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(54) Title: ETHYLENE BRASSYLATE-CO-DIOXANONE POLYMERS AND USES THEREOF

(57) Abstract: Described are poly(ethylene brassylate-co-dioxanone) polymers and polymeric nanoparticles or macroimplants formed therefrom. The nanoparticles show stability in several media, as well as enhanced uptake by brain cancer cells compared to nanoparticles formed from poly(ethylene glycol)-poly(lactic acid). Also described are *in vitro* and *in vivo* methods of using the particles, macroimplants, and compositions thereof, in drug delivery platforms and gene editing platforms.

**ETHYLENE BRASSYLATE-CO-DIOXANONE
POLYMERS AND USES THEREOF**

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of and priority to U.S. Provisional
5 Application No. 63/491,328 filed March 21, 2023, which is incorporated
herein by reference in its entirety.

**STATEMENT REGARDING FEDERALLY SPONSORED
RESEARCH**

This invention was made with government support under HL139756
10 and CA149128 awarded by National Institutes of Health. The government
has certain rights in the invention.

FIELD OF THE INVENTION

The field of the invention is generally related to sustained delivery of
diagnostic, prophylactic, and/or therapeutic agents, particularly delivery of
15 these agents to the brain and other organs *in vivo*.

BACKGROUND OF THE INVENTION

Polymeric particles, especially nanoparticles, have great potential for
the controlled spatial and temporal delivery of a wide variety of diagnostic,
prophylactic, and/or therapeutic agents, to disease-afflicted organs *in vivo*
20 (Salata, Journal of Nanobiotechnology 2004, **2**(1): 3; Lee and Yeo, Chemical
Engineering Science 2015, **125**, 75-84). Localizing these agents to target
sites can circumvent toxicity, unwanted side effects, unnecessarily high
systemic doses, and widespread distribution of payload.

Enormous preclinical and clinical effort/resources have been
25 expended to produce polymeric particles capable of site-specific delivery of
therapeutic agents, diagnostic agents, and/or prophylactic agents with limited
and/or reduced off-target toxicity, and these efforts are still ongoing. This is
because achieving successful and tissue-specific delivery is difficult, as these
particles can be rapidly cleared from the bloodstream by the mononuclear
30 phagocyte system, renal filtration, and endogenous enzymes (Albanese, *et*
al., Annu. Rev. Biomed. Eng. 2012, **14**(1): 1-16; Owens and Peppas,

International Journal of Pharmaceutics 2006, **307**(1): 93-102). Another challenge resides in the difficulty in developing agent-loaded particles with effective amounts of payload, suitable size, and surface properties to locally deliver agents. Further, the particles must be versatile for a variety of manufacturing methods and scaleup, possess limited toxicity to healthy cells/tissue, and maintain stability in relevant tissue microenvironments.

To address these limitations, platforms for the efficient production of delivery systems that effectively and selectively deliver therapeutic, diagnostic, and/or prophylactic agents *in vivo* are needed.

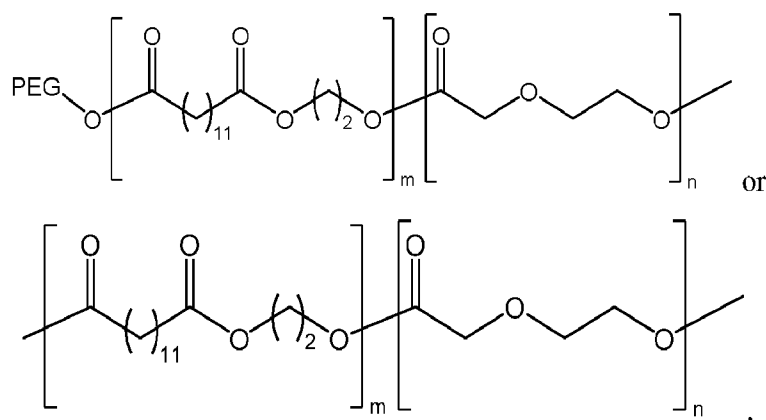
Therefore, it is an object of the invention to provide effective ways of delivering therapeutic, diagnostic, and/or prophylactic agents *in vivo*.

It is also an object of the invention to provide polymeric particles and nanoparticles, that are suitable for *in vivo* delivery of therapeutic, diagnostic, and/or prophylactic agents.

It is a further object of the invention to provide polymeric particles and nanoparticles, that are suitable for *in vivo* delivery of therapeutic, diagnostic, and/or prophylactic agents, and are stable in several media as determined by narrow fluctuations in the particles' sizes and polydispersity indices.

SUMMARY OF THE INVENTION

Poly(ethylene brassylate-*co*-dioxanone) polymers, particles and macroimplants containing these polymers are disclosed. In some forms, the polymers contain the structure:



wherein, m and n are independently integers from 1 to 1500, with the proviso that m+n is at least 10 (such as from 10 to 3000). In some forms, the polymers have a weight-average molecular weight between about 10 kDa

and about 150 kDa, between about 10 kDa and about 130 kDa, or between about 10 kDa and about 125 kDa, as measured using gel permeation chromatography, such as between about 15 kDa and about 25 kDa, between about 45 kDa and about 72 kDa, and between about 50 kDa and about 125 kDa.

The particles show significantly improved internalization in cancer cells (*e.g.*, glioma cells), compared to particles formed from other types of polymers, such as poly(ethylene glycol)-poly(lactic acid). In some forms, the polymers preferably show improved biological properties (internalization, transfection, stability) compared to other polymers that lack the ethylene brassylate-co-dioxanone combination. Accordingly, if needed, such specific polymers with less effective biological properties can be excluded from the instant compositions.

The particles and macroimplants are stable over several days in different media, as determined by their average sizes and polydispersity indices over time, and are retained in brain cells for at least five days post-delivery.

The particles and macroimplants can include therapeutic agents, diagnostic agents, prophylactic agents, or a combination thereof, to be delivered to desired cells, tissues, and/or organs.

Also described are methods of using this platform technology for delivery and/or controlled release of agents to cells, tissues, and/or organs, in drug delivery platforms or gene editing platforms. The drug-loaded particles and macroimplants, or compositions thereof, can be used in combination therapy settings, to deliver two or more types of drugs that belong to the same or different therapeutic class and display the same or different mechanism of action. One type of drug is encapsulated, while a second drug is provided as free or soluble drug, or in a different carrier or dosage form. The drug-loaded particles or compositions thereof demonstrate effective killing of glioma cells.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGs. 1A, 1B, and 1C are scatter plots showing size distributions (**FIG. 1A**), zeta potentials (**FIG. 1B**), and polydispersities (**FIG. 1C**) of different nanoparticle formulations. **PEG-EB-co-DO** represents the poly(ethylene glycol)-ethylene brassylate-*co*-dioxanone polymer, **PLA-PEG** represents poly(lactide)-poly(ethylene glycol) polymer, **PDI** represents Polydispersity Index, the numbers **175, 297, 333** represent different analogs of ataxia telangiectasia and Rad3-related (ATR) inhibitors, **DMSO** represents nanoparticles formulated using dimethylsulfoxide in a nanoprecipitation process.

FIGs. 2A, 2B, and 2C are scatter plots showing encapsulation efficiencies (**FIG. 2A**), polymer yields (**FIG. 2B**), and drug loadings (**FIG. 2C**) of different nanoparticle formulations. **PEG-EB-co-DO** represents the poly(ethylene glycol)-ethylene brassylate-*co*-dioxanone polymer, **PLA-PEG** represents poly(lactic acid)-poly(ethylene glycol) polymer, **PDI** represents polydispersity index, the numbers **175, 297, 333** represent different analogs of ataxia telangiectasia and Rad3-related (ATR) inhibitors, **DMSO** represents nanoparticles formulated using dimethylsulfoxide in a nanoprecipitation process.

FIG. 3 is a scatter plot showing a relationship between particle size and poly(ethylene glycol)-ethylene brassylate-*co*-dioxanone polymer concentration used.

FIGs. 4A and 4B are line graphs tracking the stabilities of **PEG-EB-co-DO** nanoparticles in various media by monitoring the sizes (**FIG. 4A**) and polydispersity indices (**FIG. 4B**) of the particles. **PEG-EB-co-DO** represents the poly(ethylene glycol)-ethylene brassylate-*co*-dioxanone polymer, **ACSF** represents nanoparticles incubated in artificial Cerebrospinal Fluid, **H₂O** represents nanoparticles incubated in water, **PBS** represents nanoparticles incubated in phosphate buffered saline, and **SFM** represents nanoparticles incubated in serum-free media. The hydrodynamic diameter measured through Dynamic Light Scattering is somewhat higher in ACSF and PBS than water, likely due to the surface interactions between the salts in the buffer with the nanoparticles.

FIG. 5 is a line graph showing the viability of RG2 rat glioma cells in culture. **PEG-EB-co-DO** represents the poly(ethylene glycol)-ethylene brassylate-co-dioxanone polymer, **LogP** is a measure of lipophilicity of the drug substance and **MW** represents molecular weight; the numbers **175, 297, 333** represent different analogs of ATR inhibitors, **Free** represents cells given free, unencapsulated drug, **DMSO** represents a DMSO only control. **LD50** is the half maximal lethal dose of the particular analog used. LN229 cells were plated at 1,000 cells per well and treatments administered 24 hours afterward. Cells were allowed to grow for 5 days and Cell Titer Glo was implemented to evaluate cell viability.

FIG. 6 is a line graph showing drug release profile under different conditions for nanoparticles formed from a given polymer. **PEG-EB 333** represents nanoparticles formed from poly(ethylene glycol)-ethylene brassylate-co-dioxanone polymer and containing ATRIN 333, **Beta-CD (0.5%)** represents nanoparticles incubated in a 0.5% beta-cyclodextrin solution, **ACSF** represents nanoparticles incubated in artificial Cerebrospinal Fluid, **H₂O** represents nanoparticles incubated in water, **PBS** represents nanoparticles incubated in phosphate buffered saline, and **SFM** represents nanoparticles incubated in serum-free media.

FIGS. 7A and 7B are scatter plots showing uptake of **PEG-EB-co-DO** DiD dye loaded particles at various time points compared to PLA-PEG nanoparticles in LN229 cells (**FIG. 7A**) and RG2 cells (**FIG. 7B**). **PEG-EB** represents poly(ethylene glycol)-ethylene brassylate-co-dioxanone polymer, **PLA-PEG** represents poly (lactic acid)-poly(ethylene glycol) (such as poly (lactic acid)-5000 Da-poly(ethylene glycol)-10000 Da).

FIGS. 8A, 8B, and 8C are images showing retention of PEG-EB-co-DO DiD dye loaded particles in rat brains after intracranial delivery (such as intracranial convection enhanced delivery), three hours (**FIG. 8A**), 24 hours (**FIG. 8B**), and five days (**FIG. 8C**) post-delivery. **PEG-EB-co-DO** represents poly(ethylene glycol)-ethylene brassylate-co-dioxanone polymer.

FIGS. 9A and 9B are point graphs showing percent conversion of ethylene brassylate (EB) and dioxanone (DO) versus time for the reaction at 80°C (calculated using ¹H NMR) (**FIG. 9A**), and weight-average molecular

weight and PDI versus time for the copolymerization reaction (determine in DCM by GPC against polystyrene standards) (**FIG. 9B**).

FIGs. 10A, 10B, and 10C are line graphs showing cumulative *in vitro* DEX release from 1 cm poly(EB-co-DO) implants of 37k, 20% DO, and 28-40% drug loading (**FIG. 10A**); varying drug loading from 28-40% for implants of 40k and 0% DO (**FIG. 10B**); and varying DO content from 0-40% for implants of 37-45k and 28% drug loading (**FIG. 10C**). (n=3 for Day 0-120, n=2 for Day 120+).

FIGs. 11A-11D are line graphs (**FIGs. 11A and 11B**) and point graphs (**FIGs. 11C and 11D**) effect on M_w with varying DO content (**FIG. 11A**); effect on M_w with drug loading at 28% and varying DO content from 0 to 40% (**FIG. 11B**); effect on M_w of DEX loading on 20% EB-co-DO polymer (**FIG. 11C**); and effect on M_w of DEX loading on EB polymer (**FIG. 11D**).

FIGs. 12A-12F are line graphs (**FIGs. 12A, 12B, and 12D-12F**) and chemical structures (**FIG. 12C**) showing cumulative release of implants with 28% LNG loading (**FIG. 12A**); cumulative release of implants with 28% DTG loading (**FIG. 12B**); chemical structures of DEX, LNG, and DTG with corresponding log P values (**FIG. 12C**); daily release of LNG implants (**FIG. 12D**); daily release of DTG implants (**FIG. 12E**); and cumulative release of DEX, DTG, and LNG implants (**FIG. 12F**).

FIGs. 13A-13D are column graphs showing flexural modulus of unloaded implants; ANOVA, $F(4,21) = 26.10$, $P < 0.0001$ (**FIG. 13A**); maximum flexural force before fracture of unloaded implants; ANOVA, $F(4,21) = 22.47$, $P < 0.0001$ (**FIG. 13B**); flexural modulus of 28% DEX implants; ANOVA, $F(4,20) = 12.95$, $P < 0.0001$ (**FIG. 13C**); and maximum flexural force before fracture of 28% DEX implants; ANOVA, $F(4,20) = 49.65$, $P < 0.0001$ (**FIG. 13D**).

FIG. 14 shows scanning electron microscopy (SEM) images of poly(EB-co-DO) unloaded implants with varying DO content at 5k magnification.

FIG. 15 shows SEM images representing cross-sections of DEX-loaded poly(EB-co-DO) implants. SEM images of poly(EB-co-DO) with 28% drug loading and 0%, 7%, 20% and 40% DO over a period of four

months at 5k magnification. The delineated box (last column, second and third rows) emphasizes a particular image taken at different magnification (Month 2: 40% - 10k magnification, Month 4: 40% - 2k magnification).

FIGs. 16A and 16B are point graphs and an array showing encapsulation thickness for average of 3 mice with implants at two to eight months (**FIG. 16A**) and GPC characterization of the implant at the specified time (in months) (**FIG. 16B**).

FIGs. 17A-17C are a line graph (**FIG. 17A**) and point graphs (**FIGs. 17B and 17C**) showing a lot of percentage loss of mass versus change in temperature using thermogravimetric analysis (**FIG. 17A**); melting temperature as a function of DO content in EB-co-DO (**FIG. 17B**); and density vs DO content of EB-co-DO polymers (**FIG. 17C**). In **FIG. 17C**, the data point at about (0,1.16) refers to a polymer possessing a weight-average molecular weight of 52 kDa, and the remaining dots refer to polymers with weight-average molecular weights of about 40 kDa.

