other things, this Court

[1]Citations to the record are designated as "Dkt. __" and the page numbers in the citations refer to ECF page numbers in the heading of the document.

(1) has personal jurisdiction over Boston Scientific; (2) Boston Scientific has committed acts of infringement within Texas and this District; and (3) because The Board of Regents is an arm of The State of Texas and therefore, has sovereign immunity. *See id*. ¶¶ 6-10. The complaint further makes clear that The Board of Regents "neither waves its sovereign immunity nor consents to any suit or proceeding filed separate from this action, including but not limited to any declaratory judgment action or *inter partes* review." *Id*. ¶ 2.

On February 1, 2018, Boston Scientific moved the Court to dismiss The Board of Regents' complaint for improper venue. Dkt. 11. Boston Scientific does not dispute that the Court has personal jurisdiction over Boston Scientific or that acts of infringement were committed within Texas. *See id*. at 4. Boston Scientific also does not dispute that, as an arm of The State of Texas, The Board of Regents is a sovereign entity, entitled to sovereign immunity. *See id*. at 5-6. Instead, Boston Scientific asserts that it is a citizen of a different state (Delaware) and does not have a regular and established place of business in the Western District of Texas. *Id*. at 4-5. On this basis, Boston Scientific argues that under the patent venue statute, venue is improper in this District, *id*. at 5, but proper in the District of Delaware, *id*. at 6. Thus, Boston Scientific requests that the Court dismiss this action, or in the alternative, transfer it to the Delaware district court. As set forth in detail below, Boston Scientific's arguments should be rejected.

II. ARGUMENT

A. The Board of Regents' Suit In Texas Did Not Constitute Consent to Suit in Any Other Forum.

1. The Board of Regents is a Sovereign and is Empowered to Choose the Forum in Which it Litigates its Property Rights.

The State of Texas is sovereign and The Board of Regents is an arm of The State of Texas entitled to sovereign immunity. *Northern Ins. Co. of N.Y. v. Chatham Cty., Ga.*, 547 U.S. 189, 193 (2006) ("States and arms of the State possess immunity from suits authorized by federal law."); TEX. GOV'T CODE § 441.101(3); *Tegic Comm'ns, Corp. v. Board of Regents of Univ. of Tex. Sys.,* 458 F.3d 1335, 1340 (Fed. Cir. 2006) ("The University of Texas System is deemed to be an arm of The State Texas[.]"); *Xechem Int'l, Inc. v. Univ. of Tex. M.D. Anderson Cancer Ctr.*, 382 F.3d 1324, 1327–28 (Fed. Cir. 2004) (recognizing the status of The University of Texas System as an arm of the state). Boston Scientific does not deny this.

A State's sovereign immunity is ***broader*** than the immunity guaranteed in the Eleventh Amendment against suits against a State by third parties. *Fed. Maritime Comm'n v. S. Car. State Ports Auth.*, 535 U.S. 743, 754 (2002). Indeed, sovereign immunity protects two State interests: the State's treasury against private lawsuits to which the State has not consented, and the State's dignity as a sovereign. *Hess v. Port Auth. Trans–Hudson Corp.*, 513 U.S. 30, 48 (1994); *see Seminole Tribe of Fla. v. Florida*, 517 U.S. 44, 58 (1996). A state has a sovereign right to protect its property and a dignity interest in choosing the forum in which to litigate its property rights—a private party cannot dictate the forum in which such litigation occurs.

The Eleventh Amendment provides The Board of Regents with sovereign immunity from suits against the State in federal courts. U.S. CONST., Amend. XI. The Eleventh

Amendment "stands not so much for what it says, but for the presupposition . . . which it confirms." *Kimel v. Florida Bd. of Regents*, 528 U.S. 62, 72-73 (2000). The Eleventh Amendment reaffirms two things: (1) "each State is a sovereign entity in our federal system" and (2) "it is inherent in the nature of sovereignty not to be amenable to the suit of an individual without its consent." *Seminole Tribe of Fla. v. Florida*, 517 U.S. 44, 54 (1996). "The very object and purpose of the 11th Amendment were to prevent the indignity of subjecting a State to the coercive process of judicial tribunals at the instance of private parties." *In re Ayers*, 123 U.S. 443, 505 (1887).[2]

