(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 July 2016 (14.07.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/112071 A2

(51) International Patent Classification:
A61K 47/34 (2006.01) *C08K 3/22* (2006.01)

(21) International Application Number:
PCT/US2016/012282

(22) International Filing Date:
6 January 2016 (06.01.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/100,284 6 January 2015 (06.01.2015) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17 :

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(H))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(in))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) **Title:** MAGNETICALLY TRIGGERABLE ELECTROACTIVE COMPOSITES, METHOD OF MAKING THE MAGNETICALLY TRIGGERABLE ELECTROACTIVE COMPOSITES, AND METHOD OF USING THE MAGNETICALLY TRIGGERABLE ELECTROACTIVE COMPOSITES

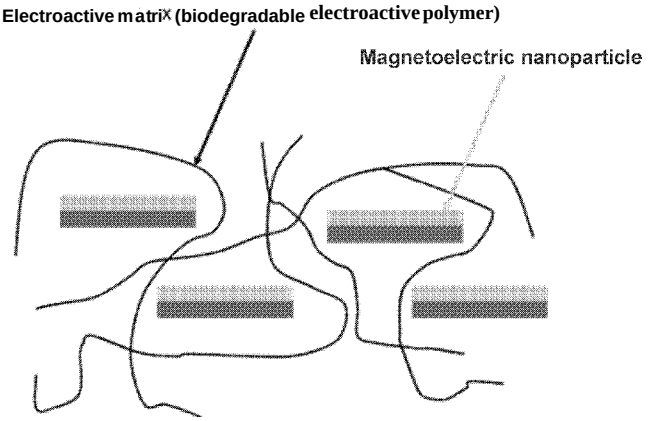

Fig. 1

(57) **Abstract:** Embodiments of the present disclosure provide for magnetically triggered electroactive composites, methods of making the magnetically triggered electroactive composites, methods of using the magnetically triggered electroactive composites, and the like.

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MAGNETICALLY TRIGGERABLE ELECTROACTIVE COMPOSITES, METHOD OF MAKING THE MAGNETICALLY TRIGGERABLE ELECTROACTIVE COMPOSITES, AND METHOD OF USING THE MAGNETICALLY TRIGGERABLE ELECTROACTIVE COMPOSITES

CLAIM OF PRIORITY TO RELATED APPLICATION

This application claims priority to co-pending U.S. application entitled "Magnetically Triggerable Electroactive Biomaterials" having Serial No. 62/100,284, filed on January 6, 2015, which is entirely incorporated herein by reference.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

This invention was made with government support under grant numbers DMR-1 150665 and DMR-1410564, awarded by the National Science Foundation. The government has certain rights in the invention.

BACKGROUND

It has been suggested to deliver drugs in vivo by encapsulating them in an electroactive biomaterial and then applying an electrical potential to the biomaterial. This would require an electrical connection (usually a wire) between an electrical power source and the electroactive material implanted in the patient. It would be advantageous to be able to deliver drugs in vivo without the need to make an electrical connection with the patient.

SUMMARY

Embodiments of the present disclosure provide for magnetically triggered electroactive composites, methods of making the magnetically triggered electroactive composites, methods of using the magnetically triggered electroactive composites, and the like.

An embodiment of the present disclosure provides for a composite, among others, that includes: a matrix of an electroactive polymer and a magnetoelectric material. In an embodiment, the electroactive polymer includes an aromatic functional group. In a particular embodiment, the electroactive polymer is selected from the group consisting of: polypyrrole, polyaniline, polythiophene, poly(3,4-ethylenedioxythiophene), poly fluorenes, polyphenylenes, polypyrenes, polyazulenes,

polynapthalenes, polyindoles, polyazepines, poly(p-phenylene sulfide)s, poly(p-phenylene vinylene)s, and polyfurans. In an embodiment, the electroactive polymer can be biodegradable and can contain electroactive oligomeric components. In an embodiment, the oligomeric component can be water-soluble and can have a molecular weight of about 1,000 to 70,000 Daltons. In an embodiment, the magnetoelectric material comprises a piezoelectric material and a magnetostrictive material.

In an embodiment, the present disclosure includes a method of delivering an agent, among others, that includes: introducing a composite to a subject, wherein the composite includes a matrix of an electroactive polymer and a magnetoelectric material, wherein the composite includes the agent; subjecting the composite to an external magnetic field, wherein the magnetoelectric material produces an electrical field in response to the magnetic field; and releasing the agent from the composite so the agent interacts with the subject.

BRIEF DESCRIPTION OF THE DRAWINGS

Many aspects of the present disclosure can be better understood with reference to the following drawing.

Fig. 1 is a schematic diagram of an electroactive composite material in accordance with a preferred embodiment, in which the magnetoelectric particles/fibers are incorporated within the electroactive polymer *(e.g.* a biodegradable electroactive polymer), and the particles and electroactive polymer interact though non-covalent/physical interactions.

Fig. 2 is a schematic of electroactive polymers in accordance with a preferred embodiment, in which the magnetoelectric nanoparticles or nanofibers are incorporated within the electroactive polymer, and the electroactive polymer is covalently attached to the magnetoelectric nanoparticles/nanofibers (in this example, the electroactive polymer is polypyrrole, PPy) and dexamethasone phosphate (DMP) is an example of a therapeutic drug encapsulated in the matrix.

Fig. 3 shows the release of DMP from the composite of the present disclosure, such as the composite in Figure 1.

Fig. 4 schematically illustrates the electrospinning set-up for bi- and tri-layer fibers, and the resultant morphologies, including bi-layer c) particles and d) fibers and e) tri- and f) six layered fibers.

Fig. 5 shows Fourier Transform Infrared (FTIR) spectra confirming successful surface modification of the as-synthesized Janus-type magnetoelectric fibers and fibers surface modified with -thiol, poly(ethylene glycol) (PEG), and aminopropyltriethoxysilane (APTMS) groups.

Fig. 6 a) is a graph that shows the results of a lactase dehydrogenase (LDH) assay, which measures LDH that is released by dead, dying, or damaged cells, revealing that bare, polyethylene glycol-, and thiol-functionalized Janus fibers are not cytotoxic.

Fig. 6 b) is a bright field image of the fibers.

Fig. 6 c) is a Live/Dead assay showing that the cells preferentially grow on the functionalized magnetoelectric fibers.

DISCUSSION

This disclosure is not limited to particular embodiments described, and as such may, of course, vary. The terminology used herein serves the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present disclosure will be limited only by the appended claims.

Where a range of values is provided, each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the disclosure. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges and are also encompassed within the disclosure, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the disclosure.

As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present disclosure. Any recited method may be carried out in the order of events recited or in any other order that is logically possible.

Embodiments of the present disclosure will employ, unless otherwise indicated, techniques of organic chemistry, biochemistry, microbiology, molecular

biology, pharmacology, medicine, and the like, which are within the skill of the art. Such techniques are explained fully in the literature.