FIGs. 18A-18C are line graphs showing daily *in vitro* DEX release from 1cm poly(EB-co-DO) implants (n=3 for Day 0-120, n=2 for Day 120+). Varying drug loading from 28%-40% for implants of 37k M_w and 20% DO (**FIG. 18A**); varying drug loading from 28%-40% for implants of 40k M_w and 0% DO (**FIG. 18B**); and varying DO content from 0%-40% for implants of 37-45k M_w and 28% drug loading (**FIG. 18C**).

FIGs. 19A-19D are column graphs showing the compressive modulus of unloaded implants; ANOVA, $F(4,20) = 50.89$, $p < 0.0001$ (**FIG. 19A**); maximum compressive force before fracture of unloaded implants; ANOVA, $F(4,20) = 59.00$, $p < 0.0001$ (**FIG. 19B**); compressive modulus of implants with varying DO contents and 28% DEX, organized by varying DO content; ANOVA, $F(4,20) = 18.59$, $p < 0.0001$ (**FIG. 19C**); maximum compressive force before fracture of implants with varying DO contents and 28% DEX, organized by varying DO content; ANOVA, $F(4,20) = 27.56$, $p < 0.0001$ (**FIG. 19D**).

FIG. 20 shows SEM images of 20% DO implants with 28%, 35%, and 40% DEX loading over a period of four months at 5k magnification. The box delineated column one, last row, emphasizes a particular image taken at 2k magnification.

FIG. 21 shows SEM images of 0% DO implants with 28%, 35%, and 40% DEX loading over a period of four months at 5k magnification.

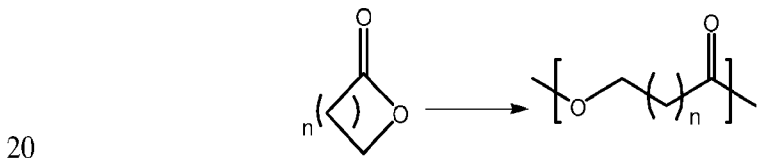
DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

“Hydrophilic,” as used herein, refers to the property of having affinity for water. For example, hydrophilic polymers (or hydrophilic polymer segments) are polymers (or polymer segments) which are primarily soluble in aqueous solutions and/or have a tendency to absorb water. In general, the more hydrophilic a polymer is, the more that polymer tends to dissolve in, mix with, or be wetted by water.

“Hydrophobic,” as used herein, refers to the property of lacking affinity for, or even repelling water. For example, the more hydrophobic a polymer (or polymer segment), the more that polymer (or polymer segment) tends to not dissolve in, not mix with, or not be wetted by water.

The terms “lactone” and “lactone unit” are used to describe a chemical compound that includes a cyclic ester, or the open chain chemical structure that results from the cleavage of the ester bond in the cyclic ester. For example, lactone is used to describe the cyclic ester shown below, and the corresponding lactone-derived open chain structure:



n being an integer. The open chain structure is formed via methods known in the art, including but not limited to, solvolysis, such as hydrolysis, and enzymatic cleavage.

Nanoparticles are particles (nanospheres and nanocapsules) with diameters between 1 nm and less than 1 micron. A nanoparticle may be spherical or nonspherical and may have a regular or irregular shape. Nanoparticles can have an average diameter from about 50 nm to 150 nm. The term "diameter" is used herein to refer to either of the physical diameter or the hydrodynamic diameter. The diameter of an essentially spherical particle may refer to the physical or hydrodynamic diameter. The diameter of a non-spherical particle may refer preferentially to the hydrodynamic

diameter. The diameter of a non-spherical particle may refer to the largest linear distance between two points on the surface of the particle. When referring to multiple particles, the diameter of the particles typically refers to the average diameter of the particles. Particle diameter can be measured
5 using a variety of techniques in the art including, but not limited to, dynamic light scattering.

It is to be understood that the disclosed compounds, compositions, and methods are not limited to specific synthetic methods, specific analytical techniques, or to particular reagents unless otherwise specified, and, as such,
10 may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular forms and embodiments only and is not intended to be limiting.

“Substituted,” as used herein, refers to all permissible substituents of the compounds or functional groups described herein. In the broadest sense,
15 the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, but are not limited to, halogens, hydroxyl groups, or any other organic groupings containing any number of carbon atoms, preferably 1-14 carbon atoms, and
20 optionally include one or more heteroatoms such as oxygen, sulfur, or nitrogen grouping in linear, branched, or cyclic structural formats.

Representative substituents include a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted
25 phenyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, a substituted or unsubstituted aralkyl, a halogen, a hydroxyl, an alkoxy, a phenoxy, an aroxy, a silyl, a thiol, an alkylthio, a substituted alkylthio, a phenylthio, an arylthio, a cyano, an
30 isocyano, a nitro, a substituted or unsubstituted carbonyl, a carboxyl, an amino, an amido, an oxo, a sulfinyl, a sulfonyl, a sulfonic acid, a phosphonium, a phosphanyl, a phosphoryl, a phosphonyl, an amino acid. Such a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted

heterocyclyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, a substituted or unsubstituted aralkyl, a halogen, a hydroxyl, an alkoxy, a phenoxy, an aroxy, a silyl, a thiol, an alkylthio, a substituted alkylthio, a phenylthio, an arylthio, a cyano, an isocyano, a nitro, a substituted or unsubstituted carbonyl, a carboxyl, an amino, an amido, an oxo, a sulfinyl, a sulfonyl, a sulfonic acid, a phosphonium, a phosphanyl, a phosphoryl, a phosphoryl, and an amino acid can be further substituted.

10 Heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. It is understood that “substitution” or “substituted” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the
15 substituent, and that the substitution results in a stable compound, *i.e.*, a compound that does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

“Alkyl,” as used herein, refers to the radical of saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl, and
20 cycloalkyl (alicyclic). In some forms, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C₁-C₃₀ for straight chains, C₃-C₃₀ for branched chains), 20 or fewer, 15 or fewer, or 10 or fewer. Alkyl includes methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *t*-butyl, pentyl, hexyl, heptyl, octyl, decyl, tetradecyl, hexadecyl, eicosyl, tetracosyl
25 and the like. Likewise, a cycloalkyl is a non-aromatic carbon-based ring composed of at least three carbon atoms, such as a nonaromatic monocyclic or nonaromatic polycyclic ring containing 3-30 carbon atoms, 3-20 carbon atoms, or 3-10 carbon atoms in their ring structure, and have 5, 6 or 7 carbons in the ring structure. Cycloalkyls containing a polycyclic ring system
30 can have two or more non-aromatic rings in which two or more carbons are common to two adjoining rings (*i.e.*, “fused cycloalkyl rings”). Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctanyl, etc.

"Substituted alkyl" refers to alkyl moieties having one or more substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can be any substituents described above, e.g., halogen (such as fluorine, chlorine, bromine, or iodine), hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), aryl, alkoxyl, aralkyl, phosphonium, phosphanyl, phosphonyl, phosphoryl, phosphate, phosphonate, a phosphinate, amino, amido, amidine, imine, cyano, nitro, azido, oxo, sulfhydryl, thiol, alkylthio, silyl, sulfinyl, sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, heterocyclyl, an aromatic or heteroaromatic moiety. -NRR', wherein R and R' are independently hydrogen, alkyl, or aryl, and wherein the nitrogen atom is optionally quaternized; -SR, wherein R is a phosphonyl, a sulfinyl, a silyl a hydrogen, an alkyl, or an aryl; -CN; -NO₂; -COOH; carboxylate; -COR, -COOR, or -CON(R)₂, wherein R is hydrogen, alkyl, or aryl; imino, silyl, ether, haloalkyl (such as -CF₃, -CH₂-CF₃, -CCl₃); -CN; -NCOCOCH₂CH₂; -NCOCOCHCH; and -NCS; and combinations thereof.

It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include halogen, hydroxy, nitro, thiols, amino, aralkyl, azido, imino, amido, phosphonium, phosphanyl, phosphoryl (including phosphonate and phosphinate), oxo, sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), haloalkyls, -CN and the like. Cycloalkyls can be substituted in the same manner.

Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group, as defined above, but having from one to ten carbons, more preferably from one to six carbon atoms in its backbone structure. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths.

"Heteroalkyl," as used herein, refers to straight or branched chain, or cyclic carbon-containing alkyl radicals, or combinations thereof, containing at least one heteroatom on the carbon backbone. Suitable heteroatoms

include, but are not limited to, O, N, Si, P and S, wherein the nitrogen, phosphorous and sulfur atoms are optionally oxidized, and the nitrogen heteroatom is optionally quaternized. For example, the term “heterocycloalkyl group” is a cycloalkyl group as defined above where at least one of the carbon atoms of the ring is substituted with a heteroatom such as, but not limited to, nitrogen, oxygen, sulphur, or phosphorus.

The term “alkenyl” as used herein is a hydrocarbon group of from 2 to 24 carbon atoms and structural formula containing at least one carbon-carbon double bond. Alkenyl groups include straight-chain alkenyl groups, branched-chain alkenyl, and cycloalkenyl. A cycloalkenyl is a non-aromatic carbon-based ring composed of at least three carbon atoms and at least one carbon-carbon double bond, such as a nonaromatic monocyclic or nonaromatic polycyclic ring containing 3-30 carbon atoms and at least one carbon-carbon double bond, 3-20 carbon atoms and at least one carbon-carbon double bond, or 3-10 carbon atoms and at least one carbon-carbon double bond in their ring structure, and have 5, 6 or 7 carbons and at least one carbon-carbon double bond in the ring structure.

Cycloalkenyls containing a polycyclic ring system can have two or more non-aromatic rings in which two or more carbons are common to two adjoining rings (i.e., “fused cycloalkenyl rings”) and contain at least one carbon-carbon double bond. Asymmetric structures such as (AB)C=C(C'D) are intended to include both the *E* and *Z* isomers. This may be presumed in structural formulae herein wherein an asymmetric alkene is present, or it may be explicitly indicated by the bond symbol C. The term “alkenyl” as used throughout the specification, examples, and claims is intended to include both “unsubstituted alkenyls” and “substituted alkenyls,” the latter of which refers to alkenyl moieties having one or more substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. The term “alkenyl” also includes “heteroalkenyl.”

The term “substituted alkenyl” refers to alkenyl moieties having one or more substituents replacing one or more hydrogen atoms on one or more carbons of the hydrocarbon backbone. Such substituents can be any substituents described above, e.g., halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl,

formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphonium, phosphanyl, phosphoryl, phosphate, phosphonate, phosphinate, amino (e.g. quarternized amino), amido, amidine, imine, cyano, nitro, azido, oxo, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, polyaryl, polyheteroaryl, and combinations thereof.

“Heteroalkenyl,” as used herein, refers to straight or branched chain, or cyclic carbon-containing alkenyl radicals, or combinations thereof, containing at least one heteroatom. Suitable heteroatoms include, but are not limited to, O, N, Si, P and S, wherein the nitrogen, phosphorous and sulfur atoms are optionally oxidized, and the nitrogen heteroatom is optionally quaternized. For example, the term “heterocycloalkenyl group” is a cycloalkenyl group where at least one of the carbon atoms of the ring is substituted with a heteroatom such as, but not limited to, nitrogen, oxygen, sulphur, or phosphorus.

The term “alkynyl group” as used herein is a hydrocarbon group of 2 to 24 carbon atoms and a structural formula containing at least one carbon-carbon triple bond. Alkynyl groups include straight-chain alkynyl groups, branched-chain alkynyl, and cycloalkynyl. A cycloalkynyl is a non-aromatic carbon-based ring composed of at least three carbon atoms and at least one carbon-carbon triple bond, such as a nonaromatic monocyclic or nonaromatic polycyclic ring containing 3-30 carbon atoms and at least one carbon-carbon triple bond, 3-20 carbon atoms and at least one carbon-carbon triple bond, or 3-10 carbon atoms and at least one carbon-carbon triple bond in their ring structure, and have 5, 6 or 7 carbons and at least one carbon-carbon triple bond in the ring structure. Cycloalkynyls containing a polycyclic ring system can have two or more non-aromatic rings in which two or more carbons are common to two adjoining rings (i.e., “fused cycloalkynyl rings”) and contain at least one carbon-carbon triple bond. Asymmetric structures such as $(AB)C\equiv C(C'D)$ are intended to include both the *E* and *Z* isomers. This may be presumed in structural formulae herein wherein an asymmetric alkyne is present, or it may be explicitly indicated by the bond symbol C. The term “alkynyl” as used throughout the

specification, examples, and claims is intended to include both "unsubstituted alkynyls" and "substituted alkynyls," the latter of which refers to alkynyl moieties having one or more substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. The term "alkynyl" also
5 includes "heteroalkynyl."

The term "substituted alkynyl" refers to alkynyl moieties having one or more substituents replacing one or more hydrogen atoms on one or more carbons of the hydrocarbon backbone. Such substituents can be any substituents described above, e.g., halogen, azide, alkyl, aralkyl, alkenyl,
10 alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxy, carbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphonium, phosphanyl, phosphoryl, phosphate, phosphonate, phosphinate, amino (e.g. quaternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio,
15 sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, polyaryl, polyheteroaryl, and combinations thereof.

"Heteroalkynyl," as used herein, refers to straight or branched chain, or cyclic carbon-containing alkynyl radicals, or combinations thereof,
20 containing at least one heteroatom. Suitable heteroatoms include, but are not limited to, O, N, Si, P and S, wherein the nitrogen, phosphorous and sulfur atoms are optionally oxidized, and the nitrogen heteroatom is optionally quaternized. For example, the term "heterocycloalkynyl group" is a cycloalkynyl group where at least one of the carbon atoms of the ring is
25 substituted with a heteroatom such as, but not limited to, nitrogen, oxygen, sulphur, or phosphorus.

"Aryl," as used herein, refers to C₅-C₂₆-membered aromatic or fused aromatic ring systems. Examples of aromatic groups are benzene, naphthalene, anthracene, phenanthrene, chrysene, pyrene, corannulene,
30 coronene, etc.

The term "substituted aryl" refers to an aryl group, wherein one or more hydrogen atoms on one or more aromatic rings are substituted with one or more substituents including, but not limited to, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, carbonyl (such as a

ketone, aldehyde, carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxyl, phosphoryl, phosphate, phosphonate, phosphinate, amino (or quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, 5 imino, alkylthio, sulfate, sulfonate, sulfamoyl, sulfoxide, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl (such as CF₃, -CH₂-CF₃, -CCl₃), -CN, aryl, heteroaryl, and combinations thereof.