Consistent with these principles, more than 30 years ago, the Supreme Court emphasized that a "State's constitutional interest in immunity encompasses not merely ***whether*** it may be sued, but ***where*** it may be sued." *Pennhurst State School & Hosp. v. Halderman*, 465 U.S. 89, 99 (1984). In *Port Authority Trans-Hudson Corp. v. Feeney*, 495 U.S. 299, 207 (1990), the Court reiterated that a State may control the venue in which it litigates, stating that "issues of venue are closely related to those concerning sovereign immunity."[3]

Here, The Board of Regents was entitled to choose the forum in which it litigates its

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[2] The Eleventh Amendment does not establish the full parameters of state sovereign immunity. The Eleventh Amendment overruled the Supreme Court decision in *Chisholm v. Georgia*, 2 U.S. (2 Dall.) 419 (1793) and addresses only the specific issues that formed *Chisholm's* rationale. *Alden v. Maine*, 527 U.S. 706, 723 (1999). The Eleventh Amendment's "greater significance lies in its affirmation that the fundamental principle of sovereign immunity limits the grant of judicial authority in Art[icle] III." *Pennhurst State Sch. & Hosp. v. Halderman*, 465 U.S. 89, 98 (1984). The "sovereign immunity enjoyed by the States extends beyond the literal text of the Eleventh Amendment." *Fed. Maritime Comm'n,* 535 U.S. at 754. The Eleventh Amendment therefore reinforces the common law principle that states are immune from deprivation of their property at the hands of private litigants.

[3] The *Hess* Court held that the state's waiver could be properly limited by State statute to suits "laid within a county or judicial district" that is "situated wholly or partially within the Port of New York District." *Id*. at 303.

property rights. By filing suit in the Western District of Texas, The Board of Regents consented to suit in that forum but has not consented to suit in any other forum. Moreover, because Boston Scientific does not claim that Texas lacks personal jurisdiction over it, (*see* Dkt. 11), Boston Scientific has waived that defense and the Court's personal jurisdiction over Boston Scientific is uncontestable. FED. R. CIV. P. 12(b), 12(g)(2), 12(h)(1)(A)-(B)(i).

2. Waiver is Limited to Compulsory Counterclaims in the State's Chosen Forum.

Notwithstanding a State's immunity from federal court jurisdiction,[4] if a State voluntarily files a claim in federal court it waives its Eleventh Amendment immunity—but the waiver applies only to compulsory counterclaims in that forum. *Lapides v. Bd. of Regents of the Univ. Sys. of Ga.*, 535 U.S. 613, 619 (2002) ("It would seem anomalous or inconsistent for a State both (1) to invoke federal jurisdiction, thereby contending that the Judicial power of the United States extends *to the case at hand*, and (2) to claim Eleventh Amendment immunity, thereby denying that the Judicial power of the United States extends *to the case at hand*.") (emphasis added).

Applying these principles in patent cases, the Federal Circuit has held that waiver of immunity is limited to compulsory counterclaims in the same forum, and that such waiver does not extend to a suit in another forum, even if the same parties and subject matter are

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[4] While this immunity from suit is not absolute, the Supreme Court has recognized "only two circumstances in which an individual may sue a state." *Coll. Sav. Bank v. Fla. Prepaid Postsecondary Educ. Expense Bd.*, 527 U.S. 666, 670 (1999). "Those circumstances occur where Congress validly authorizes such a suit 'in the exercise of its power to enforce the Fourteenth Amendment,' or where a State has waived its sovereign immunity by consenting to suit." *Biomedical Patent Management Corp. v. California, Department of Health Services*, 505 F.3d 1328, 1339 (Fed. Cir. 2007) ("*BPMC*") (quoting *Coll. Sav. Bank*, 527 U.S. at 670). This case does not involve congressional exercise of its power to enforce the Fourteenth Amendment, but it does involve the Board of Regents' limited waiver of its immunity in the forum in which it consented to suit.

involved. In *Regents of the University of New Mexico v. Knight*, 321 F.3d 1111, 1126 (Fed. Cir. 2003), for example, the Federal Circuit held that "when a state files suit in federal court to enforce its claims to certain patents, the state shall be considered to have consented to have litigated *in the same forum* all compulsory counterclaims." *Id*. (emphasis added). Waiver as to compulsory counter claims filed by the defending party "in the same form" was clear from the State's filing of the suit in that forum, for the State could "surely anticipate" that such counterclaims would be asserted or otherwise forever barred. *Id*.