Prior to describing the various embodiments, the following definitions are provided and should be used unless otherwise indicated.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art of microbiology, molecular biology, medicinal chemistry, and/or organic chemistry. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described herein.

As used in the specification and the appended claims, the singular forms "a," "an," and "the" may include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a support" includes a plurality of supports. In this specification and in the claims that follow, reference will be made to a number of terms that shall be defined to have the following meanings unless a contrary intention is apparent.

Definitions:

By "administration" is meant introducing a magnetically triggered electroactive composite of the present disclosure into a subject. The route of administration can include any route of administration, such as intravenous oral, topical, subcutaneous, peritoneal, intraarterial, inhalation, vaginal, rectal, nasal, introduction into the cerebrospinal fluid, or instillation into body compartments can be used. In regard to the agent, the agent can be administered to the subject via the magnetically triggered electroactive composite, where the agent can be subsequently released upon application of a magnetic field to the magnetically triggered electroactive composite.

The terms "therapeutically effective amount" and "an effective amount" are used interchangeably herein and refer to that amount of the magnetically triggered electroactive composite or an agent being administered that is sufficient to effect the intended application including, but not limited to, condition treatment. For example, an effective amount of the agent will relieve to some extent one or more of the symptoms of the condition, *i.e.,* infection, being treated, and/or that amount that will prevent, to some extent, one or more of the symptoms of the disease, *i.e.,* infection,

that the host being treated has or is at risk of developing. The therapeutically effective amount may vary depending upon the intended application *(in vitro* or *in vivo),* or the subject and disease condition being treated, *e.g.,* the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. The specific dose will vary depending on the particular agent chosen, the dosing regimen to be followed, whether it is administered in combination with other agents, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

The term "unit dosage form," as used herein, refers to physically discrete units suitable as unitary dosages for human and/or animal subjects, each unit containing a predetermined quantity of the agent calculated in an amount sufficient to produce the desired effect in association with a pharmaceutically acceptable diluent, carrier or vehicle. The specifications for unit dosage forms depend on the particular agent employed, the route and frequency of administration, and the effect to be achieved, and the pharmacodynamics associated with each agent in the subject.

As used herein, a "pharmaceutical composition" and a "pharmaceutical formulation" are meant to encompass embodiments of the present disclosure or agent suitable for administration to a subject, such as a mammal, especially a human. In general, a "pharmaceutical composition" or "pharmaceutical formulation" is sterile, and preferably free of contaminants that are capable of eliciting an undesirable response within the subject *(e.g.,* the agent or the polymer assembly in the pharmaceutical composition is pharmaceutical grade). Pharmaceutical compositions can be designed for administration to subjects or patients in need thereof via a number of different routes of administration including oral, intravenous, buccal, rectal, parenteral, intraperitoneal, intradermal, intracheal, intramuscular, subcutaneous, inhalational and the like.

As used herein, the terms "treatment", "treating", and "treat" are defined as acting upon a condition with an agent to reduce or ameliorate the pharmacologic and/or physiologic effects of the condition and/or its symptoms. "Treatment", as used herein, covers any treatment of a condition in a subject *(e.g.,* a mammal, typically a human or non-human animal of veterinary interest), and includes: (a) reducing the risk of occurrence of the condition in a subject determined to be predisposed to the condition but not yet diagnosed with the condition (b) impeding the development of

the condition, and (c) relieving the condition, i.e., causing regression of the condition and/or relieving one or more condition symptoms. "Treatment" is also meant to encompass delivery of agent or polymer assembly to provide a pharmacologic effect, even in the absence of a condition. For example, "treatment" encompasses delivery of an agent or polymer assembly that provides for enhanced or desirable effects in the subject.

As used herein, the terms "prophylactically treat" and "prophylactically treating" refer completely or partially preventing a condition or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a condition and/or adverse effect attributable to the condition.

As used herein, the term "subject" includes humans, mammals (e.g., cats, dogs, horses, *etc.),* birds, and the like. Typical subjects to which embodiments of the present disclosure may be administered will be mammals, particularly primates, especially humans. For veterinary applications, a wide variety of subjects will be suitable, *e.g.,* livestock such as cattle, sheep, goats, cows, swine, and the like; poultry such as chickens, ducks, geese, turkeys, and the like; and domesticated animals particularly pets such as dogs and cats. For diagnostic or research applications, a wide variety of mammals will be suitable subjects, including rodents *(e.g.,* mice, rats, hamsters), rabbits, primates, and swine such as inbred pigs and the like. Additionally, for *in vitro* applications, such as *in vitro* diagnostic and research applications, body fluids and cell samples of the above subjects will be suitable for use, such as mammalian (particularly primate such as human) blood, urine, or tissue samples, or blood, urine, or tissue samples of the animals mentioned for veterinary applications. In some embodiments, a system includes a sample and a host. The term "living host" refers to the entire host or organism and not just a part excised (e.g., a liver or other organ) from the living host.

Discussion:

Embodiments of the present disclosure provide for magnetically triggered electroactive composites, methods of making the magnetically triggered electroactive composites, methods of using the magnetically triggered electroactive composites, and the like. In an embodiment, the magnetically triggered electroactive composite has electroactive characteristics so that an electrical stimulation can be periodically applied to the magnetically triggered electroactive composite, where an electric field

(e.g., electrical stimulation) can be produced as a result of applying a magnetic field onto the magnetoelectric material which causes current flow in the electroactive polymer. In this regard, the magnetically-triggerable electroactive composite can be used to deliver drugs or to stimulate cells or tissue.

In an embodiment, the magnetically triggered electroactive composite includes a matrix of an electroactive polymer and a magnetoelectric material. The magnetoelectric material can be dispersed throughout the electroactive polymer. In an embodiment, the magnetoelectric material can be in the form of a scaffold that supports the electroactive polymer or the electroactive polymer can be in the form of a scaffold that supports the magnetoelectric material. Subjecting the matrix to a magnetic field (e.g., externally applied) causes the matrix to become electrically active. In addition, one or more agents can be disposed in the matrix and released from the matrix when the matrix is exposed to an appropriate magnetic field. In this regard, the magnetically triggered electroactive composite of the present disclosure can be used to deliver agents such as drugs, antibacterial agents, and antifungal agents. In addition, the magnetically triggered electroactive composite can also be used as electroactive actuators capable of mechanotransduction of cells, such as stem cells, or tissue.

In an embodiment the electroactive polymer and the magnetoelectric material can interact with one another covalently and/or non-covalently. In an embodiment, the electroactive polymer and the magnetoelectric material can interact with one another through covalent bonds or non-covalent physical interactions (e.g., chain entanglement), which can yield an interpenetrating network.

In an embodiment the matrix can be embodied in any of a variety of material morphologies or combination of morphologies (e.g., scaffolds, fibers, films, foams, gels, particulates, and combinations thereof), optionally with micrometer or nanometer-scale features (e.g., grooves, bumps, pores, where the grooves and pores can be an indention into the surface and/or extend through the matrix). In an embodiment, the magnetoelectric material can be a fiber(s) (e.g., nanofibers) or a particulate(s) (e.g., nanoparticles) that can be part of and/or form a scaffold that can interact with the electroactive polymer.