“Heterocycle” and “heterocyclyl” are used interchangeably, and refer to a cyclic radical attached via a ring carbon or nitrogen atom of a 10 non-aromatic monocyclic or polycyclic ring containing 3-30 ring atoms, 3-20 ring atoms, 3-10 ring atoms, or 5-6 ring atoms, where each ring contains carbon and one to four heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(Y) wherein Y is absent or is H, O, C₁-C₁₀ alkyl, phenyl or benzyl, and optionally containing 1-3 double bonds 15 and optionally substituted with one or more substituents. Heterocyclyl are distinguished from heteroaryl by definition. Heterocycles can be a heterocycloalkyl, a heterocycloalkenyl, a heterocycloalkynyl, etc, such as piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, dihydrofuro[2,3-*b*]tetrahydrofuran, morpholinyl, piperazinyl, piperidinyl, 20 piperidonyl, 4-piperidonyl, piperonyl, pyranyl, 2H-pyrrolyl, 4H-quinolizinyl, quinuclidinyl, tetrahydrofuranyl, 6H-1,2,5-thiadiazinyl. Heterocyclic groups can optionally be substituted with one or more substituents as defined above for alkyl and aryl.

The term “heteroaryl” refers to C₅-C₂₆-membered aromatic or fused 25 aromatic ring systems, in which one or more carbon atoms on one or more aromatic ring structures have been substituted with a heteroatom. Suitable heteroatoms include, but are not limited to, oxygen, sulfur, and nitrogen. Examples of heteroaryl groups pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyridazine and 30 pyrimidine, and the like. Examples of heteroaryl rings include, but are not limited to, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazoliny, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazoliny, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl,

decahydroquinoliny, 2H,6H-1,5,2-dithiaziny, furanyl, furazanyl,
 imidazolidiny, imidazoliny, imidazolyl, 1H-indazolyl, indolenyl, indoliny,
 indoliziny, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl,
 isoindazolyl, isoindoliny, isoindolyl, isoquinoliny, isothiazolyl, isoxazolyl,
 5 methylenedioxyphenyl, naphthyridiny, octahydroisoquinoliny, 1,2,3-
 oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,
 oxazolidiny, oxazolyl, oxindolyl, pyrimidiny, phenanthridiny,
 phenanthroliny, phenaziny, phenothiaziny, phenoxathiny, phenoxaziny,
 phthalaziny, pteridiny, puriny, pyraziny, pyrazolidiny, pyrazoliny,
 10 pyrazolyl, pyridaziny, pyridooxazole, pyridoimidazole, pyridothiazole,
 pyridiny, pyridyl, pyrimidiny, pyrrolidiny, pyrroliny, pyrroly,
 quinazoliny, quinoliny, quinoxaliny, tetrahydroisoquinoliny,
 tetrahydroquinoliny, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-
 thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl,
 15 thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl and xanthenyl.
 One or more of the rings can be substituted as defined below for “substituted
 heteroaryl.”

The term “substituted heteroaryl” refers to a heteroaryl group in
 which one or more hydrogen atoms on one or more heteroaromatic rings are
 20 substituted with one or more substituents including, but not limited to,
 halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy,
 carbonyl (such as a ketone, aldehyde, carboxyl, alkoxycarbonyl, formyl, or
 an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or
 a thioformate), alkoxy, phosphoryl, phosphate, phosphonate, phosphinate,
 25 amino (or quarternized amino), amido, amidine, imine, cyano, nitro, azido,
 sulfhydryl, imino, alkylthio, sulfate, sulfonate, sulfamoyl, sulfoxide,
 sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl (such as CF₃, -CH₂-
 CF₃, -CCl₃), -CN, aryl, heteroaryl, and combinations thereof.

The term “polyaryl” refers to a chemical moiety that includes two or
 30 more fused aryl groups. When two or more fused heteroaryl groups are
 involved, the chemical moiety can be referred to as a “polyheteroaryl.”

The term “substituted polyaryl” refers to a polyaryl in which one or more of
 the aryls are substituted, with one or more substituents including, but not
 limited to, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl,

hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxyl, phosphoryl, phosphate, phosphonate, phosphinate, amino (or quarternized amino), amido, amidine, imine, cyano, nitro, azido, 5 sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfoxide, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, and combinations thereof. When a polyheteroaryl is involved, the chemical moiety can be referred to as a “substituted polyheteroaryl.”

The term “cyclic ring” or “cyclic group” refers to a substituted or 10 unsubstituted monocyclic ring or a substituted or unsubstituted polycyclic ring (such as those formed from single or fused ring systems), such as a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted cycloalkynyl, or a substituted or unsubstituted heterocyclyl, that have from three to 30 carbon atoms, as 15 geometric constraints permit. The substituted cycloalkyls, cycloalkenyls, cycloalkynyls, and heterocyclyls are substituted as defined above for the alkyls, alkenyls, alkynyls, and heterocyclyls, respectively.

The term “aralkyl” as used herein is an aryl group or a heteroaryl group having an alkyl, alkynyl, or alkenyl group as defined above attached to 20 the aromatic group, such as an aryl, a heteroaryl, a polyaryl, or a polyheteroaryl. An example of an aralkyl group is a benzyl group.

The terms “alkoxyl” or “alkoxy,” “aroxy” or “aryloxy,” generally describe compounds represented by the formula -OR^v, wherein R^v includes, but is not limited to, a substituted or unsubstituted alkyl, a substituted or 25 unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted heterocycloalkenyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, a substituted or unsubstituted arylalkyl, a 30 substituted or unsubstituted heteroalkyl, a substituted or unsubstituted alkylaryl, a substituted or unsubstituted alkylheteroaryl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted carbonyl, a phosphonium, a phosphanyl, a phosphoryl, a sulfinyl, a silyl, a thiol, an

amido, and an amino. Exemplary alkoxy groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. A “lower alkoxy” group is an alkoxy group containing from one to six carbon atoms. An “ether” is two functional groups covalently linked by an oxygen as defined below. Accordingly, the

5 substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxy, such as can be represented by one of -O-alkyl, -O-alkenyl, -O-alkynyl, -O-aralkyl, -O-aryl, -O-heteroaryl, -O-polyaryl, -O-polyheteroaryl, -O-heterocyclyl, etc.

The term “substituted alkoxy” refers to an alkoxy group having one

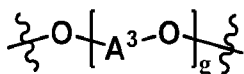
10 or more substituents replacing one or more hydrogen atoms on one or more carbons of the alkoxy backbone. Such substituents can be any substituents described above, e.g., halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate,

15 or a thioformate), alkoxy, phosphonium, phosphanyl, phosphoryl, phosphate, phosphonate, phosphinate, amino (e.g. quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, oxo, sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, and combinations thereof.

20 The term “ether” as used herein is represented by the formula A^2OA^1 , where A^2 and A^1 can be, independently, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted

25 aralkyl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, a phosphonium, a phosphanyl, a phosphoryl, a sulfinyl, a silyl, a thiol, a substituted or unsubstituted carbonyl, an alkoxy, an amido, or an amino, described above.

The term “polyether” as used herein is represented by the formula:



30 where A^3 , A^2 , and A^1 can be, independently, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted heterocyclyl, a substituted or

unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, a phosphonium, a phosphanyl, a substituted or unsubstituted carbonyl, an alkoxy, an amido, or an amino, described above; g

5 can be a positive integer from 1 to 30.

The term “phenoxy” is art recognized and refers to a compound of the formula $-OR^v$ wherein R^v is C_6H_5 (*i.e.*, $-O-C_6H_5$). One of skill in the art recognizes that a phenoxy is a species of the aroxy genus.

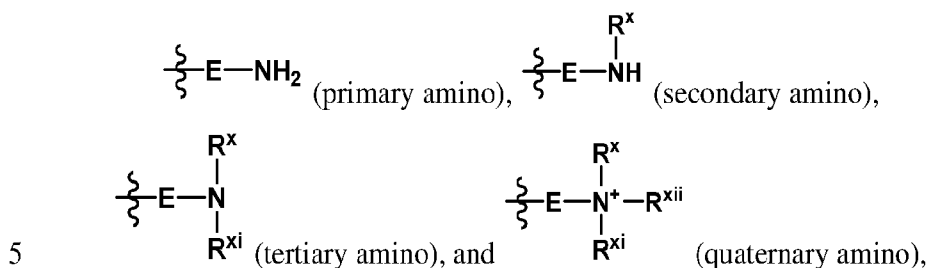
The term “substituted phenoxy” refers to a phenoxy group, as defined
10 above, having one or more substituents replacing one or more hydrogen atoms on one or more carbons of the phenyl ring. Such substituents include, but are not limited to, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate,
15 or a thioformate), alkoxy, phosphonium, phosphanyl, phosphanyl, phosphoryl, phosphate, phosphonate, phosphinate, amino (e.g. quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, $-CN$, aryl, heteroaryl, and combinations thereof.

20 The terms “aroxy” and “aryloxy,” as used interchangeably herein, are represented by $-O$ -aryl or $-O$ -heteroaryl, wherein aryl and heteroaryl are as defined herein.

The terms “substituted aroxy” and “substituted aryloxy,” as used interchangeably herein, represent $-O$ -aryl or $-O$ -heteroaryl, having one or
25 more substituents replacing one or more hydrogen atoms on one or more ring atoms of the aryl and heteroaryl, as defined herein. Such substituents can be any substituents described above, e.g., halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a
30 thioacetate, or a thioformate), alkoxy, phosphonium, phosphanyl, phosphanyl, phosphoryl, phosphate, phosphonate, phosphinate, amino (e.g. quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, heterocyclyl,

alkylaryl, haloalkyl, -CN, aryl, heteroaryl, polyaryl, polyheteroaryl, and combinations thereof.

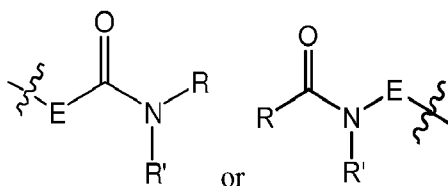
The term "amino" as used herein includes the group



wherein, E is absent, or E is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, substituted or unsubstituted heterocyclyl, wherein independently of E, R^{x} , R^{xi} , and R^{xii} each independently represent a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted carbonyl, substituted or unsubstituted carboxyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted aralkyl (e.g. a substituted or unsubstituted alkylaryl, a substituted or unsubstituted arylalkyl), a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, a substituted or unsubstituted heterocyclyl, a hydroxyl, an alkoxy, a phosphonium, a phosphanyl, a phosphonyl, a sulfinyl, a silyl, a thiol, an amido, an amino, or $-(\text{CH}_2)_m\text{---R}^{\text{'''}}$; $\text{R}^{\text{'''}}$ represents a hydroxyl group, a substituted or unsubstituted carbonyl group, a substituted or unsubstituted aryl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, an alkoxy, a phosphonium, a phosphanyl, an amido, or an amino; and m is zero or an integer ranging from 1 to 8. The term "quaternary amino" also includes the groups where the nitrogen, R^{x} , R^{xi} , and R^{xii} with the N^+ to which they are attached complete a heterocyclyl or heteroaryl having

from 3 to 14 atoms in the ring structure. It is understood by those of ordinary skill in the art, that the E groups listed above are divalent (e.g., methylene, ethane-1,2-diyl, ethene-1,2-diyl, 1,4-phenylene, cyclohexane-1,2-diyl).

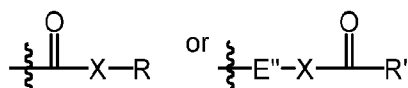
- 5 The terms “amide” or “amido” are used interchangeably, refer to both “unsubstituted amido” and “substituted amido” and are represented by the general formula:



- Wherein, E is absent, or E is a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, or a substituted or unsubstituted heterocyclyl, wherein independently of E, R and R' each
- 15 independently represent a hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted carbonyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted aralkyl (e.g. a substituted or unsubstituted alkylaryl, a substituted or unsubstituted arylalkyl), a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, a substituted or unsubstituted heterocyclyl, a hydroxyl, an alkoxy, a phosphonium, a phosphanyl, a phosphonyl, a sulfinyl, a silyl, a thiol, an amido, an amino, or $-(CH_2)_m-R'''$, or R and R' taken together with the N
- 20 atom to which they are attached complete a heterocycle having from 3 to 14 atoms in the ring structure; R''' represents a hydroxyl group, a substituted or unsubstituted carbonyl group, a substituted or unsubstituted aryl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, an
- 30

alkoxy, a phosphonium, a phosphanyl, an amido, or an amino; and m is zero or an integer ranging from 1 to 8. In some forms, when E is oxygen, a carbamate is formed. It is understood by those of ordinary skill in the art, that the E groups listed above are divalent (e.g., methylene, ethane-1,2-diyl, ethene-1,2-diyl, 1,4-phenylene, cyclohexane-1,2-diyl).

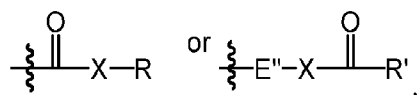
“Carbonyl,” as used herein, is art-recognized and includes such moieties as can be represented by the general formula:



wherein X is a bond, or represents an oxygen or a sulfur, and R represents a hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted heterocyclyl, unsubstituted aralkyl (e.g. unsubstituted alkylaryl, unsubstituted arylalkyl), unsubstituted aryl, unsubstituted heteroaryl, unsubstituted polyaryl, unsubstituted polyheteroaryl, unsubstituted heterocyclyl, a hydroxyl, an alkoxy, a phosphonium, a phosphanyl, an amido, an amino, or $-(\text{CH}_2)_m\text{---R}''$, or a pharmaceutical acceptable salt; E'' is absent, or E'' is unsubstituted alkylene, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aralkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted polyaryl, unsubstituted polyheteroaryl, unsubstituted heterocyclyl; R' represents a hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted heterocyclyl, unsubstituted aralkyl (e.g. unsubstituted alkylaryl, unsubstituted arylalkyl), unsubstituted aryl, unsubstituted heteroaryl, unsubstituted polyaryl, unsubstituted polyheteroaryl, unsubstituted heterocyclyl, a hydroxyl, an alkoxy, a phosphonium, a phosphanyl, an amido, an amino, or $-(\text{CH}_2)_m\text{---R}''$; R'' represents a hydroxyl group, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted cycloalkenyl, unsubstituted heterocyclyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted polyaryl, unsubstituted polyheteroaryl, an alkoxy, a phosphonium, a phosphanyl, an amido, or an amino; and m is zero or an integer ranging from 1 to 8. It is understood by those of ordinary skill in the art, that the E'' groups listed above are divalent (e.g., methylene, ethane-1,2-diyl, ethene-1,2-diyl, 1,4-phenylene, cyclohexane-1,2-diyl). Where X is oxygen and R is defined as above, the moiety is also referred to as a carboxyl

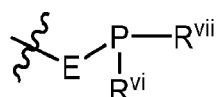
group. When X is oxygen and R is hydrogen, the formula represents a “carboxylic acid.” Where X is oxygen and R’ is hydrogen, the formula represents a “formate.” Where X is oxygen and R or R’ is not hydrogen, the formula represents an “ester.” In general, where the oxygen atom of the
 5 above formula is replaced by a sulfur atom, the formula represents a “thiocarbonyl” group. Where X is sulfur and R or R’ is not hydrogen, the formula represents a “thioester.” Where X is sulfur and R is hydrogen, the formula represents a “thiocarboxylic acid.” Where X is sulfur and R’ is hydrogen, the formula represents a “thioformate.” Where X is a bond and R
 10 is not hydrogen, the above formula represents a “ketone.” Where X is a bond and R is hydrogen, the above formula represents an “aldehyde.”