Three years after *Knight*, the Federal Circuit held that The University of Texas' waiver of immunity in *this* forum did not extend to waive immunity from suit in another federal forum (Washington), even though the same patents were involved. *Tegic Commc'ns Corp. v. Bd. of Regents of Univ. of Texas Sys.*, 458 F.3d 1335, 1342-43, 1345 (Fed. Cir. 2006). The Federal Circuit reinforced *Tegic* one year later. *BPMC,* 505 F.3d at 1339. And more recently, in *A123 Sys., Inc. v. Hydro-Quebec*, the Federal Circuit held that sovereign immunity prevented an accused infringer from pursuing a declaratory judgment action in Massachusetts against a State patent owner (The Board of Regents of The University of Texas System) because even though The Board of Regents later filed a suit in Texas against the accused infringer, it had not consented to suit in Massachusetts and thus could not be joined as a party there. *See* 626 F.3d 1213, 1215, 1219 (Fed. Cir. 2010).[5]

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[5] *See also Ali v. Carnegie Inst. of Wash.*, 967 F. Supp. 2d 1367, 1375 (D. Or. 2013), *aff'd*, 684 F. App'x 985 (Fed. Cir. 2017), and *aff'd*, 684 F. App'x 985 (Fed. Cir. 2017), and *aff'd*, 684 F. App'x 985 (Fed. Cir. 2017) ("A state's filing of a patent infringement suit does not effectuate a complete waiver of sovereign immunity, even with respect to the infringed patents. Any such waiver is limited to the complete adjudication of the state's suit, including any compulsory counterclaims, ***in the state's chosen forum***") (emphasis added).

Here, The Board of Regents sued Boston Scientific in the Western District of Texas. That choice must be respected as a fundamental aspect of The Board of Regents and The State of Texas' sovereign immunity.[6] If Boston Scientific has compulsory counterclaims to file, then The Board of Regents has waived its immunity to them in this Court only.

B. The Board of Regents Cannot be Forced to Waive Sovereign Immunity In a Different Forum Just to Protect Its Property Rights.

In its motion to dismiss, Boston Scientific characterizes The Board of Regents' sovereignty as "irrelevant to the venue analysis." Dkt. 11 at 6. Instead, Boston Scientific asserts that the Texas litigation should be dismissed or should be transferred to a different forum (Delaware), based on the patent venue statue. *Id.* Boston Scientific's argument means that The State of Texas can only enforce its property rights in a forum in which Boston Scientific resides or has a regular and established place of business. *Id.* at 3. Taken to its logical conclusion, Boston Scientific's argument means that for a State to enforce its patent rights against an infringer that is not a State resident and lacks an established place of business in the State, the State must waive its rights to choose the forum and instead seek redress in a forum outside of the State's borders. This would result in an untenable affront to State dignity for at least two reasons.

First, Boston Scientific's rationale conflicts with the Supreme Court's long-held recognition that a state can control "not merely ***whether*** it may be sued, but ***where*** it may be sued." *Pennhurst*, 465 U.S. at 99; *see also Port Authority*, 495 U.S. at 207 (recognizing that

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[6] *See Fed. Maritime Comm'n*, 535 U.S. at 754 (noting that the Eleventh Amendment's bar against lawsuits against a State brought by a citizen of another State "does not define the scope of the States' sovereign immunity; it is but one particular exemplification of that immunity").

"issues of venue are closely related to those concerning sovereign immunity.").

Second, venue is a creature of statute, therefore it is subservient to constitutional issues.[7] Nothing in the patent venue statute expressly waives the States' sovereign immunity, nor could it by invoking the Fourteenth Amendment. Therefore, the patent venue statute cannot compel a State to waive its right to choose the forum for enforcing the State's patent rights and thereby allowing the defendant to choose the forum of suit as a condition to a State exercising its right to engage in the "otherwise lawful activity" of enforcing patent rights. Such a coercive condition is unconstitutional because "where the constitutionally guaranteed protection of the States' sovereign immunity is involved the point of coercion is automatically passed—and the voluntariness of waiver destroyed—when what is attached to the refusal to waive is the exclusion of the State from otherwise lawful activity." *Coll. Sav. Bank,* 527 U.S. at 687.[8]

Ultimately, Boston Scientific cannot effectively force The Board of Regents to waive its sovereign right to choose the forum for adjudicating its lawful rights as a condition of exercising those rights. No part of *TC Heartland, LLC v Kraft Foods Group Brands, LLC*[9] affected the holding in *College Savings Bank* that waivers cannot be so coerced. The State of

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[7] *See e.g., U.S. v. Eichman,* 496 U.S. 310, 318-19 (1990) (holding Congressional statute unconstitutional for conflicting with First Amendment).