In an embodiment the matrix can be biodegradable. In an embodiment, the electroactive polymer is water soluble, which facilitates degradation of the entirety of the material. The term "biodegradable" refers to polymers that degrade through the

action of a physicochemical *(e.g.,* hydrolysis, pH) or biological *(e.g.,* enzyme) trigger that the polymer is exposed to in use.

In an embodiment, the electroactive polymer can include an aromatic functional group. The aromatic functional group can be non-heterocyclic or heterocyclic group. In an embodiment, the electroactive polymer can include a pyrrole, an aniline, an aniline derivative, a furan, a furan derivative, a thiophene, a thiophene derivative *(e.g.,* poly(3,4-ethylenedioxythiophene)), ferrocene, a ferrocene derivative, a porphyrin, a porphyrin derivative, a fluorine, a fluorene derivative, the polymerizable unit include a phenylene, a phenylene derivative, a pyrene, a pyrene derivative, an azulene, an azulene derivative, a naphthalene, a napthalene derivative, an indole, an indole derivative, an azepinesp-phenylene, an azepinesp-phenylene derivative, a sulfide p-phenylene vinylene, a sulfide p-phenylene vinylene derivative, or a combination thereof, each of which can be a polymer, co-polymer of two or more monomers, and the like. In an embodiment, the electroactive polymer (conducting polymer) can include polymers such as polypyrrole, polyaniline, polythiophene, poly(3,4-ethylenedioxythiophene), polyfluorenes, polyphenylenes, polypyrenes, polyazulenes, polynapthalenes, polyindoles, polyazepines, poly(p-phenylene sulfide)s, poly(p-phenylene vinylene)s, and polyfurans. In an embodiment, there are biodegradable versions, in which there are block of conducting units within a polymer chain containing biodegradable bonds *(e.g.* esters and amides), that can also be used as the conducting polymer. In an embodiment, the electroactive polymer can be used in conjunction with a dopant. The dopant can be a species that has the opposite charge to the conducting polymer, and can be low molecular weight *(e.g.,* chlorine ions, tosylate ions, and the like) or high molecular weight *(e.g.,* collagen, hyaluronic acid, and the like). In a particular embodiment, the polymerizable unit can be polypyrrole, or more particularly, the polymerizable unit can be 3,4-ethylenedioxythiophene; and a derivative of 3,4-ethylenedioxythiophene. The amount of the electroactive polymer in the matrix can be about 1 to 90 wt % of the composite.

In an embodiment, the electroactive polymer is a block polymer comprising electroactive blocks *(e.g.,* oligoaniline blocks) linked together by biodegradable ester bonds; and one or more other polymers *(e.g.,* polycaprolactone or polyethylene glycol). In an embodiment, the other polymer can include synthetic polymers *(e.g.,* polycaprolactone, polyesters, polyamides, PCL, PLLA, PLGA, etc.), natural polymers *(e.g.* proteins, polysaccharides, lignins, polyalanine, oligoalanine, collagen, silk,

cellulose, chitin, chitosan, and the like), or a combination thereof. In a particular embodiment, the other polymer can include a polycaprolactone polymer. In an embodiment, the other polymer can include a mixture of different types of polymer *(e.g.,* a portion of polycaprolactone and polyester). In an embodiment, the electroactive polymer is a block polymer comprising electroactive oligoaniline blocks linked together by biodegradable ester bonds; and polycaprolactone or polyethylene glycol (or derivatives thereof). In an embodiment, the other polymer can have a molecular weight of about 400 to 100,000 Daltons, about 400 to 10,000 Daltons, or about 400 to 2,000 Daltons. The amount of the other polymer in the matrix can be about 1 to 80 wt % of the composite.

In an embodiment, the magnetoelectric material can include one or more components. In an embodiment, the magnetoelectric material can be an organic material *(e.g.,* oligomer, polymer) or an inorganic material *(e.g.,* metal or metal based compound). In an embodiment, the magnetoelectric material can be about 1 to 80 % wt. of the composite.

In an embodiment, the magnetoelectric material can be an oligomer or polymer. In an embodiment, the magnetoelectric material can be an oligomer that is water-soluble and has a molecular weight of about 1000 to 70,000 Daltons. In an embodiment, the oligomer can be in the form of a particle *(e.g.,* nanoparticle having a largest dimension of about 5 to 500 nm or about 5 to 50 nm) or fiber *(e.g.,* a nanofiber having a diameter of about 5 to 500 nm or about 5 to 50 nm and an aspect ratio of 10 to 100,000).

In an embodiment, the oligomer can be oligomers of: pyrrole, an aniline, an aniline derivative, a furan, a furan derivative, a thiophene, a thiophene derivative *(e.g.,* 3,4-ethylenedioxythiophene), ferrocene, a ferrocene derivative, a porphyrin, a porphyrin derivative, a fluorine, a fluorene derivative, the polymerizable units include a phenylene, a phenylene derivative, a pyrene, a pyrene derivative, an azulene, an azulene derivative, a naphthalene, a napthalene derivative, an indole, an indole derivative, an azepinesp-phenylene, an azepinesp-phenylene derivative, a sulfide p-phenylene vinylene, a sulfide p-phenylene vinylene derivative, or a combination thereof . In an embodiment, the oligomer can have a molecular weight of about 500 to 5,000 Da.

In an embodiment, the magnetoelectric material can include a piezoelectric material and/or a magnetostrictive material. In an embodiment, the piezoelectric

material can be: barium titanate, bismuth ferrite, polyvinylidene difluoride, lead zirconate titanate, polyvinylidene difluoride- trifluoroethylene, or a combination thereof. In an embodiment, the magnetostrictive material can be: cobalt ferrite, iron oxide, terfenol-d, or a combination thereof. In an embodiment, the ratio of the piezoelectric material to the magnetostrictive material can be about 1**:99** to **99**:1. In an embodiment, the magnetoelectric material can be piezoelectric barium titanate and magnetostrictive cobalt ferrite.

In an embodiment, the composite can include one or more agents **(e**.g., a chemical or biological agent), where the agent can be disposed indirectly or directly on/in the composite. The composite can be made by a variety of different techniques, but simple examples include films dried from suspensions of the agent, electroactive polymer and magnetoelectric material, and optionally other components *(e.g.* polymers) in solution in a suitable solvent (aqueous or non-aqueous); or melting of one or more of the polymeric components with the agent, electroactive polymer and magnetoelectric material; or growth of electroactive polymers from the surface of magnetoelectric materials and their loading with an agent.