The term “substituted carbonyl” refers to a carbonyl, as defined above, wherein one or more hydrogen atoms in R or R’



15 are independently substituted. Such substituents can be any substituents described above, e.g., halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxyl, phosphonium, phosphanyl, phosphoryl,
 20 phosphate, phosphonate, phosphinate, amino (e.g. quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, and combinations thereof. It is understood by those of ordinary skill in the art, that the E and E’’ groups listed above are
 25 divalent (e.g., methylene, ethane-1,2-diyl, ethene-1,2-diyl, 1,4-phenylene, cyclohexane-1,2-diyl).

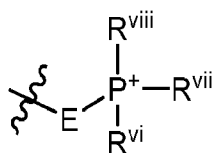
The term “phosphanyl” is represented by the formula



wherein, E is absent, or E is a substituted or unsubstituted alkyl, a
 30 substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted cycloalkyl,

a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, a substituted or unsubstituted heterocyclyl, wherein independently of E, R^{vi} and R^{vii} each independently represent a hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted carbonyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted aralkyl (e.g., a substituted or unsubstituted alkylaryl, a substituted or unsubstituted arylalkyl, etc.), a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, a substituted or unsubstituted heterocyclyl, a hydroxyl, an alkoxy, a phosphonium, a phosphanyl, a phosphonyl, a sulfinyl, a silyl, a thiol, an amido, an amino, or $-(CH_2)_m-R'''$, or R^{vi} and R^{vii} taken together with the P atom to which they are attached complete a heterocycle having from 3 to 14 atoms in the ring structure; R''' represents a hydroxyl group, a substituted or unsubstituted carbonyl group, a substituted or unsubstituted aryl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, an alkoxy, a phosphonium, a phosphanyl, an amido, or an amino; and m is zero or an integer ranging from 1 to 8. Such substituents can be any substituents described above, e.g., halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphoryl, phosphate, phosphonate, phosphinate, amino (e.g. quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, polyaryl, polyheteroaryl, and combinations thereof. It is understood by those of ordinary skill in the art, that the E groups listed above are divalent (e.g., methylene, ethane-1,2-diyl, ethene-1,2-diyl, 1,4-phenylene, cyclohexane-1,2-diyl).

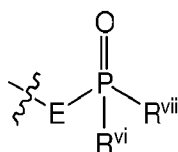
The term “phosphonium” is represented by the formula



wherein, E is absent, or E is a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, a substituted or unsubstituted heterocyclyl, wherein independently of E, R^{vi}, R^{vii}, and R^{viii} each independently represent a hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted carbonyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted aralkyl (e.g. a substituted or unsubstituted alkylaryl, a substituted or unsubstituted arylalkyl, etc.), a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, a substituted or unsubstituted heterocyclyl, a hydroxyl, an alkoxy, a phosphonium, a phosphanyl, a phosphonyl, a sulfinyl, a silyl, a thiol, an amido, an amino, or $-(\text{CH}_2)_m\text{-R}^{\text{'''}}$, or R^{vi}, R^{vii}, and R^{viii} taken together with the P⁺ atom to which they are attached complete a heterocycle having from 3 to 14 atoms in the ring structure; R^{'''} represents a hydroxyl group, a substituted or unsubstituted carbonyl group, a substituted or unsubstituted aryl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, an alkoxy, a phosphonium, a phosphanyl, an amido, or an amino; and m is zero or an integer ranging from 1 to 8. Such substituents can be any substituents described above, e.g., halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate,

or a thioformate), alkoxy, phosphoryl, phosphate, phosphonate, phosphinate, amino (e.g. quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, polyaryl, polyheteroaryl, and combinations thereof. It is understood by those of ordinary skill in the art, that the E groups listed above are divalent (e.g., methylene, ethane-1,2-diyl, ethene-1,2-diyl, 1,4-phenylene, cyclohexane-1,2-diyl).

The term “phosphonyl” is represented by the formula



10

wherein E is absent, or E is unsubstituted alkylene, unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aralkyl (e.g., a substituted or unsubstituted alkylaryl, a substituted or unsubstituted arylalkyl, etc.), a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, a substituted or unsubstituted heterocyclyl, oxygen, alkoxy, aroxy, or substituted alkoxy or substituted aroxy, wherein, independently of E, R^{vi} and R^{vii} are independently a hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted carbonyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted aralkyl (e.g. a substituted or unsubstituted alkylaryl, a substituted or unsubstituted arylalkyl, etc.), a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, a substituted or unsubstituted heterocyclyl, a hydroxyl, an alkoxy, a phosphonium, a phosphanyl, a phosphonyl, a sulfinyl, a silyl, a thiol, an amido, an amino, or $-(CH_2)_m-R'''$, or R^{vi} and R^{vii} taken together with the P atom to which they are attached complete a heterocycle having from 3 to 14 atoms in the ring structure; R''' represents a hydroxyl group, a substituted or unsubstituted carbonyl group, a substituted or

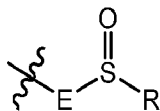
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unsubstituted aryl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, an alkoxy, a phosphonium, a phosphanyl, an amido, or an amino; and m is zero or an integer ranging from 1 to 8. Such substituents can be any substituents described above, e.g., halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphoryl, phosphate, phosphonate, phosphinate, amino (e.g. quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, polyaryl, polyheteroaryl, and combinations thereof. It is understood by those of ordinary skill in the art, that the E groups listed above are divalent (e.g., methylene, ethane-1,2-diyl, ethene-1,2-diyl, 1,4-phenylene, cyclohexane-1,2-diyl).

The term “phosphoryl” defines a phosphonyl in which E is absent, oxygen, alkoxy, aroxy, substituted alkoxy or substituted aroxy, as defined above, and independently of E, R^{vi} and R^{vii} are independently hydroxyl, alkoxy, aroxy, substituted alkoxy or substituted aroxy, as defined above. When E is oxygen, the phosphoryl cannot be attached to another chemical species, such as to form an oxygen-oxygen bond, or other unstable bonds, as understood by one of ordinary skill in the art. When E, R^{vi} and R^{vii} are substituted, the substituents include, but are not limited to, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphoryl, phosphate, phosphonate, phosphinate, amino (e.g. quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, polyaryl, polyheteroaryl, and combinations thereof. It is understood by those of ordinary skill in the art, that the E

groups listed above are divalent (e.g., methylene, ethane-1,2-diyl, ethene-1,2-diyl, 1,4-phenylene, cyclohexane-1,2-diyl).

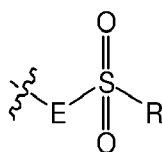
The term “sulfinyl” is represented by the formula



- 5 wherein E is absent, or E is a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aralkyl (e.g., a substituted or unsubstituted alkylaryl, a substituted or unsubstituted arylalkyl, etc.), a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or
- 10 unsubstituted heterocyclyl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, wherein independently of E, R represents a hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted carbonyl, a substituted or unsubstituted heterocyclyl, a
- 15 substituted or unsubstituted aralkyl (e.g. a substituted or unsubstituted alkylaryl, a substituted or unsubstituted arylalkyl), a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, a substituted or unsubstituted heterocyclyl, a hydroxyl, an alkoxy, a
- 20 phosphonium, a phosphanyl, a phosphonyl, a silyl, a thiol, an amido, an amino, or $-(CH_2)_m-R'''$, or E and R taken together with the S atom to which they are attached complete a heterocycle having from 3 to 14 atoms in the ring structure; R''' represents a hydroxyl group, a substituted or unsubstituted carbonyl group, a substituted or unsubstituted aryl, a substituted or
- 25 unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, an alkoxy, a phosphonium, a phosphanyl, an amido, or an amino; and m is zero or an
- 30 integer ranging from 1 to 8. Such substituents can be any substituents described above, e.g., halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl,

or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxyl, phosphoryl, phosphate, phosphonate, phosphinate, amino (e.g. quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, polyaryl, polyheteroaryl, and combinations thereof. It is understood by those of ordinary skill in the art, that the E groups listed above are divalent (e.g., methylene, ethane-1,2-diyl, ethene-1,2-diyl, 1,4-phenylene, cyclohexane-1,2-diyl).

The term “sulfonyl” is represented by the formula



wherein E is absent, or E is a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aralkyl (e.g., a substituted or unsubstituted alkylaryl, a substituted or unsubstituted arylalkyl, etc.), a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, wherein independently of E, R represents a hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted carbonyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted aralkyl (e.g. a substituted or unsubstituted alkylaryl, a substituted or unsubstituted arylalkyl), a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, a substituted or unsubstituted heterocyclyl, a hydroxyl, an alkoxy, a phosphonium, a phosphanyl, an amido, an amino, or $-(CH_2)_m-R'''$, or E and R taken together with the S atom to which they are attached complete a heterocycle having from 3 to 14 atoms in the ring structure; R''' represents a hydroxyl group, a substituted or unsubstituted carbonyl group, a substituted or unsubstituted aryl, a substituted or unsubstituted cycloalkyl, a substituted

or unsubstituted cycloalkenyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, an alkoxy, a phosphonium, a phosphanyl, an amido, or an amino; and m is zero or an integer ranging from 1 to 8. Such substituents can be any substituents described above, e.g., halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphoryl, phosphate, phosphonate, phosphinate, amino (e.g. quaternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, polyaryl, polyheteroaryl, and combinations thereof. It is understood by those of ordinary skill in the art, that the E groups listed above are divalent (e.g., methylene, ethane-1,2-diyl, ethene-1,2-diyl, 1,4-phenylene, cyclohexane-1,2-diyl).

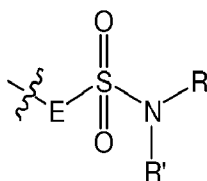
The term “sulfonic acid” refers to a sulfonyl, as defined above, wherein R is hydroxyl, and E is absent, or E is substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkylaryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, or substituted or unsubstituted heteroaryl. Such substituents can be any substituents described above, e.g., halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphoryl, phosphate, phosphonate, phosphinate, amino (e.g. quaternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, polyaryl, polyheteroaryl, and combinations thereof. It is understood by those of ordinary skill in the art, that the E groups listed above are divalent (e.g., methylene, ethane-1,2-diyl, ethene-1,2-diyl, 1,4-phenylene, cyclohexane-1,2-diyl).

The term “sulfate” refers to a sulfonyl, as defined above, wherein E is absent, oxygen, alkoxy, aroxy, substituted alkoxy or substituted aroxy, as defined above, and R is independently hydroxyl, alkoxy, aroxy, substituted alkoxy or substituted aroxy, as defined above. When E is oxygen, the sulfate cannot be attached to another chemical species, such as to form an oxygen-oxygen bond, or other unstable bonds, as understood by one of ordinary skill in the art. Such substituents can be any substituents described above, e.g., halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphoryl, phosphate, phosphonate, phosphinate, amino (e.g. quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, polyaryl, polyheteroaryl, and combinations thereof. It is understood by those of ordinary skill in the art, that the E groups listed above are divalent (e.g., methylene, ethane-1,2-diyl, ethene-1,2-diyl, 1,4-phenylene, cyclohexane-1,2-diyl).

The term “sulfonate” refers to a sulfonyl, as defined above, wherein E is oxygen, alkoxy, aroxy, substituted alkoxy or substituted aroxy, as defined above, and R is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted amino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aralkyl, substituted or unsubstituted alkylaryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, $-(CH_2)_m-R'''$, R''' represents a hydroxy group, substituted or unsubstituted carbonyl group, an aryl, a cycloalkyl ring, a cycloalkenyl ring, a heterocycle, an amido, an amino, or a polycycle; and m is zero or an integer ranging from 1 to 8. When E is oxygen, sulfonate cannot be attached to another chemical species, such as to form an oxygen-oxygen bond, or other unstable bonds, as understood by one of ordinary skill in the art. Such substituents can be any substituents described

above, e.g., halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphoryl, phosphate, phosphonate, phosphinate, amino (e.g. quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, polyaryl, polyheteroaryl, and combinations thereof. It is understood by those of ordinary skill in the art, that the E groups listed above are divalent (e.g., methylene, ethane-1,2-diyl, ethene-1,2-diyl, 1,4-phenylene, cyclohexane-1,2-diyl).

The term “sulfamoyl” refers to a sulfonamide or sulfonamide represented by the formula



wherein E is absent, or E is substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aralkyl (e.g., a substituted or unsubstituted alkylaryl, a substituted or unsubstituted cycloalkyl, etc.), a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, a substituted or unsubstituted heterocyclyl, wherein independently of E, R and R' each independently represent a hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted carbonyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted aralkyl (e.g. a substituted or unsubstituted alkylaryl, a substituted or unsubstituted arylalkyl, etc.), a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, a substituted or unsubstituted heterocyclyl, a hydroxyl, an alkoxy, a phosphonium, a phosphanyl, an amido, an amino, or $-(CH_2)_m-R'''$, or R and R' taken together with the N atom to which they are attached

complete a heterocycle having from 3 to 14 atoms in the ring structure; R''' represents a hydroxyl group, a substituted or unsubstituted carbonyl group, a substituted or unsubstituted aryl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, an alkoxy, a phosphonium, a phosphanyl, an amido, or an amino; and m is zero or an integer ranging from 1 to 8. Such substituents can be any substituents described above, e.g., halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphoryl, phosphate, phosphonate, phosphinate, amino (e.g. quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, polyaryl, polyheteroaryl, and combinations thereof. It is understood by those of ordinary skill in the art, that the E groups listed above are divalent (e.g., methylene, ethane-1,2-diyl, ethene-1,2-diyl, 1,4-phenylene, cyclohexane-1,2-diyl).

The term "silyl group" as used herein is represented by the formula -SiRR'R," where R, R', and R" can be, independently, a hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted aralkyl (e.g. a substituted or unsubstituted alkylaryl, a substituted or unsubstituted arylalkyl, etc.), a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, a substituted or unsubstituted carbonyl, a phosphonium, a phosphanyl, a phosphoryl, a sulfinyl, a thiol, an amido, an amino, an alkoxy, or an oxo, described above. Such substituents can be any substituents described above, e.g., halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphoryl, phosphate, phosphonate,

phosphinate, amino (e.g. quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, polyaryl, polyheteroaryl, and combinations thereof.