[8] In *College Savings Bank*, the Supreme Court rejected the United States government's argument that a State's voluntary participation in activities controlled by federal statute imposes a consent to suit arising from those activities. *Id.* at 683-87. The Court further stressed that "the constitutionally grounded principle of state sovereign immunity" is no less robust when "the asserted basis for constructive waiver is conduct that the State realistically could choose to abandon, that is undertaken for profit, that is traditionally performed by private citizens and corporations." *Id.* at 684.

[9] 137 S. Ct. 1514 (2017).

Texas' sovereign immunity includes the authority to seek redress in the court of its choosing, *this court*, for harm done to the State itself. *Fed. Maritime Comm'n,* 535 U.S. at 760.[10] To hold otherwise would be an impermissible affront to the State's dignity as a sovereign.

C. The Federal Circuit's *Eli Lilly* Decision Does Not Apply.

Though it has not squarely done so, Boston Scientific may rely on *Regents of the Univ. of Calif. v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997). Any such reliance is misplaced.

In *Eli Lilly*, the Federal Circuit was presented with a *post-trial* challenge by The Regents of the University of California ("UC") to the Southern District of Indiana's hearing of a case on the merits that UC had originally filed in federal district court in California. In appealing the Indiana court's unfavorable bench trial determination, UC argued, among other things, that the Eleventh Amendment deprived the court of jurisdiction since UC had filed its case in the Northern District of California. 119 F.3d at 1563-64.[11] Lilly responded by arguing that the change in venue did not violate the Eleventh Amendment because the only claim in the case was one asserted by UC and *there was no counterclaim*. *Id.* at 1564. In

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[10] There is no competing constitutional interest at stake here—Defendant admitted it is subject to personal jurisdiction in this District because it waived its Rule 12(b)(2) defense. Thus, Defendant seeks refuge in a procedural mechanism; such procedural limitations do not (and cannot) abrogate or override sovereign interests.

[11] UC also relied only upon the Eleventh Amendment in challenging the transfer order by petition for mandamus to the Federal Circuit. *In re Regents of the Univ. of Calif.*, 964 F.2d 1128, 1134-35 (Fed. Cir. 1992). The Federal Circuit broadly claimed that "[u]pon entering the litigation arena the Regents, like all litigants, become subject to the Federal Rules" and therefore could have their lawsuits moved from state to state, for the consideration of pretrial proceedings under 28 U.S.C. § 1407. *Id.* at 1135. That decision predated the Supreme Court's rulings in *Alden,* the two *College Savings Bank* cases, and *Federal Maritime Commission,* all of which more narrowly circumscribed federal power to act in the face of state sovereign immunity.

finding for Lilly, the court reasoned that the case did not create an *Eleventh Amendment* jurisdictional issue because "[t]his case only involves UC's patent infringement claims and Lilly's defenses; it does not involve any claim or counterclaim *against* UC that places UC in the position of a defendant." *Eli Lilly,* 119 F.3d at 1564-5. The Federal Circuit's decision turned entirely on the fact that, through completion of trial on the merits, Lilly had not asserted a single counterclaim against UC. *Id*.

Unlike the *Eli Lilly* case, the present case raises both Eleventh Amendment *and* residual sovereignty jurisdictional issue. In *Eli Lilly*, UC never raised any objections to venue other than under the Eleventh Amendment. The Board of Regents asserts its full sovereign rights to choose the forum to hear the dispute over its property rights in a forum that possesses personal jurisdiction over Boston Scientific. That should end the inquiry.

But another key distinguishing feature as to *Eli Lilly* is present. Boston Scientific has not yet answered. Even assuming sovereignty did not extend to allow sovereigns the right to select the forum, unless Boston Scientific forever disclaims any right to bring compulsory counterclaims, any transfer would directly violate the Eleventh Amendment's protections against a suit against The State of Texas in a forum not of its choosing. Boston Scientific can only assert compulsory counterclaims against The Board of Regents in a forum of the sovereign's choosing. Transferring a case where compulsory counterclaims are still assertable would fall outside the boundaries of *Eli Lilly* and contradict both *Tegic* and *Hydro-Quebec*. In its motion, Boston Scientific makes no representation that it will not assert counterclaims. *See generally*, Dkt. 11. Moreover, with the initial pretrial conference set for March 13, 2018, Dkt. 13, any deadline to amend pleadings is months away. Unlike *Eli Lilly*, it cannot be said that this case lacks claims against a sovereign.