In this regard the agent can be administered to the subject to treat, image, detect, study, monitor, and/or evaluate a condition, or the like in the subject. In an embodiment, the agent can include, but is not limited to, a drug, a therapeutic agent, a radiological agent, a small molecule drug, a biological agent **(e**.g., polypeptides **(e**.g., proteins such as, but not limited to, antibodies (monoclonal or polyclonal)), antigens, nucleic acids (both monomeric and oligomeric), polysaccharides, haptens, sugars, fatty acids, steroids, purines, pyrimidines, ligands, and aptamers) and combinations thereof, that can be used to image, detect, study, monitor, evaluate, and the like, the differentiation of the stem cells. In an embodiment, the agent is included in an effective amount to accomplish its purpose, where such factors to accomplish the purpose are well known in the medical arts.

In general, the agent can be bound to the composite **(e**.g., scaffold, particles, fibers, polymers, and the like) by a physical, biological, biochemical, and/or chemical association directly or indirectly by a suitable means. The term "bound" can include, but is not limited to, chemically bonded **(e**.g., covalently or ionically), biologically bonded, biochemically bonded, and/or otherwise associated with the material. In an embodiment, being bound can include, but is not limited to, a covalent bond, a non-covalent bond, an ionic bond, a chelated bond, as well as being bound through

interactions such as, but not limited to, hydrophobic interactions, hydrophilic interactions, charge-charge interactions, π-π stacking interactions, combinations thereof, and like interactions.

As described herein, embodiments of the present disclosure provide for a method of delivering one or more agents. An embodiment of the method includes providing *(e.g.,* administering) the composite including the agent to a subject having a condition *(e.g.,* a disease, an infection, an injury, a syndrome, a disability, a disorder, and a combination thereof). The composite can be administered in one or more ways as is best suited for the particular situation. Subsequently, a magnetic field can be applied to generate an electrical stimulus that can be used to activate composite. In particular, the magnetic filed can be directed to an area where the agent is needed. For example, if the condition is pain or an infection at a particular location, the magnetic field can be directed to that area. In this way, the magnetic field causes the agent to be released from the composite at or near the location *(e.g.,* specific area of the patient) of the condition. In an embodiment, the magnetic field causes the magnetostrictive component to change shape, which imposes a strain on the piezoelectric component - thereby generating an electric field, and this electric field causes the release of the agent from the surrounding matrix of agent-loaded electroactive polymer. In an embodiment, the magnetic field can be periodically applied or pulsed. In an embodiment, the magnetic field can be applied at certain times of the day.

In regard to electrical stimulation of cells or tissue, embodiments of the disclosure provide for methods of stimulating cells or tissue. An embodiment of the present disclosure includes introducing cells to the composite, where the composite (and optionally a tissue or other cells) and the cells are cultured in an appropriate medium. Subsequently, the composite can be exposed to a magnetic field to generate electrical stimulation that can be periodically applied *(e.g.,* via the magnetic field) to the cells to cause a desired outcome.

The term "periodically" refers to applying the electrical stimulation *(e.g.,* via the magnetic field) at established time frames that may be at regular or irregular time intervals on the time frames of seconds, hours, days, weeks, or months *(e.g.,* about 1 s to 2 months, about 1 hour to 1 day, about 1 day to 1 month, or other the like) depending upon the specific circumstances. In an embodiment, the impulses of the electrical stimulation can last on the time frame of seconds, hours, or days *(e.g.,*

about 1 second to 1 day, about 10 seconds to 1 hour, about 1 minute to 12 hours, about 1 hour to 1 day, or the like) depending upon the specific circumstances. The time frame and duration of electrical stimulation can be designed based on particular circumstances and requirements of a specific situation.

While embodiments of the present disclosure are described in connection with the Examples and the corresponding text and figures, there is no intent to limit the disclosure to the embodiments in these descriptions. On the contrary, the intent is to cover all alternatives, modifications, and equivalents included within the spirit and scope of embodiments of the present disclosure.

EXAMPLE:

The release of a bioactive molecule (e.g., dexamethasone phosphate, DMP, an anti-inflammatory) is controlled from a matrix of a biodegradable electroactive polymer (as depicted in Figure 1). An example of such polymers are block copolymers composed of electroactive oligoaniline blocks and non-electroactive biodegradable polycaprolactone or polyethylene glycol, and the blocks are linked together via biodegradable ester bonds. In a preferred embodiment, the electroactive oligomer has a molecular weight below the renal filtration limit of 70,000 Da, and is sufficiently water soluble to allow its clearance via the renal system upon degradation of the polycaprolactone blocks or ester bonds. Exposure of the composite materials (as depicted in Figure 1) composed of the magnetoelectric particles/fibers, an electroactive polymer and a drug (DMP) to magnetic fields for specified times results in the release of the drug (see Figure 3). The release rate can be varied by applying and removing the field. This allows the electroactive polymer to serve as a drug storage reservoir, which can be tapped as needed by application and removal of the magnetic field.

Fabrication of the Electroactive Composite Materials

The electroactive composite materials in accordance with a preferred embodiment are composed of a conducting polymer and a Janus-type magnetoelectric nanoparticle or nanofiber (so called because the particle or fiber is made up of a piezoelectric phase and a magnetostrictive phase that are distributed semi-cylindrically). In a preferred embodiment, these magnetoelectric nanoparticles or nanofibers are composed of piezoelectric barium titanate and magnetostrictive cobalt ferrite. These magnetoelectric nanoparticles or nanofibers are synthesized via co-

electrospinning. By varying the processing conditions, fibers or particles can be produced (Fig. 4). The as-synthesized particles are surface modified for further functionalization for biological applications. Fig. 5 shows Fourier Transform Infrared Spectroscopy (FTIR) results, which confirm the modification of the surface of the fibers with thiols, amines, and polyethylene glycol. The biocompatibility of these fibers are further confirmed in Fig. 6. Fig. 3 reveals that these multiferroic composites do not exhibit cytotoxicity. These results compare the biocompatibility of as-synthesized bare fibers and fibers functionalized with polyethylene glycol and a thiol functionality using a lactase dehydrogenase assay (LDH) which measures LDH that is released by dead, dying or damaged cells (Fig. 6 a). Figs. 6 b) and 6 c) show bright-field and fluorescent microscope images, respectively, of osteosarcoma cells (MG63) on functionalized fibers, indicating that the cells preferentially adhere to the magnetoelectric fibers.

It should be noted that ratios, concentrations, amounts, and other numerical data may be expressed herein in a range format. It is to be understood that such a range format is used for convenience and brevity, and thus, should be interpreted in a flexible manner to include not only the numerical values explicitly recited as the limits of the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited. To illustrate, a concentration range of "about 0.1% to about 5%" should be interpreted to include not only the explicitly recited concentration of about 0.1 wt% to about 5 wt%, but also include individual concentrations (e.g., 1%, 2%, 3%, and 4%) and the sub-ranges *(e.g.,* 0.5%, 1.1%, 2.2%, 3.3%, and 4.4%) within the indicated range. In an embodiment, the term "about" can include traditional rounding according to significant figures of the numerical value. In addition, the phrase "about 'x' to 'y'" includes "about 'x' to about 'y'".