- 5 The terms “thiol” are used interchangeably and are represented by –SR, where R can be a hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted
- 10 aralkyl (e.g. a substituted or unsubstituted alkylaryl, a substituted or unsubstituted arylalkyl, etc.), a substituted or unsubstituted polyaryl, a substituted or unsubstituted polyheteroaryl, a substituted or unsubstituted carbonyl, a phosphonium, a phosphanyl, an amido, an amino, an alkoxy, an oxo, a phosphoryl, a sulfinyl, or a silyl, described above. Such substituents
- 15 can be any substituents described above, e.g., halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxy carbonyl, formyl, or an acyl), silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphoryl, phosphate, phosphonate, phosphinate, amino (e.g. quarternized amino), amido, amidine,
- 20 imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, polyaryl, polyheteroaryl, and combinations thereof.

The term “phenylthio” is art recognized, and refers to -S-C₆H₅, *i.e.*, a phenyl group attached to a sulfur atom.

- 25 The term “substituted phenylthio” refers to a phenylthio group, as defined above, having one or more substituents replacing a hydrogen on one or more carbons of the phenyl ring. Such substituents include, but are not limited to, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, carbonyl (such as a carboxyl, alkoxy carbonyl, formyl, or an acyl),
- 30 silyl, ether, ester, thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxy, phosphonium, phosphanyl, phosphoryl, phosphate, phosphonate, phosphinate, amino (e.g. quarternized amino), amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl,

sulfonamido, sulfonyl, heterocyclyl, alkylaryl, haloalkyl, -CN, aryl, heteroaryl, and combinations thereof.

The disclosed compounds and substituent groups, can, independently, possess two or more of the groups listed above. For example, if the
5 compound or substituent group is a straight chain alkyl group, one of the hydrogen atoms of the alkyl group can be substituted with a hydroxyl group, an alkoxy group, etc. Depending upon the groups that are selected, a first group can be incorporated within second group or, alternatively, the first group can be pendant (*i.e.*, attached) to the second group. For example, with
10 the phrase “an alkyl group comprising an ester group,” the ester group can be incorporated within the backbone of the alkyl group. Alternatively, the ester can be attached to the backbone of the alkyl group. The nature of the group(s) that is (are) selected will determine if the first group is embedded or attached to the second group.

15 “oxo” refers to =O.

Use of the term "about" is intended to describe values either above or below the stated value, which the term “about” modifies, to be within a range of approximately +/- 10%. When the term "about" is used before a range of numbers (*i.e.*, about 1-5) or before a series of numbers (*i.e.*, about 1, 2, 3, 4,
20 etc.) it is intended to modify both ends of the range of numbers and/or each of the numbers recited in the entire series, unless specified otherwise.

The compounds and substituents can be substituted with, independently, with the substituents described above in the definition of “substituted.”

25 II. Compositions

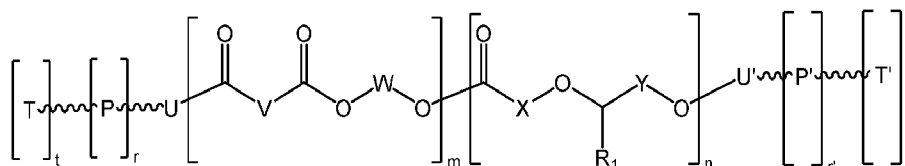
Ethylene brassylate-*co*-dioxanone polymers, particles and implants containing these polymers have been developed. In some forms, the polymers contain a hydrophilic polymer such as poly(ethylene glycol). In some forms, the polymers not only provide improved encapsulation
30 efficiencies in particles containing the polymers, compared to particles containing poly(ethylene glycol)-poly(lactic acid), the particles are also significantly internalized by cells, such as cancer cells (*e.g.*, glioma cells). The particles and implants show remarkable stabilities over several days (such as between 10 and 15 days), as determined by their average sizes and

polydispersity indices over these time frames. The particles and implants can be utilized to deliver therapeutic, diagnostic, and/or prophylactic agents to the brain and other organs of the body. For instance, brain cells retain the particles for at least five days post-delivery, when the observations ended.

5 Lastly, the particles effectively kill cancer cells *in vitro*.

A. Ethylene brassylate-*co*-dioxanone polymers

The ethylene brassylate-*co*-dioxanone polymers have a structure:



10

Formula I

wherein:

m and n are independently integers from 1 to 1500,

r, r', t, t' are independently integers from 0 to 1500,

P and P' comprise a hydrophilic polymer segment,

15 T and T' comprise a targeting moiety,

U and U' are independently absent, -O-, -S-, NRu, -C(O)-, -C(O)O-, or -C(O)NRu-,

R₁ and Ru are independently hydrogen, substituted alkyl,

unsubstituted alkyl, substituted alkenyl, unsubstituted alkenyl, substituted

20 alkynyl, unsubstituted alkynyl, substituted aryl, unsubstituted aryl,

substituted heteroaryl, unsubstituted heteroaryl, substituted polyaryl,

unsubstituted polyaryl, substituted polyheteroaryl, unsubstituted

polyheteroaryl, substituted C₃-C₂₀ cycloalkyl, unsubstituted C₃-C₂₀

cycloalkyl, substituted C₁-C₂₀ heterocyclyl, unsubstituted C₁-C₂₀

25 heterocyclyl, substituted C₃-C₂₀ cycloalkenyl, unsubstituted C₃-C₂₀

cycloalkenyl, substituted C₃-C₂₀ cycloalkynyl, unsubstituted C₃-C₂₀

cycloalkynyl, substituted polyheteroaralkyl, unsubstituted polyheteroaralkyl,

substituted polyaralkyl, unsubstituted polyaralkyl, substituted aralkyl,

unsubstituted aralkyl, hydroxyl, substituted carbonyl, unsubstituted carbonyl,

30 substituted thiocarbonyl, unsubstituted thiocarbonyl, substituted alkoxy,

unsubstituted alkoxy, substituted phosphoryl, unsubstituted phosphoryl,

- substituted phosphate, unsubstituted phosphate, substituted phosphonate, unsubstituted phosphonate, substituted phosphinate, unsubstituted phosphinate, substituted amino, unsubstituted amino, substituted amido, unsubstituted amido, substituted amidine, unsubstituted amidine, substituted imine, unsubstituted imine, cyano, nitro, azido, thiol, substituted alkylthio, unsubstituted alkylthio, substituted sulfate, unsubstituted sulfate, substituted sulfonate, unsubstituted sulfonate, substituted sulfamoyl, unsubstituted sulfamoyl, substituted sulfonamido, unsubstituted sulfonamido, substituted sulfonyl, or unsubstituted sulfonyl,
- 5 V, W, X, and Y are independently substituted alkyl, unsubstituted alkyl, unsubstituted alkylene, substituted alkenyl, unsubstituted alkenyl, substituted alkynyl, unsubstituted alkynyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, substituted polyaryl, unsubstituted polyaryl, substituted polyheteroaryl, unsubstituted polyheteroaryl, substituted C₃-C₂₀ cycloalkyl, unsubstituted C₃-C₂₀ cycloalkyl, substituted C₁-C₂₀ heterocyclyl, unsubstituted C₁-C₂₀ heterocyclyl, substituted C₃-C₂₀ cycloalkenyl, unsubstituted C₃-C₂₀ cycloalkenyl, substituted C₃-C₂₀ cycloalkynyl, unsubstituted C₃-C₂₀ cycloalkynyl, substituted polyheteroaralkyl, unsubstituted polyheteroaralkyl, substituted polyaralkyl, unsubstituted polyaralkyl, substituted aralkyl, unsubstituted aralkyl, or fused combinations thereof, with the proviso that V, W, X, and Y are each at least divalent (such as bonded to at least two non-hydrogen atoms), and
- 10 20

wherein the polymer is not (i) poly(ethylene brassylate-*co*-D,L-lactide); (ii) poly(ethylene brassylate-*co*-hexalactone) or poly(ethylene brassylate-*co*- δ -hexalactone); (iii) poly(ethylene brassylate-*co*- ϵ -caprolactone); or (iv) poly(ethylene brassylate-*co*-squaric acid).

25

In some forms, the polymers are as described above, except that Ru, when present, and R₁ are independently hydrogen, substituted alkyl, unsubstituted alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, substituted polyaryl, unsubstituted polyaryl, substituted polyheteroaryl, unsubstituted polyheteroaryl, substituted C₃-C₂₀ cycloalkyl, or unsubstituted C₃-C₂₀ cycloalkyl.

30

In some forms, the polymers are as described above, except that Ru, when present, and R₁ are independently hydrogen, substituted alkyl, unsubstituted alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, substituted polyaryl, unsubstituted polyaryl, substituted polyheteroaryl, or unsubstituted polyheteroaryl.

In some forms, the polymers are as described above, except that Ru, when present, and R₁ are independently hydrogen, substituted alkyl, or unsubstituted alkyl.

In some forms, the polymers are as described above, except that Ru, when present, and R₁ are hydrogen.

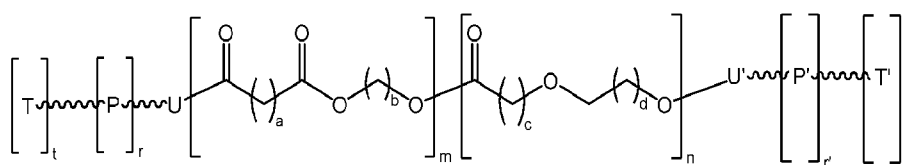
In some forms, the polymers are as described above, except that V, W, X, and Y are independently substituted alkyl, unsubstituted alkyl, unsubstituted alkylene, substituted alkenyl, unsubstituted alkenyl, substituted alkynyl, unsubstituted alkynyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, substituted C₃-C₂₀ cycloalkyl, unsubstituted C₃-C₂₀ cycloalkyl, substituted C₁-C₂₀ heterocyclyl, unsubstituted C₁-C₂₀ heterocyclyl, substituted C₃-C₂₀ cycloalkenyl, unsubstituted C₃-C₂₀ cycloalkenyl, substituted C₃-C₂₀ cycloalkynyl, unsubstituted C₃-C₂₀ cycloalkynyl, or fused combinations thereof, with the proviso that V, W, X, and Y are each at least divalent (such as bonded to at least two non-hydrogen atoms).

In some forms, the polymers are as described above, except that V, W, X, and Y are independently substituted alkyl, unsubstituted alkyl, unsubstituted alkylene, substituted alkenyl, unsubstituted alkenyl, substituted alkynyl, unsubstituted alkynyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, or fused combinations thereof, with the proviso that V, W, X, and Y are each at least divalent (such as bonded to at least two non-hydrogen atoms).

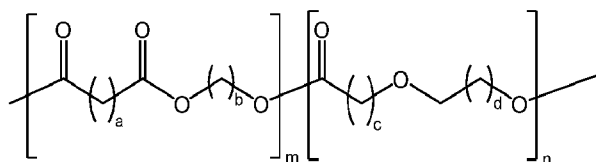
In some forms, the polymers are as described above, except that V, W, X, and Y are independently substituted alkyl, unsubstituted alkyl, unsubstituted alkylene, substituted alkenyl, unsubstituted alkenyl, substituted alkynyl, unsubstituted alkynyl, with the proviso that V, W, X, and Y are each at least divalent (such as bonded to at least two non-hydrogen atoms).

In some forms, the polymers are as described above, except that V, W, X, and Y are independently substituted alkyl, unsubstituted alkyl, unsubstituted alkylene, with the proviso that V, W, X, and Y are each at least divalent (such as bonded to at least two non-hydrogen atoms).

5 In some forms, the polymers are as described above, except that the polymers have a structure:



Formula II



Formula II'

10

wherein:

a, b, c, and d are independently integers from 1 to 20, such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, preferably a is an integer from 1 to 15, 5 to 15, or 10 to 15, such as 11, b is an integer from 1 to 15, 10, or 1 to 5, such as 2, c is an integer from 1 to 10, or 1 to 5, such as 1, and d is an integer from 1 to 10, or 1 to 5, such as 2.

15

i. Hydrophilic polymers

In some forms, the polymers contain a hydrophilic polymer segment, denoted P or P' as described herein. Suitable hydrophilic polymers that can be included in the hydrophilic polymer segment include, but are not limited to, polyalkylene glycols and polyalkylene oxides such as poly(ethylene glycol) (PEG); polysaccharides such as celluloses, alginates, glucosaminoglycans, and dextrans; hydrophilic polypeptides and poly(amino acids) such as poly-L-glutamic acid, gamma-polyglutamic acid, poly-L-aspartic acid, and poly-L-serine; poly(oxyethylated polyol); poly(olefinic alcohol) such as poly(vinyl alcohol) and aminoacetalized poly(vinyl alcohol); poly(N-vinylpyrrolidone); acrylic or acrylate, and alkacrylic or alkacrylate polymers such as poly(acrylic acid), poly(methacrylic acid), poly(hydroxyethyl acrylate); poly(N,N-dimethylaminoethyl methacrylate),

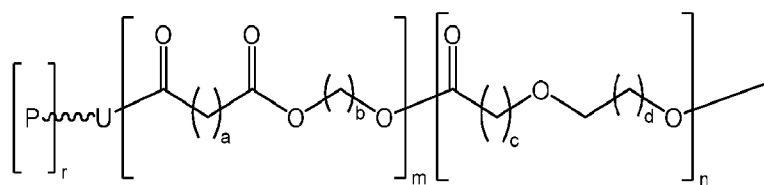
25

poly(hydroxyalkyl methacrylate) e.g. poly(hydroxyethyl methacrylate); acrylamide polymers such as poly(acrylamide), poly(hydroxyalkyl methacrylamide) e.g. poly(hydroxyethyl methacrylamide); and poly(4-vinylpyridine); and copolymers thereof.

- 5 Preferably, the hydrophilic polymer segment contains a neutral hydrophilic polymer, such as a neutral uncharged hydrophilic polymer. Examples of neutral uncharged hydrophilic polymers include, but are not limited to, polyalkylene glycols and polyalkylene oxides such as poly(ethylene glycol); polysaccharides such as celluloses and dextrans;
- 10 hydrophilic polypeptides and poly(amino acids) such as poly-L-serine; poly(oxyethylated polyol); poly(olefinic alcohol) such as poly(vinyl alcohol); poly(N-vinylpyrrolidone); poly(hydroxyethyl acrylate); poly(hydroxyalkyl methacrylate), *e.g.*, poly(hydroxyethyl methacrylate).

- Preferably, the hydrophilic polymer segment contains a neutral
- 15 uncharged hydrophilic polymer, such as polyalkylene glycols and polyalkylene oxides such as poly(ethylene glycol).