Importantly, the Supreme Court decided both *Federal Maritime Commission* and *Alden* after the Federal Circuit ruled in *Eli Lilly*. In *Eli Lilly*, the Federal Circuit did not determine any sovereign immunity issue outside of UC's invocation of its Eleventh Amendment rights. In *Alden*, however, the Court held that resorting ***only*** to the words of the Eleventh Amendment "in interpreting the scope of the States' sovereign immunity" constitutes "ahistorical literalism we have rejected." 527 U.S. at 730. Thus, two years after *Eli Lilly*, the Supreme Court disavowed the same analytical framework that the Federal Circuit had applied. Three years after *Alden,* in *Federal Maritime Commission*, the Court reinforced its previous determinations that rejected the view that the Eleventh Amendment and state sovereign immunity are coextensive by reiterating that state sovereign immunity "extends beyond" the Constitution's text. 535 U.S. at 754. Therefore, the *Eli Lilly* decision does not instruct that transfer is appropriate here.

III. CONCLUSION

The Board of Regents is a sovereign and is empowered to choose the forum in which it litigates its property rights. The Board of Regents cannot be coerced into waiving its sovereign right to choose the venue for disputes related to State property as a condition for exercising its lawful rights to enforce its patents. Accordingly, Boston Scientific's motion to dismiss must be denied.

Dated: February 15, 2018

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on February 15, 2018, the foregoing instrument was electronically filed with the Clerk of the Court using the Court's CM/ECF system which will send notification of the filing to all counsel of record for parties.

/s/ Chijioke E. Offor

Chijioke E. Offor

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF TEXAS
AUSTIN DIVISION

BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM; and TISSUEGEN, INC., Plaintiffs, v. BOSTON SCIENTIFIC CORP., Defendant.	Case No. 1:17-CV-01103-LY

DEFENDANT BOSTON SCIENTIFIC CORPORATION'S REPLY IN SUPPORT OF ITS MOTION TO DISMISS PLAINTIFFS' COMPLAINT UNDER FED. R. CIV. P. 12(B)(3)

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I. INTRODUCTION

When federal venue is improper, a district court "shall dismiss, or if it be in the interest of justice, transfer such case to any district or division in which it could have been brought." 28 U.S.C. § 1406(a). In its Motion to Dismiss, Defendant Boston Scientific Corporation ("BSC") explained that under the patent venue statute and recent Supreme Court decision *TC Heartland*, venue is not proper in this District, because BSC neither resides here nor has a regular and established place of business here. Plaintiffs Board of Regents, the University of Texas System ("Board of Regents") and TissueGen, Inc. ("TissueGen") do not contest that venue is improper under the patent venue statute. Plaintiffs instead argue that "the exclusive provision controlling venue in patent infringement proceedings" does not control venue in this patent infringement proceeding because Board of Regents' sovereign immunity allows Plaintiffs to ignore the patent venue statute. Siding with Plaintiffs here then requires finding: (1) Eleventh Amendment sovereign immunity protections apply to a party which has voluntarily availed itself of federal court, in contravention to Supreme Court and Federal Circuit precedent; (2) sovereign immunity allows a plaintiff in federal court to ignore federal venue requirements and prevent transfer, arguments with no reliable precedent; (3) the patent venue statute is unconstitutional, based on case law that contradicts such an argument; and (4) a private entity may claim the benefits of sovereign immunity, an argument Plaintiffs never present. None of these are tenable, much less all of them.

II. THERE IS NO DISAGREEMENT THAT VENUE IS IMPROPER UNDER THE PATENT VENUE STATUTE

Venue in patent cases is dictated by the patent venue statute, 28 U.S.C. § 1400(b), "the exclusive provision controlling venue in patent infringement proceedings." *TC Heartland LLC v. Kraft Foods Grp. Brands LLC*, 137 S. Ct. 1515, 1518 (2017) (*quoting Stonite Prods. Co. v.*

Melvin Lloyd Co., 315 U.S. 561, 563 (1942)). Under § 1400(b), venue in patent infringement cases is proper only in a district where either (1) "the defendant resides" or (2) "the defendant has committed acts of infringement and has a regular and established place of business." In *TC Heartland*, the Supreme Court clarified that "a domestic corporation 'resides' only in its State of incorporation for purposes of the patent venue statute." 137 S. Ct. at 1517. And the Federal Circuit has explained that "a regular and established place of business" requires a defendant to have a "physical place in the district." *In re Cray Inc.*, 871 F.3d 1355, 1360 (Fed. Cir. 2017).