Many variations and modifications may be made to the above-described embodiments. All such modifications and variations are intended to be included herein within the scope of this disclosure and protected by the following claims.

CLAIMS

We claim:

1. A composite, comprising:

a matrix of an electroactive polymer and a magnetoelectric material.

2. The composite of claim 1, wherein the electroactive polymer includes an aromatic functional group.

3. The composite of claim 2, wherein the electroactive polymer is selected from the group consisting of: polypyrrole, polyaniline, polythiophene, poly(3,4-ethylenedioxythiophene), poly fluorenes, polyphenylenes, polypyrenes, polyazulenes, polynapthalenes, polyindoles, polyazepines, poly(p-phenylene sulfide)s, poly(p-phenylene vinylene)s, and polyfurans.

4. The composite of claim 1, wherein the electroactive polymer includes an oligomer component, wherein the oligomer component is water-soluble and has a molecular weight of about 1000 to 70,000 Daltons.

5. The composite of claim 4, wherein the oligomer component is selected from the group consisting of: pyrrole, an aniline, an aniline derivative, a furan, a furan derivative, a thiophene, a thiophene derivative, ferrocene, a ferrocene derivative, a porphyrin, a porphyrin derivative, a fluorine, a fluorene derivative, the polymerizable units include a phenylene, a phenylene derivative, a pyrene, a pyrene derivative, an azulene, an azulene derivative, a naphthalene, a napthalene derivative, an indole, an indole derivative, an azepinesp-phenylene, an azepinesp-phenylene derivative, a sulfide p-phenylene vinylene, a sulfide p-phenylene vinylene derivative,and a combination thereof .

6. The composite of claim 1, wherein the magnetoelectric material comprises a piezoelectric material, a magnetostrictive material, or a combination thereof.

7. The composite of claim 6, wherein the piezoelectric material is selected from the group consisting of: barium titanate, bismuth ferrite, polyvinylidene difluoride,

lead zirconate titanate, polyvinylidene difluoride-trifluoroethylene, and a combination thereof.

8. The composite of claim 6, wherein the magnetostrictive material is selected from the group consisting of: cobalt ferrite, iron oxide, terfenol-d, and a combination thereof.

9. The composite of claim 10, wherein the magnetoelectric material comprises piezoelectric barium titanate, magnetostrictive cobalt ferrite, or a combination thereof.

10. A method of delivering an agent, comprising:

introducing a composite to a subject, wherein the composite includes a matrix of an electroactive polymer and a magnetoelectric material, wherein the composite includes the agent;

subjecting the composite to a magnetic field, wherein the magnetoelectric material produces an electrical field in response to the magnetic field; and

releasing the agent from the composite so the agent interacts with the subject.

11. The method of claim 10, wherein the electroactive polymer is selected from the group consisting of: polypyrrole, polyaniline, polythiophene, poly(3,4-ethylenedioxythiophene), poly fluorenes, polyphenylenes, polypyrenes, polyazulenes, polynapthalenes, polyindoles, polyazepines, poly(p-phenylene sulfide)s, poly(p-phenylene vinylene)s, and polyfurans.

12. The method of claim 10, wherein the electroactive polymer includes an oligomer component, wherein the oligomer component is water-soluble and has a molecular weight of about 1000 to 70,000 Daltons.

13. The method of claim 10, wherein the oligomer component is selected from the group consisting of: pyrrole, an aniline, an aniline derivative, a furan, a furan derivative, a thiophene, a thiophene derivative, ferrocene, a ferrocene derivative, a porphyrin, a porphyrin derivative, a fluorine, a fluorene derivative, the polymerizable units include a phenylene, a phenylene derivative, a pyrene, a pyrene derivative, an azulene, an azulene derivative, a naphthalene, a napthalene derivative, an indole, an

indole derivative, an azepinesp-phenylene, an azepinesp-phenylene derivative, a sulfide p-phenylene vinylene, a sulfide p-phenylene vinylene derivative, and a combination thereof .

14. The method of claim 10, wherein the magnetoelectric material comprises a piezoelectric material, a magnetostrictive material, or a combination thereof.

15. The method of claim 14, wherein the piezoelectric material is selected from the group consisting of: barium titanate, bismuth ferrite, polyvinylidene difluoride, lead zirconate titanate, polyvinylidene difluoride-trifluoroethylene, and a combination thereof.

16. The method of claim 10, wherein the magnetostrictive material is selected from the group consisting of: cobalt ferrite, iron oxide, terfenol-d, and a combination thereof.

17. The method of claim 10, wherein the magnetoelectric material comprises piezoelectric barium titanate, magnetostrictive cobalt ferrite, or a combination thereof.

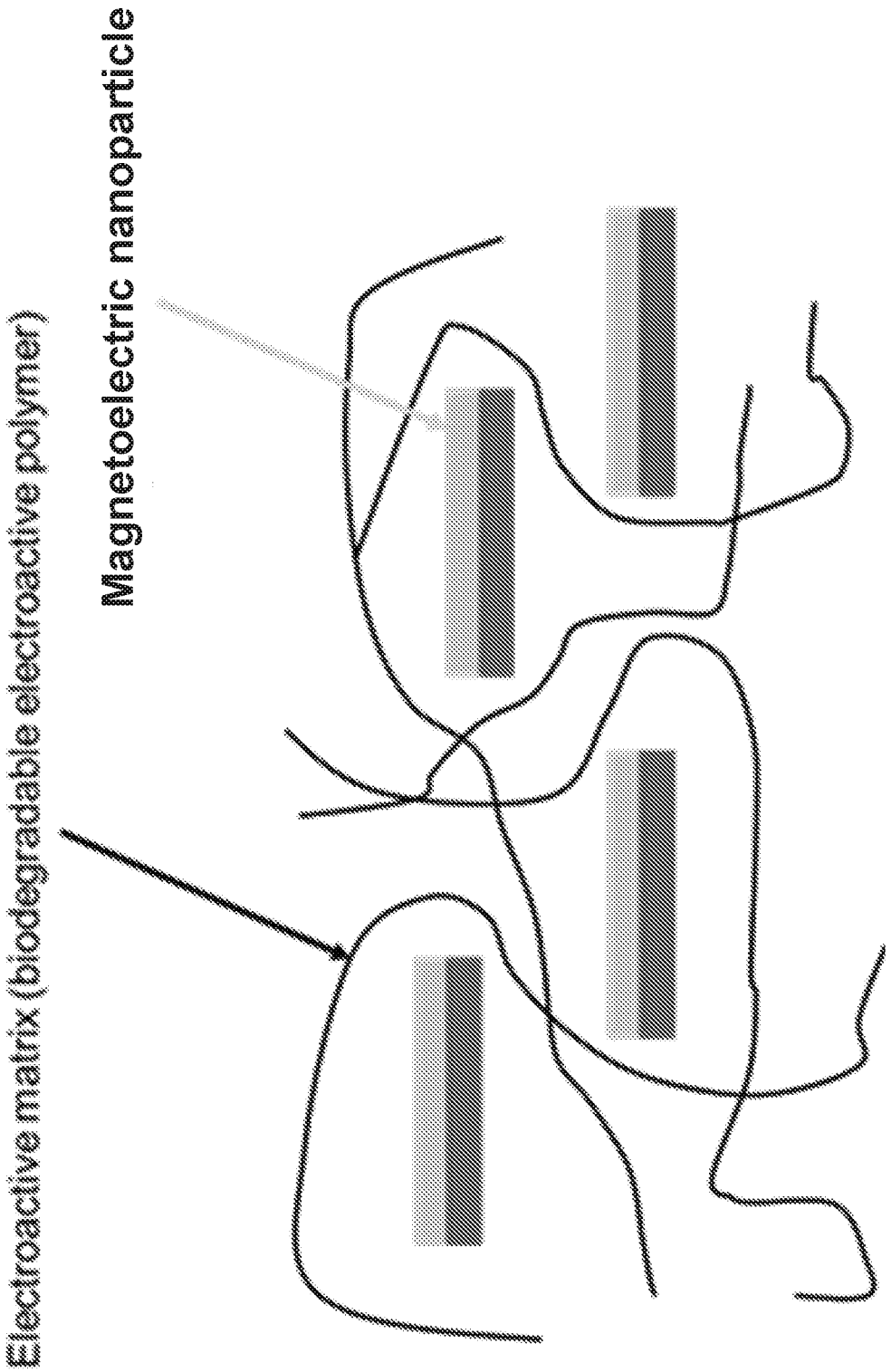
Magnetoelectric nanoparticle
Electroactive matrix (biodegradable electroactive polymer)