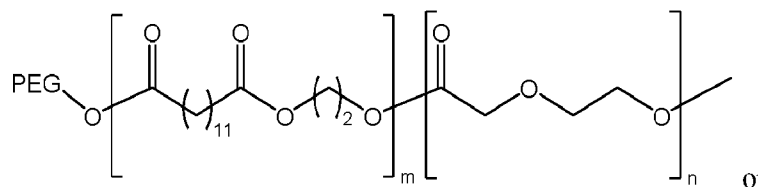
- In some forms, the polymer is as described above for Formulae I and II, except that (i) U' is absent, (ii) P' is absent, (iii) T' is absent, or (iv) U', P', and T' are absent. In some forms, the polymer is as described above for
- 20 Formulae I and II, except that the polymer has a structure:

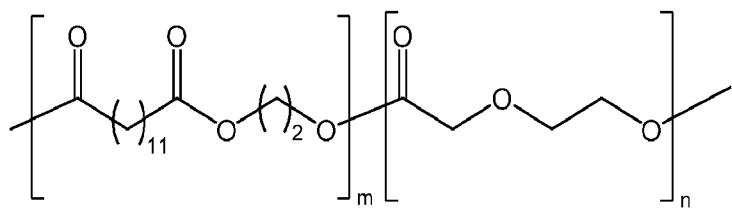


Formula III

In some forms, the polymer is as described above for Formulae I, II, and III, except that U is -O-.

- 25 In some forms, the polymer is as described above for Formulae I, II, and III, except that the polymer has a structure:





wherein, m and n are independently integers from 1 to 1500, with the proviso that m+n is at least 10 (such as from 10 to 3000). In some forms, the polymers have a weight-average molecular weight between about 10 kDa and about 150 kDa, between about 10 kDa and about 130 kDa, or between about 10 kDa and about 125 kDa, as measured using gel permeation chromatography, such as between about 15 kDa and about 25 kDa, between about 45 kDa and about 72 kDa, and between about 50 kDa and about 125 kDa.

ii. Targeting moieties

In some forms, one or more targeting moieties (also referred to herein as targeting agents and denoted above as T and T') can be covalently conjugated, non-covalently conjugated, or both, to the polymers. In some forms, the one or more targeting moieties are covalently conjugated to at least one hydrophilic polymer. A targeting moiety binds to or localizes to a specific locale. The targeting moiety may be, for example, a protein, glycoprotein, nucleic acid, nucleic acid analog, carbohydrate, or small molecule (molecular weight between 100 Da and 2,500 Da). In general, the targeting moiety can have a molecular weight between 100 Da and 20 kDa. The locale may be a tissue, a particular cell type, a subcellular compartment, or extracellular matrix. The targeting moiety or a sufficient plurality of targeting moieties may be used to direct the localization of a particle or an active entity. The active entity may be useful for therapeutic, prophylactic, or diagnostic purposes.

The binding or localization to a specific local results in binding of the polymer or a particle containing the polymer to the target cell, tissue, organ, subcellular locale, or extracellular matrix. The targeting moieties can be conjugated to one or more polymers prior or after formation of particles containing the polymers. In some forms, the targeting moieties are conjugated to the polymers prior to formation of a particle containing the

copolymers. In other forms, the targeting moieties are conjugated to the polymers post-particle formation. The targeting moieties can be covalently conjugated to one or more polymers, directly or indirectly via a linker. In some forms, the targeting moiety increases or enhances targeting of the particles to the brain. The targeting moieties can be specific to cells of the nervous system which may include astrocytes, microglia, neurons, oligodendrites, and Schwann cells; or brain extracellular matrix material.

In some forms, the mole ratio of the ethylene brassylate:dioxanone residues in the polymers is between about 95:5 and about 5:95, or between about 95:5 and about 50:50, as determined using $^1\text{H-NMR}$.

In general, and with respect to the polymers described herein, the values of m and n , and in the presence of absence of P , P' , T , T' , U , and/or U' are such that the weight-average molecular weight between about 2 kDa and about 1 Mda, between about 2 kDa and about 750 kDa, between about 2 kDa and about 500 kDa, between about 2 kDa and about 250 kDa, or between about 2 kDa and about 100 kDa, between about 2 kDa and about 60 kDa, between about 5 kDa and about 60 kDa, between about 10 kDa and about 60 kDa, between about 2 kDa and about 25 kDa, between about 5 kDa and about 25 kDa, between about 10 kDa and about 25 kDa, or between about 15 kDa and about 25 kDa, such as about 20 kDa, as measured using gel permeation chromatography.

In some forms, the polymers have a weight-average molecular weight between about 10 kDa and about 150 kDa, between about 10 kDa and about 130 kDa, or between about 10 kDa and about 125 kDa, as measured using gel permeation chromatography, such as between about 15 kDa and about 25 kDa, between about 45 kDa and about 72 kDa, and between about 50 kDa and about 125 kDa.

B. Particles and macroimplants containing ethylene brassylate-co-dioxanone polymers

Also described are particles and macroimplants containing, or formed from, the polymers described herein. In some forms, the particles are nanoparticles. Macroimplants refer to composition of matter containing the ethylene brassylate-co-dioxanone polymers described herein, which have a dimension between 1 mm and 5 cm.

In some forms, particles and macroimplants can contain a blend of an ethylene brassylate-co-dioxanone polymer described herein and a second polymer. In some forms, the second polymer can be a hydrophobic polymer. Preferably, the hydrophobic polymer is biodegradable. Suitable

5 biodegradable hydrophobic polymers include, but are not limited to, polyesters, polyanhydrides, poly(*p*-dioxanone)s, polycarbonates, or a combination thereof. These polymers include poly(α -hydroxy acid)s, poly(lactone)s, or combination thereof, such as poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, poly(caprolactone)s,

10 poly(pentadecalactone)s, poly(hydroxybutyrate-co-hydroxyvalerate)s, poly(hydroxybutyrate)s, or a combination thereof.

i. Therapeutic, diagnostic, and/or prophylactic agents

Preferably, the particles and macroimplants contain one or more therapeutic, prophylactic, or diagnostic agents (collectively called “agents”).

15 In some forms, these agents include small molecule drugs (such as small molecule chemotherapeutic drugs; anti-inflammatories (*e.g.*, dexamethasone), progestins (*e.g.*, levonorgestrel), or integrase inhibitors (*e.g.*, dolutegravir), between 100 Da and 2,500 Da) or macromolecules, such as proteins; nucleic acids, such as mRNAs, siRNAs, miRNAs, ribozymes,

20 triplex forming molecules, sgRNAs, or DNAs; ribonucleoproteins; or a combination thereof. The agents to be incorporated can be non-covalently conjugated and/or covalently conjugated to the polymer. Preferably, at least one of the agents is non-covalently encapsulated within the particles. In some forms, the particles and macroimplants contain a higher proportion of

25 the agents encapsulated within the particles and macroimplants than on the surface of the particles. In some forms, the agents are encapsulated within the particles and macroimplants, and are not on the surface of the particles and macroimplants.

In some forms, the agents are small molecule or macromolecule

30 chemotherapeutic agents. These chemotherapeutic agents are generally classified into the following classes: alkylating agents (*e.g.*, DNA alkylators), DNA damage response inhibitors, antimetabolites, anthracyclines, plant alkaloids, topoisomerase inhibitors, monoclonal antibodies, antitumor antibiotics; biologic response modifiers, histone

deacetylase inhibitors, hormonal agents, protein kinase inhibitors, taxanes, or other anti-tumor agents.

Examples of chemotherapeutic agents that fall within these classes are provided herein: alkylating agents, *e.g.*, DNA alkylators, (such as

5 dianhydrogalactitol (VAL-083), temozolomide, lomustine, cisplatin, carboplatin, oxaliplatin, mechlorethamine, cyclophosphamide, chlorambucil, dacarbazine, carmustine, procarbazine, chlorambucil, and ifosfamide); DNA damage response inhibitors (such as ataxia telangiectasia and Rad3-related (ATR) inhibitors or analogs thereof; PARP inhibitors or analogs thereof;

10 checkpoint kinase inhibitors or analogs thereof); antimetabolites (such as fluorouracil (5-FU), gemcitabine, methotrexate, cytosine arabinoside, fludarabine, and floxuridine); anthracyclines (such as doxorubicin, daunorubicin, valrubicin, idarubicin, epirubicin, and actinomycins such as actinomycin D); plant alkaloids (such as vinblastine, vincristine, and

15 vinorelbine); topoisomerase inhibitors (such as camptothecin, etoposide, irinotecan, teniposide, and topotecan); monoclonal antibodies (such as alemtuzumab, atezolizumab, avelumab, bevacizumab, blinatumomab, and trastuzumab); antitumor antibiotics (such as mitomycin, plicamycin, and bleomycin); biologic response modifiers (such as aldesleukin (IL-2),

20 denileukin diftitox, interferon gamma); histone deacetylase inhibitors (such as belinostat, panobinostat, romidepsin, and vorinostat); hormonal agents (antiandrogens: abiraterone, apalutamide, bicalutamide, cyproterone, enzalutamide, flutamide, and nilutamide); protein kinase inhibitors (abemaciclib, acalabrutinib, Imatinib, ivosidenib, ixazomib, sorafenib,

25 sunitinib, and talazoparib); taxanes (such as cabazitaxel, docetaxel, and paclitaxel); or other anti-tumor agents (such as asparaginase (pegaspargase), bexarotene, eribulin, everolimus, hydroxyurea, ixabepilone, lenalidomide, mitotane, omacetaxine, pomalidomide, tagraxofusp, telotristat, temsirolimus, thalidomide, and venetoclax). DNA damage response inhibitors are

30 described in Qui, *et al.*, Radiother. Oncol. 2018, 126(3), 450-464, the contents of which are hereby incorporated by reference.

Exemplary diagnostic agents include paramagnetic molecules, fluorescent compounds, magnetic molecules, and radionuclides, x-ray imaging agents, and contrast agents. Exemplary diagnostic agents include,

but are not limited to, metal oxides, such as iron oxide, metallic particles, such as gold particles, etc. Biomarkers can also be conjugated to the nanoparticles for diagnostic applications. For imaging, radioactive materials such as Technetium99 (^{99m}Tc) or magnetic materials such as Fe_2O_3 could be used. Examples of other imaging materials include gases or gas emitting compounds, which are radio-opaque.

In some forms, the particles and macroimplants constitute from about 0.01% wt/wt to about 60% wt/wt, about 0.01% wt/wt to about 55% wt/wt, about 0.01% wt/wt to about 50% wt/wt, about 0.01% wt/wt to about 45% wt/wt, about 0.01% wt/wt to about 40% wt/wt, about 0.01% wt/wt to about 35% wt/wt, about 0.01% wt/wt to about 30% wt/wt, about 0.01% wt/wt to about 25% wt/wt, about 0.01% wt/wt to about 20% wt/wt, about 0.01% wt/wt to about 10% wt/wt, about 0.01% wt/wt to about 5% wt/wt, about 0.5% wt/wt to about 5% wt/wt, the therapeutic, prophylactic, or diagnostic agents.

ii. Size and morphology

Agent-containing populations of nanoparticles are typically spherical or about spherical shape with an average diameter from about 50 nm to about 500 nm, about 50 nm to about 400 nm, about 50 nm to about 300 nm, or about 50 nm to about 250 nm, preferably between about 50 nm and about 250 nm. In some forms, the particles have a core-shell structure. Preferably, the core-shell structure contains a hydrophobic core and the hydrophilic polymer is oriented towards the surface of the particles. Techniques to observe and measure nanostructures include dynamic light scattering, scanning electron microscopy, transmission electron microscopy, and/or atomic force microscopy.

These particles generally have a surface charge, *e.g.*, having a zeta potential at a physiological environment between about -50 mV and +10 mV.

The macroimplants can have shapes such as cylinders or disks.

III. Formulations

Formulations containing the particles and macroimplants can be prepared using a pharmaceutically acceptable “carrier” composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side effects or unwanted

interactions. The “carrier” includes all components present in the pharmaceutical formulation other than the active ingredient or ingredients.

Dosage formulations may be prepared as described in references such as

“Pharmaceutical dosage form tablets”, eds. Liberman, *et al.* (New York,

- 5 Marcel Dekker, Inc., 1989), “Remington – The science and practice of pharmacy”, 20th ed., Lippincott Williams & Wilkins, Baltimore, MD, 2000, and “Pharmaceutical dosage forms and drug delivery systems”, 6th Edition, Ansel, *et al.*, (Media, PA: Williams and Wilkins, 1995).

IV. Methods of Making and Reagents therefor

10 A. Polymers

The block polymers can be synthesized using a variety of methods known to those of skill art including, but not limited to, chemical synthesis, biochemical synthesis, chemoenzymatic synthesis, semisynthesis, or a combination thereof.

- 15 Preferably, the block polymers are synthesized via catalytic polymerization of reactants, preferably in a process, wherein an enzyme serves as the catalyst. In some forms, the enzyme catalyst is a lipase, such as a solvent-free lipase. In some forms, the lipase is lipase B from *Candida antartica* (CALB).

- 20 The reactants include a monomer, such as ethylene brassylate and/or dioxanone, that can polymerize to form a segment of the polymer segment. The reactants can further include a hydrophilic polymer containing a nucleophilic group to initiate ring-opening of the ethylene brassylate and/or the dioxanone, such as polyalkylene oxide (*e.g.*, poly(ethylene glycol)). In
25 some forms, the molar feed ratios of the ethylene brassylate:dioxanone can be between about 95:5 and about 5:95, between about 90:10 and about 10:90, such as 90:10, 80:20, 70:30, 60:40, 50:50, and 40:60.

- Scheme 1**, in the Example section, illustrates a non-limiting synthesis of polymers described herein. In some forms, the method of synthesizing the
30 polymers involves incubating the reactants and enzyme catalyst at a temperature from between 60 °C and 95 °C, inclusive, preferably between 75 °C and 85 °C.

Suitable hydrophilic polymers include those described herein, such as polyalkylene glycols and polyalkylene oxides such as poly(ethylene glycol);

polysaccharides such as celluloses, alginates, glucosaminoglycans, and dextrans; hydrophilic polypeptides and poly(amino acids) such as poly-L-glutamic acid, gamma-polyglutamic acid, poly-L-aspartic acid, and poly-L-serine; poly(oxyethylated polyol); poly(olefinic alcohol) such as poly(vinyl alcohol) and aminoacetalized poly(vinyl alcohol); poly(N-vinylpyrrolidone); acrylic or acrylate, and alkacrylic or alkacrylate polymers such as poly(acrylic acid), poly(methacrylic acid), poly(hydroxyethyl acrylate); poly(N,N-dimethylaminoethyl methacrylate), poly(hydroxyalkyl methacrylate), *e.g.*, poly(hydroxyethyl methacrylate); acrylamide polymers such as poly(acrylamide), poly(hydroxyalkyl methacrylamide), *e.g.*, poly(hydroxyethyl methacrylamide; and poly(4-vinylpyridine); and copolymers thereof.