Plaintiffs' Complaint does not even refer to § 1400(b), much less plead allegations that would make venue proper under § 1400(b). (*See generally* Doc. No. 1.) Nor could it. As explained in BSC's Motion to Dismiss, BSC does not reside in this District because it is incorporated in the District of Delaware. (Doc. No. 11 at 2–4.) And it does not own or lease a place of business here. (Doc. No. 11 at 4–5.) Plaintiffs' Response in Opposition to BSC's Motion to Dismiss only refers to the patent venue statute in passing and does not attempt to refute BSC's argument that venue is improper under § 1400(b). (*See generally* Doc. No. 14.)

III. PLAINTIFFS' CLAIMS ARE NOT COVERED BY THE ELEVENTH AMENDMENT NOR OTHER SOVEREIGN IMMUNITY CONSIDERATIONS

Unable to refute BSC's argument that venue is improper under the patent venue statute, Plaintiffs instead claim that Board of Regents' sovereign immunity allows them to disregard the patent venue statute and select a venue that is improper. As discussed in BSC's motion to dismiss, and as discussed further below, this assertion is wrong as a matter of law. In response to BSC's motion, Plaintiffs now argue that if a state can be required to comply with the patent venue statute, the statute must be unconstitutional. This argument also should be rejected.

A. Eleventh Amendment Sovereign Immunity Does Not Apply to Plaintiffs' Claims Against BSC

Claims brought by a State in federal court are not subject to sovereign immunity under the Eleventh Amendment: "[W]here a state voluntarily become [sic] a party to a cause, and submits its rights for judicial determination, it would be bound thereby, and cannot escape the result of its own voluntary act by invoking the prohibitions of the 11th Amendment." *Gunter v. Atlantic Coast Line R.R.*, 200 U.S. 273, 284 (1906) (*citing Clark v. Barnard*, 108 U.S. 436, 477 (1883)); *see* U.S. Const. amend. XI ("The Judicial power of the United States shall not be construed to extend to any suit in law or equity, commenced or prosecuted *against* one of the United States by Citizens of another State, or by Citizens or Subjects of any Foreign State." (emphasis added)). As the Supreme Court has noted, it would be "anomalous or inconsistent for a State both (1) to invoke federal jurisdiction, thereby contending that the 'Judicial power of the United States' extends to the case at hand, and (2) to claim Eleventh Amendment immunity, thereby denying that the 'Judicial power of the United States' extends to the case at hand." *Lapides v. Bd. of Regents of Univ. Sys. of Ga.*, 535 U.S. 613, 619 (2002) (holding that a state's removal of suit to federal court constituted waiver of its Eleventh Amendment immunity).[1]

As discussed in BSC's Motion to Dismiss, the Court of Appeals for the Federal Circuit explicitly rejected the same Eleventh Amendment venue argument made by Plaintiffs here in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998).[2] As Plaintiffs argue here, the University of California ("UC")

[1] Although Plaintiffs themselves cite this statement from *Lapides*, (Doc. No. 14 at 5), they fail to note the next sentence of *Lapides*, which points out that "a Constitution that permitted States to follow their litigation interests freely asserting both claims in the same case could generate seriously unfair results." 535 U.S. at 619.

[2] In patent suits, "the question of Eleventh Amendment waiver is a matter of Federal Circuit law." *Regents of Univ. of N.M. v. Knight*, 321 F.3d 1111, 1124 (Fed. Cir. 2003).

argued that the state entity had only waived its sovereign immunity to suit in the specific federal district in which it had filed suit. The Federal Circuit rightly concluded that there was no "waiver" issue at all, insofar as the state entity itself had filed suit: "[W]e need not determine whether UC waived its immunity only in California, because this case does not create an Eleventh Amendment jurisdictional issue concerning which the question of waiver even arises. This case only involves UC's patent infringement claims and Lilly's defenses; it does not involve any claim or counterclaim against UC that places UC in the position of the defendant." *Id.* at 1565.