Fig. 1

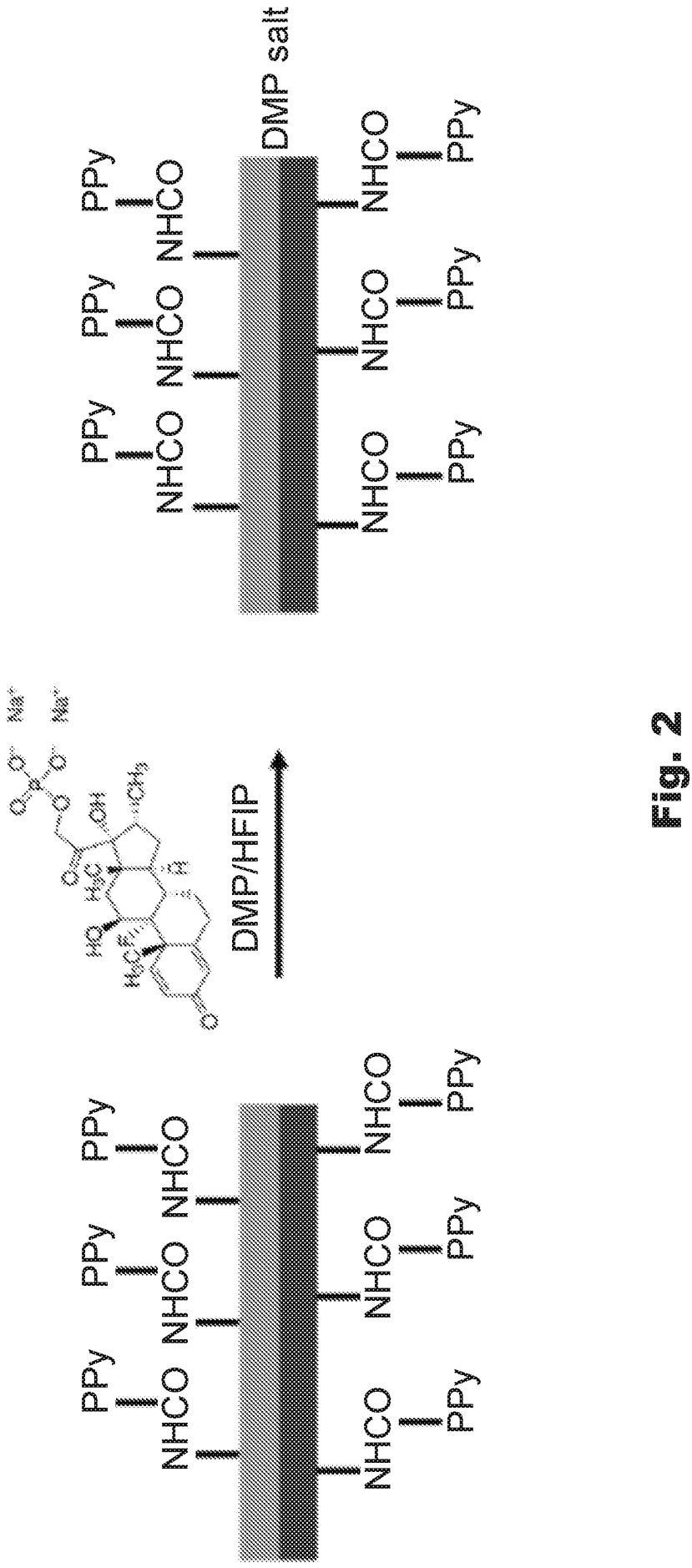

Fig. 2

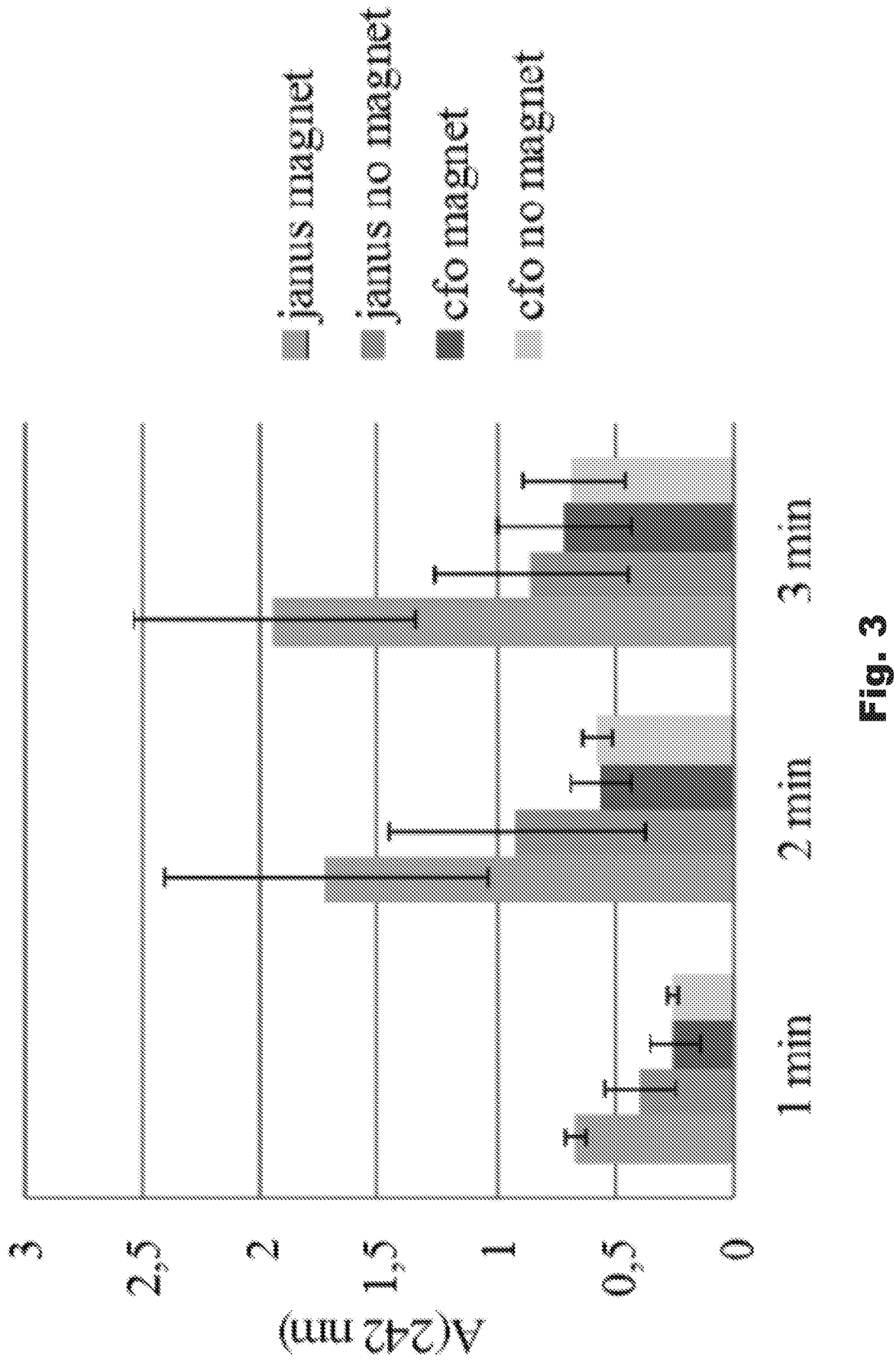
jamus magnet
jamus no magnet
cfo magnet
cfo no magnet
A(242 nm)
3
2,5
2
1,5
1
0,5
0
1 min
2 min
3 min