B. Particles

The block polymers are processed into particles (such as nanoparticles) to encapsulate or otherwise associate with or deliver one or more agents. Techniques for making particles are known in the art and include, but are not limited to, nanoprecipitation, emulsion, solvent evaporation, solvent removal, spray drying, phase inversion, and low temperature casting. Suitable methods of particle formulation are briefly described below. The therapeutic, prophylactic, or diagnostic agent and pharmaceutically acceptable excipients, including pH modifying agents, disintegrants, preservatives, and antioxidants, can optionally be incorporated into the particles during particle formation. As described above, one or more agents can also be incorporated into the nanoparticle during particle formation.

In the nanoprecipitation method, a solution containing one or more therapeutic, prophylactic, or diagnostic agents is added dropwise to a solution containing the polymers. As the therapeutic, prophylactic, or diagnostic agents are complexed by the amphiphilic block polymers (*e.g.*, through electrostatic charges), nanoparticles precipitate from solution. The resulting particles are isolated from solution, for example by dialysis, filtration or centrifugation, washed, and dried using a lyophilizer.

The diameter (nm), polydispersity index (PDI) and surface charge (zeta potential, mV) of nanoparticles can be measured by dynamic light

scattering on Zetasizer Nano ZS90 (Malvern Instruments, Southborough, MA). The morphology of the nanoparticles can be characterized by transmission electron microscopy (TEM) or scanning electron microscopy (SEM).

5 **C. Macroimplants**

Macroimplants can be produced with or without drugs loaded with them, using the ethylene brassylate-co-dioxanone polymers described herein. Macroimplants refer to composition of matter containing the ethylene brassylate-co-dioxanone polymers described herein, which have a dimension
10 between 1 mm and 5 cm. In some forms, the ethylene brassylate-co-dioxanone polymers were used to produce unloaded and drug-loaded implants according to an established melt-molding technique (W. Saltzman, E. Quijano, F. Yang, J. Jiang, D. Owen, Biodegradable Contraceptive Implants, 2020).

15 **V. Methods of Using**

A. Conditions to be treated

This platform technology has a wide range of applications and application locations, for delivery of therapeutic agents, diagnostic agents, and/or prophylactic agents. It can be particularly useful in the controlled
20 release of these agents to cells, tissues, and/or organs of interest. The platform includes: drug delivery platforms, transfection platforms, and gene editing platforms.

The methods of treatment typically include using particles or macroimplants loaded with one or more agents, to deliver the one or more
25 agents into desired cells, tissues, organs, and/or their environment. The methods typically include contacting the agent-loaded particles or macroimplants with one more cells. The contacting can occur *in vivo* or *in vitro* or *ex vivo*.

The nanoparticles, macroimplants, and compositions thereof, can be
30 used to treat diseases or disorders in cells, tissues, and/or organs. The compositions typically include an effective amount of the agents to be delivered. The precise dosage will vary according to a variety of factors such as subject-dependent variables (*e.g.*, age, immune system health, etc.), the disease, and the treatment being effected.

i. Drug delivery platform

In some forms, the disease can be cancer. Cancers to be treated include, but are not limited to, brain tumor (such as glioma), breast cancer (such as metastatic or locally advanced breast cancer), prostate cancer (such as hormone refractory prostate cancer), renal cell carcinoma, lung cancer (such as small cell lung cancer and non-small cell lung cancer (such as adenocarcinoma, squamous cell carcinoma, bronchoalveolar carcinoma and large cell carcinoma)), pancreatic cancer, gastric cancer (such as gastroesophageal, upper gastric or lower gastric cancer), colorectal cancer, squamous cell cancer of the head and neck, ovarian cancer (such as advanced ovarian cancer, platinum-based agent resistant or relapsed ovarian cancer), lymphoma (such as Burkitt's, Hodgkin's or non-Hodgkin's lymphoma), leukemia (such as acute myeloid leukemia) and gastrointestinal cancer.

ii. Gene editing platform

In some forms, the therapeutic, diagnostic, and/or prophylactic agents are, or encode, a gene editing technology. In some forms, the disease can be an erythrocyte disorder, such as hereditary spherocytosis, which is amenable to treatment via gene editing.

Gene editing technologies can be used alone or in combination with a potentiating agent and/or other agents. Exemplary gene editing technologies include, but are not limited to, triplex-forming (such as triplex-forming molecules, including triplet-forming oligonucleotides and peptide nucleic acids (PNAs)), pseudo-complementary oligonucleotides, CRISPR/Cas, zinc finger nucleases, TALENs, and small fragment homologous replacement. WO2018/187493 by Saltzman, *et al.*, provides extensive details on gene therapy technologies. The gene editing composition can be a pseudo-complementary oligonucleotide or PNA oligomer.

B. Methods of administration

The particles and macroimplants can be formulated in dosage forms appropriate for each route of administration. Routes of administration include, but are not limited to, intracranial (*e.g.*, intracranial convection enhanced delivery), intrathecal, intramuscular, pulmonary, intranasal, oral, intravenous, intraperitoneal, transdermal, subcutaneous, topical, sublingual,

rectal, and other suitable means. Such administration routes and appropriate formulations are generally known to those of skill in the art.

The administration may be localized (such as to a particular region, physiological system, tissue, organ, or cell type) or systemic, depending on
5 the condition being treated.

The particles, macroimplants, and formulations thereof can be used to deliver small molecules and macromolecules (such as peptide and protein medicines), such as those for the treatment of tumors (such as brain tumors) via one or more routes of administration described herein.

10 In one preferred form, the particles, macroimplants, and formulations thereof are designed to deliver a drug to the brain across the BBB or within the brain. In another preferred form, the particles, macroimplants, and formulations thereof are designed for drug delivery that penetrates brain tissue.

15 The particles in the circulation preferentially accumulate in a diseased site. In some forms, they naturally penetrate to the brain, particularly at brain locations with injuries such as tumors. In some forms, the particles, macroimplants and methods are used to treat cancer, particularly brain cancer.

20 *Combination Therapy*

The particles, macroimplants, and compositions thereof can be used in combination with standard chemotherapy, radiation therapy, and other anti-cancer treatments. As used herein, “combination” or “combined” refer to either concomitant, simultaneous, or sequential administration of the
25 therapeutics.

The combination therapies can include administration of the agents together in the same admixture, or in separate admixtures.

In some forms, particles and macroimplants containing the polymers described herein, may encapsulate two or more agents to be co-administered.

30 In other forms, each agent to be co-administered may be encapsulated in separate particles or macroimplants containing the polymers described herein. In these forms, the formulation can include two or more different types of these particles or macroimplants having the same or different agent(s) associated therewith, such as encapsulated therein.

In other forms, some agents are encapsulated in particles or macroimplants containing the polymers described herein, while others are not encapsulated, and can be, for example, free or soluble, or in a different carrier or dosage form. For example, such agents can be free or soluble
5 active agent(s), or agent(s) in a different carrier or dosage form but are nonetheless part of the same composition as the particle, macroimplant, or composition thereof.

In the non-limiting example of chemotherapeutics, the different agents can belong to the same or different therapeutic classes, and/or have
10 the same or different mechanisms of action. For instance, the agents can be selected from alkylating agents (*e.g.*, DNA alkylators), DNA damage response inhibitors, antimetabolites, anthracyclines, plant alkaloids, topoisomerase inhibitors, monoclonal antibodies, antitumor antibiotics, biologic response modifiers, histone deacetylase inhibitors, hormonal agents,
15 protein kinase inhibitors, taxanes, or combinations thereof, such that the agents belong to the same or different therapeutic classes. The different combinations of selections, such that the agents are from the same or different chemotherapeutic classes, are considered contemplated and expressly disclosed. Some examples include: DNA damage response
20 inhibitors and DNA alkylators; a pair of DNA damage response inhibitors, *etc.* In some forms, the combination results in an additive effect on the treatment of the disease or disorder. In some forms, the combinations result in a more than additive effect on the treatment of the disease or disorder.

In some forms, the particles, macroimplants, or compositions thereof,
25 and other therapeutic agents are administered separately through the same route of administration. In other forms, the particles, macroimplants, or compositions thereof, and other therapeutic agents are administered separately through different routes of administration. The combinations can be administered concomitantly (*e.g.*, as an admixture), separately but
30 simultaneously (*e.g.*, via separate intravenous lines into the same subject; one agent is given orally while the other agent is administered separately through the same route of administration). In other forms, the particles, macroimplants, or compositions thereof, and other therapeutic agents are administered separately through different routes of administration. The

combinations can be administered either concomitantly (*e.g.*, as an admixture), separately but simultaneously (*e.g.*, via separate intravenous lines into the same subject; one agent is given orally while the other agent is given by infusion or injection, *etc.*), or sequentially (*e.g.*, one agent is given first followed by the second). Exemplary non-limiting combination therapies are discussed in more detail below.

The methods, compounds, and compositions herein described are further illustrated in the following examples, which are provided by way of illustration and are not intended to be limiting. It will be appreciated that variations in proportions and alternatives in elements of the components shown will be apparent to those skilled in the art and are within the scope of disclosed forms. Theoretical aspects are presented with the understanding that Applicants do not seek to be bound by the theory presented. All parts or amounts, unless otherwise specified, are by %weight/weight.

Examples

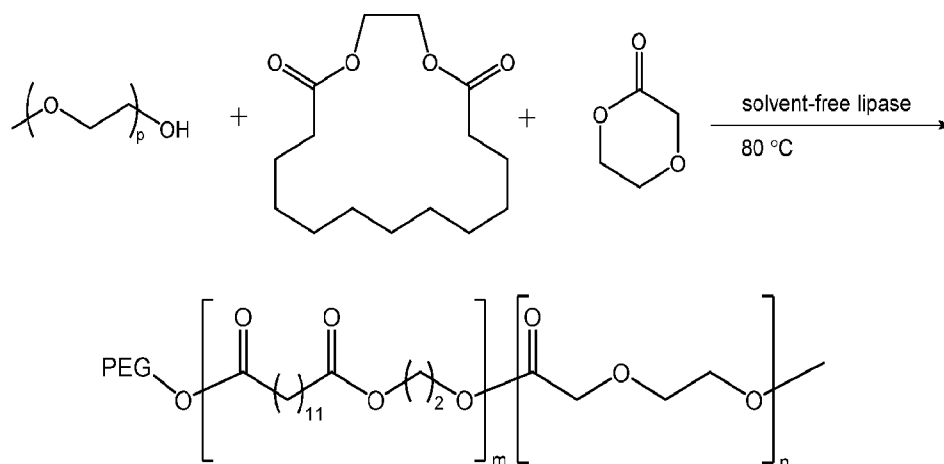
Example 1: Poly(ethylene glycol)-ethylene brassylate-*co*-dioxanone polymer drug delivery particles

Materials and methods

(i) *Synthesis of polymers*

Scheme 1 is a non-limiting example of the synthesis of a poly(ethylene glycol)-ethylene brassylate-*co*-dioxanone polymer (PEG-EB-*co*-DO).

Scheme 1



where p, m, and n can be independently integers from 1 to 1500.

(ii) *Fabrication of nanoparticles with or without drug*

The nanoparticles were prepared following a nanoprecipitation method.

5 *Results***Table 1.** Nanoparticles fabricated from PEG-EP-co-DO polymer by nanoprecipitation

Polymer	Solvent	Drug	Weight used (mg)	Drug (mg)	Size	PDI	Zeta	Yield ^a	EE ^b	DL ^c
PEG-EB-co-DO	DMSO	none	22.0	N/A	187.7	0.09	- 29.0	50.0	N/A	N/A
PEG-EB-co-DO	DMSO	ATRIN 175	20.7	1.2	145.1	0.13	3.5	82.1	49.3	3.4
PEG-EB-co-DO	DMF	none	21.0	N/A	144.4	0.096	- 27.7	66.7	N/A	N/A
PEG-EB-co-DO	DMF	ATRIN 175	20.2	1.0	164.6	0.206	-6.3	79.2	28.8	1.8
PEG-EB-co-DO	DMF	ATRIN 297	21.0	1.1	144.1	0.207	- 15.1	71.4	39.3	2.9
PEG-EB-co-DO	DMF	ATRIN 333	19.7	1.1	129.8	0.191	- 16.1	55.8	11.6	1.2

^a polymer yield^b encapsulation efficiency^c drug loading

Uptake of PEG-EB-co-DO DiD dye loaded particles was compared to uptake of PLA-PEG at the same concentration in LN229 cells. **PEG-EB-co-DO** represents poly(ethylene glycol)-ethylene brassylate-co-dioxanone polymer, **PLA-PEG** represents poly (lactic acid)-poly(ethylene glycol). The data showed significantly increased uptake of PEG-EB-co-DO compared to PLA-PEG.

FIGs. 8A, 8B, and 8C demonstrated retention of PEG-EB-co-DO DiD dye loaded nanoparticles in rat brains after intracranial delivery (such as intracranial convection enhanced delivery), at three hours (**FIG. 8A**), 24 hours (**FIG. 8B**), and five days (**FIG. 8C**) post-delivery. The data showed that the PEG-EB-co-DO nanoparticles are retained for at least five days in rat brains post-delivery.

Drug-loaded PEG-EB-*co*-DO nanoparticles also demonstrated synergy in killing LN229 human glioma cells as well as in U251 human glioma cells in combination with free drug such as a DNA alkylator, such as temozolomide (TMZ), lomustine, VAL083; or a PARP Inhibitor, such as BGB290. Comparisons were made between (i) the corresponding free drug and a free ATR inhibitor (such as ATRIN 333) on the one hand, and (ii) the corresponding free drug and nanoparticle-encapsulated ATR inhibitor (such as ATRIN 333).

Example 2: Poly(ethylene brassylate-*co*-dioxanone) polymers and fabrication of biodegradable implants

Materials and methods

All chemicals were purchased from Fisher Scientific and used as received unless stated otherwise. Ethylene brassylate (EB) was purchased from Sigma Aldrich. Benzyl alcohol was distilled from calcium hydride under high vacuum. 7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), 1,8-Diazabicyclo(5.4.0)undec-7-ene (DBU) was purchased from Tokyo Chemical Industry Co. LTD. and 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) from Acros Organics. Benzene-*d*₆ and chloroform-*d* were purchased from Cambridge Isotope Laboratories and distilled from calcium hydride. Experiments were conducted using pre-dried glassware in an MBRAUN or INERT stainless-steel glovebox under N₂ atmosphere. NMR experiments were conducted on a Bruker Avance III 300 MHz or 400 MHz spectrometer. Gel Permeation Chromatography (GPC) was performed at 40 °C using HPLC grade dichloromethane eluent on an Agilent Infinity GPC system equipped with three Agilent PLGel columns 7.5 mm × 300 mm (5 μm, pore sizes: 10³, 10⁴, 50 Å). *M*_n and *M*_w/*M*_n were determined versus polystyrene standards (500 g/mol-3150 kg/mol, Polymer Laboratories). Differential Scanning Calorimetry (DSC) experiments were conducted using a Shimadzu DSC-60A instrument, calibrated with an indium standard using aluminum pans under inert conditions.