Plaintiffs' attempts to distinguish this action from *Eli Lilly* are unavailing. Their first attempt to do so centers on the assertion of "sovereign rights," unmoored from the Eleventh Amendment that would allow a state entity and its business partners unfettered power to choose federal venue wherever personal jurisdiction exists. (Doc. No. 14 at 10.) There is no support cited (or available) for this proposition. "[T]he Constitution does not provide for federal jurisdiction over suits against nonconsenting States." *Kimel*, 528 U.S. at 73. But states do not have an unconditional right to select federal venue for a forum in which to bring suit, even where venue is improper under federal law. Plaintiffs also assert that, "[u]nlike *Eli Lilly*, it cannot be said that this case lacks claims against a sovereign." (Doc. No. 14 at 10.) BSC, however, has not filed any counterclaims against the Plaintiffs. There are no claims against any sovereign entity before the Court.

Lastly, Plaintiffs' contention that the Supreme Court's decision in *Alden v. Maine*, 527 U.S. 706 (1999), and/or the Federal Circuit's decision in *Federal Maritime Commission v. South Carolina State Ports Authority*, 535 U.S. 743 (2002), somehow altered or limited the holding of *Eli Lilly* is without merit. Neither case involved an examination of the proper federal venue for

suit against a state entity. Indeed, neither case involved suits originally filed in federal court. In both, state entities were defendants seeking to avoid adjudication of complaints against them, one in state court, *Alden*, 527 U.S. at 712, and one in a federal agency, *Federal Maritime Commission*, 535 U.S. at 747–49. In short, Plaintiffs' attempts to distinguish *Eli Lilly* are premised upon mischaracterizations of *Eli Lilly*, the facts of this case, and case law subsequent to *Eli Lilly*.

The case law that Plaintiffs introduce in support of their position fares no better. In particular, the cases cited by Plaintiffs merely stand for the accepted proposition that the Eleventh Amendment provides each state with "sovereign immunity from suits *against* the State in federal courts." (Doc. No. 14 at 3 (emphasis added).)[3] None of the cases involve a state entity that voluntarily availed itself of the court system. And none of the cases involve a state entity that claimed that the Eleventh Amendment permitted it to file suit in an otherwise improper venue. Plaintiffs cite to the Court's statement in *Pennhurst* that "[a] State's constitutional interest in immunity encompasses not merely whether it may be sued, but where it may be sued." (Doc. No. 14 at 4 (*citing* 465 U.S. at 99).) Venue, however, was not at issue in *Pennhurst*. The Court's discussion of "where" a State may be sued referred to the distinction between federal and state courts, not between federal venues: "For this reason, the Court consistently has held that a State's waiver of sovereign immunity *in its own courts* is not a waiver of the Eleventh Amendment immunity *in the federal courts*." 465 U.S. at 99 n.9 (emphasis added). Moreover,

[3] *Fed. Maritime Comm'n v. S.C. State Ports Auth.*, 535 U.S. 743 (2002); *Hess v. Port Auth. Trans-Hudson Corp.*, 513 U.S. 30 (1994); *Seminole Tribe of Fla. v. Florida*, 517 U.S. 44 (1996); *Kimel v. Fla. Bd. of Regents*, 528 U.S. 62 (2000); *Ex parte Ayers*, 123 U.S. 443 (1887); *Pennhurst State Sch. & Hosp. v. Halderman*, 465 U.S. 89 (1984); *Port Auth. Trans-Hudson Corp. v. Feeney*, 495 U.S. 299 (1990).

the state entities claiming sovereign immunity were *defendants*, not plaintiffs that availed themselves of the prerogative to bring suit in federal court. *Id.* at 92.

Feeney is equally inapposite, if not more so, and certainly does not stand for the proposition that "a State may control the venue in which it litigates." (Doc. No. 14 at 4 (*citing* 495 U.S. at 307).) Whether federal venue was proper was not at issue in *Feeney*. Instead, like *Pennhurst*, the case concerned whether jurisdiction was proper in *any* federal court. *Feeney*, 495 U.S. at 300–01 ("These cases call upon the Court to determine whether the Eleventh Amendment bars respondents' suits in federal court against an entity created by New York and New Jersey . . . ."). And as in *Pennhurst*, the state entity claiming sovereign immunity was a defendant hailed into federal court, not the plaintiff. *Id*. at 301–02.[4] In *Eli Lilly*, the Federal Circuit rightly rejected the plaintiff's' reliance on *Feeney* and *Pennhurst*: "[T}he [Supreme] Court did not construe the Eleventh Amendment to apply to suits in which a state is solely a plaintiff, as UC is here. In fact, we do not believe that the Court has ever so construed the Eleventh Amendment. This is because the Eleventh Amendment applies to suits 'against' a state, not suits by a state." *Eli Lilly*, 119 F.3d at 1564.