Fig. 3

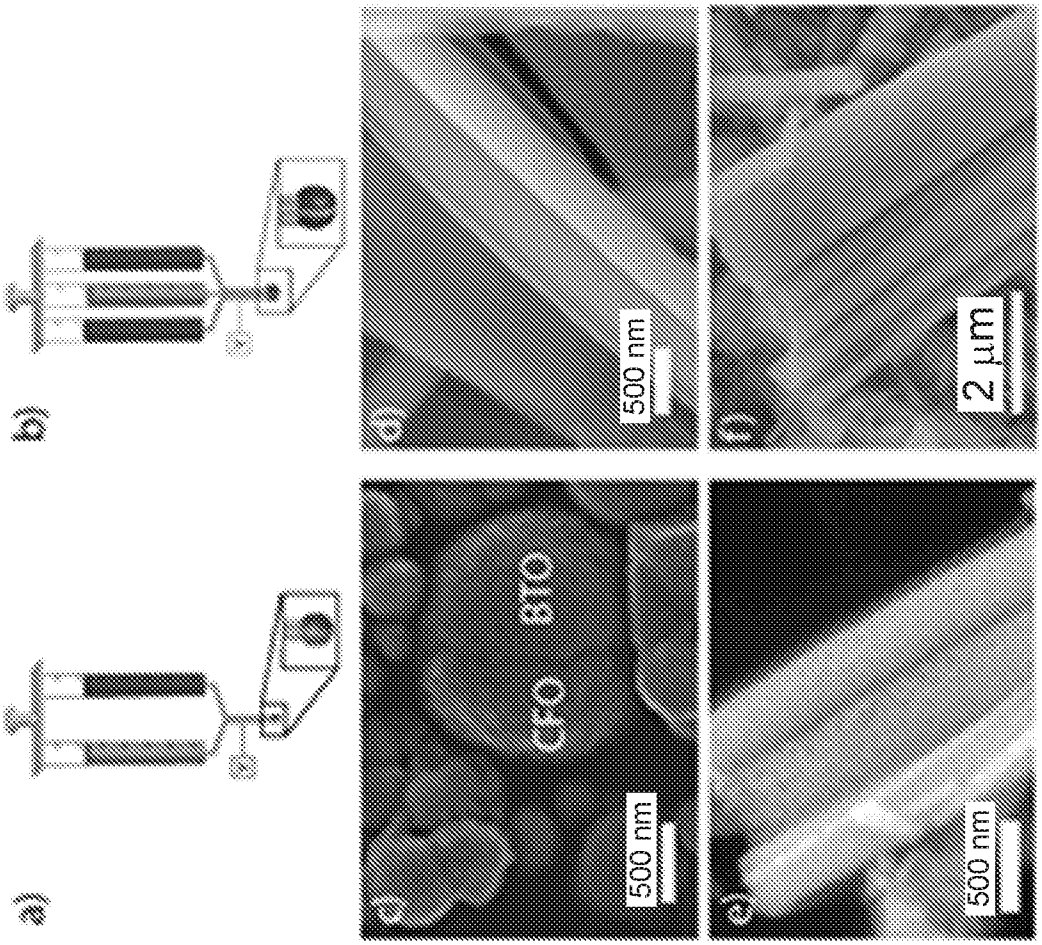

Fig. 4

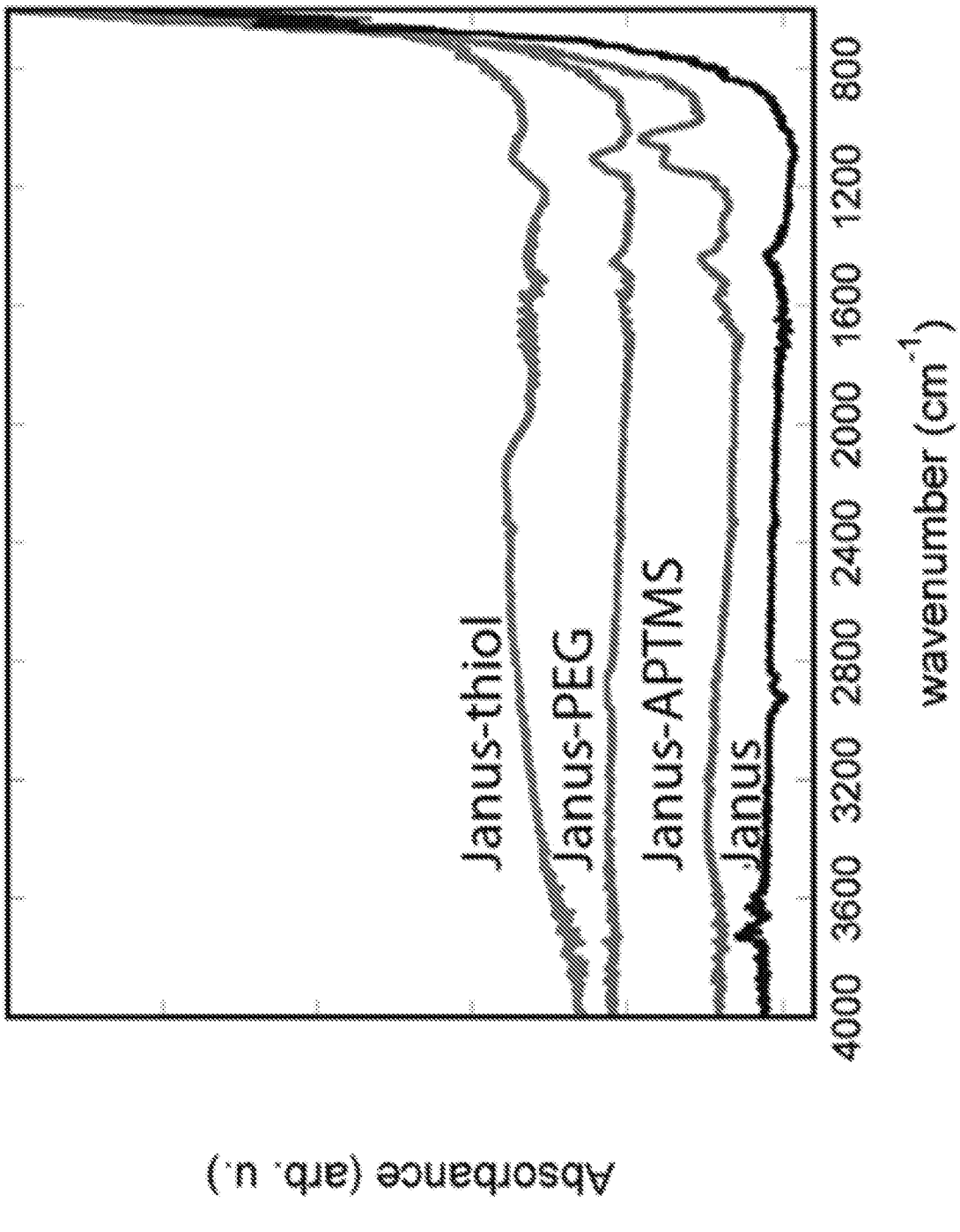
Janus-thiol
Janus-PEG
Janus-APTMS
Janus
4000
3600
3200
2800
2400
2000
1600
1200
800
wavenumber (cm-1)