Plaintiffs also wrongly claim that waiver of sovereign immunity "applies only to compulsory counterclaims in that forum." (Doc. No. 14 at 5.) For this proposition, Plaintiffs cite *Regents of University of New Mexico v. Knight*, 321 F.3d 1111 (Fed. Cir. 2003). In *Regents*, however, the issue of the proper "forum" turned — as in the cases discussed above — on whether the state entity was susceptible to a counterclaim in any federal court, not whether it

[4] Plaintiffs cite the Court's statement to the effect that "issues of venue are closely related to those concerning sovereign immunity." *Feeney*, 495 U.S. at 307. The cited language, however, explained the extent to which a state venue statute can evidence a state statutory waiver of sovereign immunity to suit in federal court.

could only be sued in a specific federal venue. *See* 321 F.3d at 1124–26 (referencing "federal court" but not "venue").[5]

B. The Patent Venue Statute Is Not Unconstitutional

Lastly, Plaintiffs argue that unless they are allowed to ignore the patent venue statute, the Board of Regents "must waive its rights to choose the forum and instead seek redress in a forum outside of the State's borders" which — they claim — would be "an untenable affront to State dignity."[6] (Doc. No. 14 at 7.) In making this argument, Plaintiffs appear to assert that transfer to another venue would be unconstitutionally coercive because it would expose a state entity to counterclaims in another federal district. Like the cases discussed above, however, *College Savings Bank v. Florida Prepaid Postsecondary Education Expense Board*, 527 U.S. 666 (1999), dealt with the issue of whether a state entity was amenable to suit in any federal district; the court was not considering whether a federal suit was properly brought in the particular venue. 527 U.S. at 690 ("[W]e hold that the federal courts are without jurisdiction to entertain this suit against an arm of the State of Florida."). *College Savings Bank* goes on to

[5] The other cases Plaintiffs cite are readily distinguishable. *Tegic Communications Corp. v. Board of Regents of the University of Texas System*, 458 F.3d 1335 (Fed. Cir. 2006), involved a "new action brought by a different party" against the state entity, which was seeking to avoid federal jurisdiction, not the requirements of federal venue. 458 F.3d at 1343. Both *Biomedical Patent Management Corp. v. California, Department of Health Services*, 505 F.3d 1328 (Fed. Cir. 2007), and *A123 Systems, Inc. v. Hydro-Quebec*, 626 F.3d 1213 (Fed. Cir. 2010), involved distinct suits against the state entity, wholly separate from the original suit filed by the state entity. The state entities were once again defendants in the separate suits and asserted sovereign immunity to avoid federal jurisdiction. 626 F.3d at 1219–20. Lack of waiver in both cases was predicated on the existence of the separate actions against the state entity. *Id.* No separate action against Plaintiffs exists here. No counterclaims have been asserted against Plaintiffs. Plaintiffs are not attempting to avoid federal jurisdiction. Plaintiffs' sovereign immunity is inapplicable.

[6] Notably, the Board of Regents has previously filed patent infringement actions outside of Texas, apparently without this concern. *See* First Amended Complaint for Patent Infringement, *Nellcor Puritan Bennett, Inc. v. Smiths Med. Int'l Ltd.*, No. 3:04-cv-01934-VRW (N.D. Cal. Dec. 9, 2004), ECF No. 37 (patent infringement suit in the Northern District of California in which the Board of Regents was a plaintiff).

confirm "the unremarkable proposition that a State waives its sovereign immunity by voluntarily invoking the jurisdiction of the federal courts." 527 U.S. at 681 n.3. Plaintiffs did so here by filing suit against BSC in this District. Because venue is improper in this district (as Plaintiffs appear) to concede, the action should be dismissed.

IV. CONCLUSION

For the reasons set forth in BSC's Motion to Dismiss and those discussed above, BSC respectfully requests the Court dismiss the Complaint for improper venue without leave to amend. In the alternative, BSC respectfully requests the Court transfer this action to the U.S. District Court for the District of Delaware.

Dated: February 22, 2018

Respectfully submitted,

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that all counsel of record who are deemed to have consented to electronic service are being served with a copy of this document via the Court's CM/ECF system on February 22, 2018.

/s/ Christopher M. Odell
Christopher M. Odell