Absorbance (arb. u.)

Fig. 5

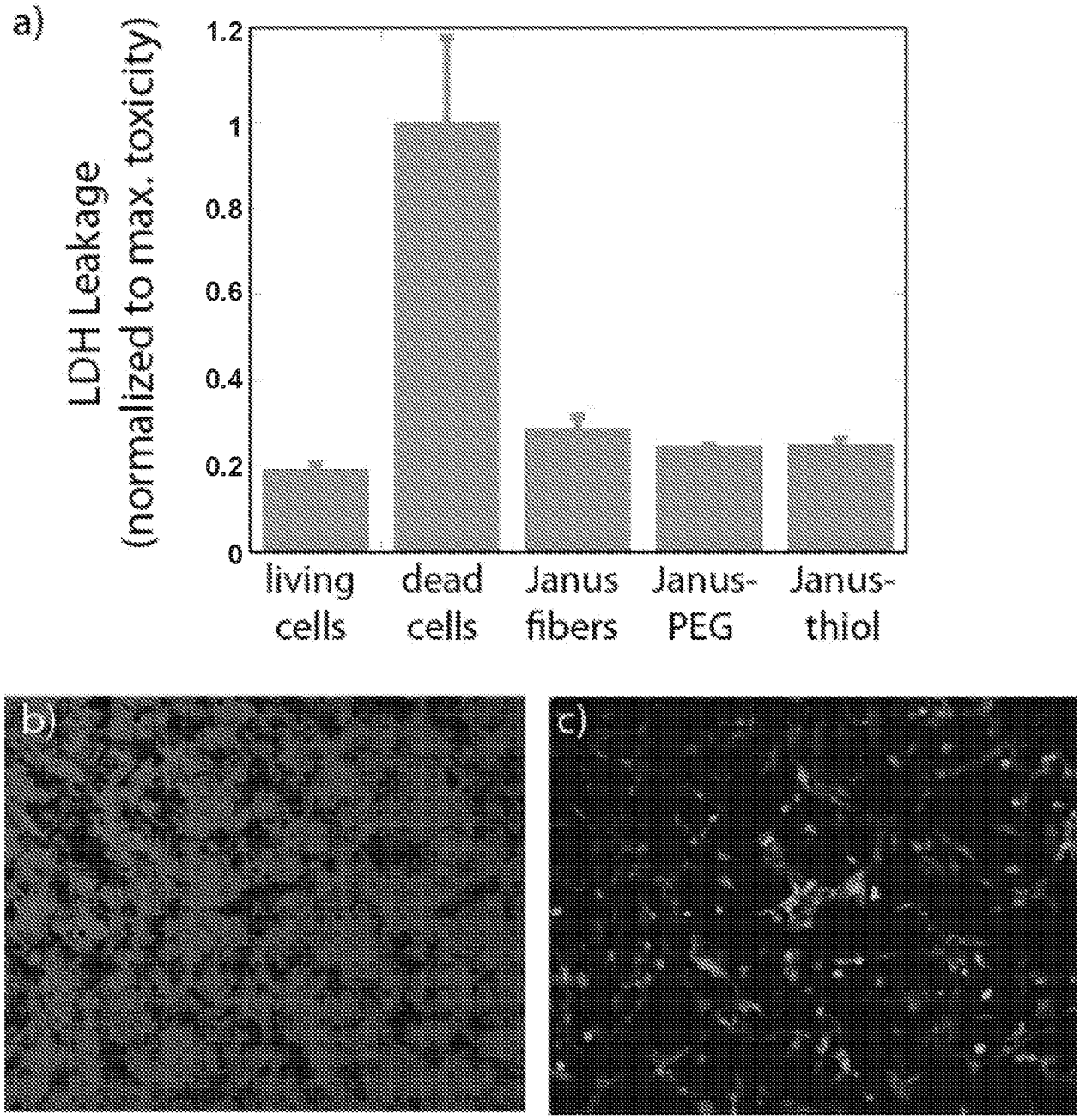
a)
LDH Leakage
(normalized to max. toxicity)
1.2
1
0.8
0.6
0.4
0.2
0
living cells
dead cells
Janus fibers
Janus-PEG
Janus-thiol
b)
c)

Fig. 6