*(i) Poly(EB-*co*-DO) copolymerization reactions*

Small-scale solvent-free copolymerization using Novozyme 435. A 1 mL vial was charged with EB (270.4 mg, 1.0 mmol), DO (102.1 mg, 1.0

mmol), and a stir bar. The contents of the vial were preheated to 80°C for 15 minutes; then Novozyme 435 (33.4 mg) was added in one portion and the vial returned to heating. Reaction progress was monitored by removing aliquots of the reaction mixture and dissolving in 600 µL of CDCl₃. The catalyst was removed from the dissolved aliquot via syringe filtration. Conversion was determined by ¹H NMR. The polymer was isolated by dissolving the reaction mixture in DCM, removing the catalyst via filtration, then precipitating the polymer with methanol.

Large scale solvent-free copolymerization using Novozyme 435. A

100 mL round bottom flask was charged with EB (7.64 g, 0.028 mol), DO (6.4 g, 0.028 mmol), and an overhead mechanical stirrer was carefully loaded into the reaction. The contents of the round bottom flask were preheated to 80°C for 15 minutes; then Novozyme 435 (0.2 g) was added. The polymer was isolated by dissolving the reaction mixture in DCM, removing the catalyst via filtration, then precipitating the polymer with methanol. The polymer was then characterized using ¹H NMR and GPC.

(ii) Characterization of poly(EB-co-DO) copolymers

The structure of poly(EB-co-DO) catalyzed by Novozyme-435 was determined via ¹H and ¹³C NMR spectroscopy. ¹H NMR was used to determine the incorporation ratio of EB and DO in the copolymer. Percentage conversion and incorporation ratio was calculated using the ¹H NMR signal of the R-COO-CH₂-CH₂-COO-R of PEB at 4.2 ppm and the -CH₂-CH₂-O-CH₂-COO- of PDO at 3.8 ppm (with reference to CDCl₃).

(iii) Implant fabrication

For DEX-loaded implants, different ratios of poly(EB-co-DO) and DEX were dissolved in dichloromethane (DCM) and methanol, respectively. Both solutions were then sonicated and vortexed together to ensure a homogeneous distribution of drug throughout the polymer matrix and poured into a clean round bottom flask. For LNG-loaded or DTG-loaded implants, polymer and drug were both dissolved in DCM only. A rotary evaporator was used to evaporate the organic solvents over 1 hour. To form two-centimeter implants, the resulting polymer-drug pellets (110 mg) were loaded into a custom-machined Teflon mold and baked for 1 hour at 100°C under argon protection and atmospheric pressure. The implants were

compressed using a stainless-steel plunger immediately after baking and demolded the next day. For *in vitro* release and mechanical testing, the implants were cut in half to create two one-centimeter implants that were 2.4 mm in diameter and approximately 50 mg in total mass.

5 (iv) *Implant characterization via SEM*

DEX-loaded poly(EB-co-DO) implants were evaluated under an ultra-high-resolution Hitachi scanning electron microscopy (SU7000). Implants were flash frozen in liquid nitrogen, broken in half using tweezers, and cross sectioned using a razor blade to about 1 mm thickness. Samples
10 were placed on a stub using carbon tape, with razor blade edge facing down. Samples were coated with gold to a thickness of 7 nm using a high-resolution sputter coater (Cressington, 208HR) with rotary planetary tilt stage and thickness controller MTM-20. SEM images were taken at 2k to 20k magnification.

15 (v) *In vitro drug release*

Drug-loaded poly(EB-co-DO) implants (1 cm long, 2.4 mm diameter, 50 mg) were individually incubated in 1 mL of PBS solution (pH=7.4) containing 3% methyl-beta-cyclodextrin (M- β -CD) at 37°C. At selected time
20 points, the buffer solution was completely replaced with fresh solution of the same composition. The collected buffer solutions, in which the implant had been continuously and completely bathed for a period of time, were flash frozen and lyophilized. High-performance liquid chromatography (HPLC) was then used to determine the representative drug loading of implants in each group.

25 To determine drug concentrations, one mL of acetonitrile (ACN) was added to DEX and LNG samples to dissolve the agent or one mL of 1:1 water:ACN was added to DTG samples. The samples were then centrifuged at 3000 rpm for 5 min to draw out any salts and M- β -CD. The supernatant was passed through 0.22 μ m syringe filters before being analyzed by HPLC
30 for drug content.

An Agilent column (883995-906, ZORBAX StableBond 300 C8, 4.6 x 150 mm, 5 μ m) and Shimadzu HPLC system (LC-2030C) with a UV-Vis detector was used for drug quantitation. For both DEX and LNG, Solvent A was 0.1% TFA in HPLC grade water, and solvent B was 0.1% TFA in HPLC

grade ACN. Initial solvent B concentration was set at 5% and allowed to increase to 100% by the 5th minute. Flow was maintained for 5 min at this level before dropping to 5% after 12 min, which was maintained until the end of the run at 13 minutes. For analysis of DTG drug release, Solvent A was 0.1% TFA in HPLC grade water, and solvent B was 100% methanol. Initial solvent B concentration was set at 55% and increased to 60% for the 6-7th minute before being brought back down to 55% for the 7-10th minute. All three drugs were detected using a UV detector at a wavelength of 240 nm. Oven temperature was 30°C for DEX and LNG, and 35°C for DTG. A volume of 45 µl was injected for each sample run.

(vi) *Mathematical diffusion model for prediction of drug release*

Fick's second law of diffusion appropriately models drug transport across polymeric matrixes by proportionally relating the diffusion rate at time, t , to the concentration gradient of drug in the implant, $\partial C/\partial r$. As shown in the equation below (1), a one-dimensional, radial release from our cylindrical implants was adopted, with a constant drug diffusion coefficient, D .

$$\frac{\partial C}{\partial t} = D \frac{1}{r} \frac{d}{dr} \left[r \frac{\partial C}{\partial r} \right] \quad (1)$$

The solution for the above partial differential equation requires specification of a set of initial conditions and boundary conditions. For the initial condition ($t=0$), a homogenous and uniform concentration of drug throughout the implant was adopted, $C=C_0$. A symmetry boundary condition is further applied at the center of the implant ($r=0$) as flux across the plane of symmetry is zero, $\partial C/\partial r=0$. Lastly, a perfect-sink boundary condition is applied at the surface of implant ($r=R$), $C=0$. Solving Equation 1 via numerical integration in MATLAB reveals predicted drug concentration in the implant, C , as a function of time, t , and radius, r . The predicted drug concentration is then integrated across the radius of the implant to determine the mass of drug remaining within the implant at each time step. *In vitro* release, then, is determined from the mass of drug in the implant at each time point subtracted from initial mass of drug within the implant ($C_0 \cdot V$). Lastly, the diffusion coefficient is determined by fitting the cumulative drug release

profile to data from *in vitro* drug release experiments and minimizing root mean squared error (RMSE).

(vii) *Mechanical testing*

The mechanical properties of the DEX loaded poly(EB-co-DO) implants were assessed via three-point bend tests and compression tests using an Instron 5960 Mechanical Testing Machine.

The three-point bend test. The three-point bend test involved placing individual implants horizontally over a metal grip with prongs separated by a length (L) of 5mm. A 2 kN load cell moved downwards at a speed of 2mm/min and exerted a force in between the two prongs until the implant fractured or a maximum displacement of 20mm was reached. Force (F), displacement (D), flexural stress (σ_f), and flexural strain (ϵ_f) were recorded by the Instron. The flexural modulus is defined as $E_f = \sigma_f / \epsilon_f$ where stress and strain are defined as $\sigma_f = FL / \pi r^3$ and $\epsilon_f = 6Dd / L^2$ respectively (P.E. Sirinek, M.M. Lin, Intracameral sustained release bimatoprost implants (Durysta), Semin Ophthalmol 37(3) (2022) 385-390). The length of the implant was 10 mm, the diameter (d) was 2.4 mm, and the radius (r) was 1.2 mm.

The compression test. The compression test was similarly performed using a 2 kN load cell travelling at a speed of 2mm/min. Implants were placed on top of a stainless-steel plate and were compressed in the transverse direction until a maximum displacement of 10mm was reached or when the implant became fractured or irreversibly deformed. Force (F), displacement (D), compression stress (σ_c), and compression strain (ϵ_c) were recorded to calculate the compressive modulus of elasticity as $E_c = \sigma_c / \epsilon_c$. The

compressive modulus can also be calculated as $E_c = \frac{8(1-\mu^2)Z^2F}{\pi dL}$, which includes the additional parameters: Poisson's ratio (μ), geometric constant (Z = radius of implant/ half contact width in radial compression), implant diameter (d), and implant length (L) (W.K. Solomon, V.K. Jindal, Comparison of axial and radial compression tests for determining elasticity modulus of potatoes, Int J Food Prop 9(4) (2006) 855-862).

(viii) *Thermal characterization of polymers*

Thermogravimetric analysis (TGA) experiments were conducted using a Shimadzu instrument. First, 10 mg of polymer was inserted into the

sample chamber and the temperature was increased at 10°C/min from 25°C to 600°C. The degradation profile was collected during scanning. For the differential scanning calorimetry (DSC) experiments, a TA instrument DSC (TA instruments - DSC250) was used (precalibrated to 10°C/min). Each experiment required 5 to 8 mg of polymer; two cycles were performed consecutively.

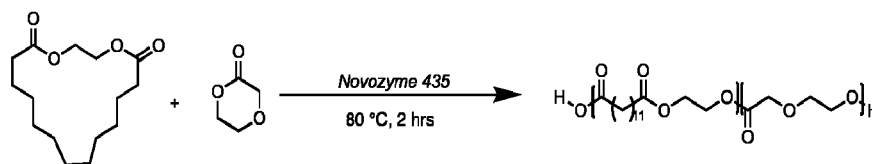
(ix) *Density measurements*

To determine density, polymer samples of ~200 mg were first massed with a Mettler Toledo XS205 DU balance with a resolution of 0.01 mg. Samples were then placed into a 1 cm³ chamber within the Micromeritics Accupyc II 1340 pycnometer, with helium as the gas for each fictive temperature characterized. Four measurements were performed for each sample. The standard deviation for the volume measurements by helium pycnometry is 0.001 cm³.

15 **Results**

(i) *Small-scale synthesis*

Scheme 2. One-pot copolymerization under solvent-free conditions using Novozyme 435 at 80°C for 2 hours.



20 The one-pot copolymerization of EB and DO proceeds under solvent-free conditions catalyzed by N435 (**Scheme 2**). Conversion versus time data were acquired using a 1:1 feed ratio of EB and DO. At room temperature, DO has poor solubility in EB; thus, heating the monomers prior to addition of the catalyst proved to be important for early incorporation of DO into the polymer. As the polymerization progressed, the reaction mixture became too viscous to stir and solidified around 30 minutes or when EB reached 50-60% conversion; the solidification of the reaction mixture explains the premature plateau in conversion for DO. In addition, the monomer equilibrium concentration ([M]_{eq}) for DO is 2.5 M, which could also explain why DO did not reach full conversion (A. Heise, C. Duxbury, A. Palmans, Enzyme-Mediated Ring-Opening Polymerization, in: P. Dubois, O. Coulembier, J.-M.

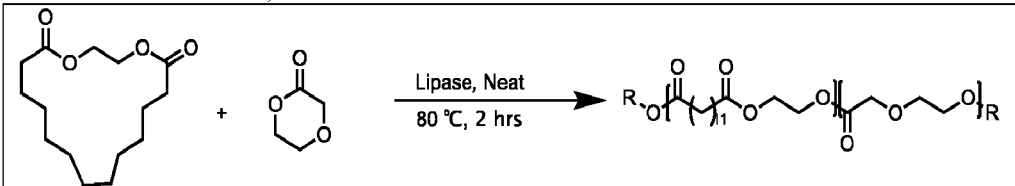
Raquez (Eds.), Handbook of Ring-Opening Polymerization 2009, pp. 379-397). The conversion versus time plot indicates the formation of a gradient block copolymer and reveals that after two hours, no further conversion of EB or DO is observed at 80°C.

5 Using the established time and temperature parameters, various monomer feed ratios and catalyst loadings were explored (**Tables 2 and 3**). The resulting polyesters possessed high weight-average molecular weights (M_w) and a broad scope of incorporation ratios. Changing the feed ratio resulted in polymers that had monomer incorporation ratios that suggest an
10 increased catalyst selectivity for EB. A feed ratio of 50:50 EB:DO yields a polymer with the incorporation ratio of 58:42 and a M_w of 71k with a 16.7% catalyst loading (entry 5, **Table 2**). Broad molecular weight distributions ($M_w/M_n > 2$) were observed, which are characteristic of solvent-free ROP due to the high viscosity of the macrolactone monomer that leads to an increase
15 in undesirable chain transfer reactions. The ^1H and ^{13}C NMR of poly(EB-co-DO) showed an incorporation ratio of 70:30.

 Analogous to a degree of polymerization (DP) screen, reactions with various amounts of enzyme were studied under the solvent-free copolymerization conditions for a 50:50 feed ratio of EB:DO at 80°C (**Table**
20 **3**). The 50:50 feed ratio achieved an incorporation ratio of approximately 60:40 with M_w values ranging from 49k to 72k g/mol. Cutting the amount of catalyst in half (**Table 3**; entries 1 and 2) resulted in the largest change in M_w (49k and 71k, respectively) and smaller differences in M_w were observed with 16.7 – 4.2 wt% catalyst loading (**Table 3**; entries 2-4). The DP or
25 lengths of the polymer chains were not directly controlled by the amount of enzyme present. The active site of CALB includes a Ser-His-Asp catalytic triad that is essential in initiation and formation of the enzyme activated monomer (EAM). A lactone enters the active site and undergoes nucleophilic attack by the terminal alcohol in the Ser residue; this step is widely accepted
30 as the rate determining step and forms the EAM. The amount of water in the active site plays a major role in polymer chain lengths and is responsible for hydrolysis and regeneration of the enzyme active site (EAS). Chain termination can occur through multiple pathways such as polycondensation, hydrolysis of the polymer chain end, or self-condensation to form cycles

(A.E. Polloni, V. Chiaradia, E.M. Figura, J. De Paoli, D. de Oliveira, J.V. de Oliveira, P.H.H. de Araujo, C. Sayer, Polyesters from Macrolactones Using Commercial Lipase NS 88011 and Novozym 435 as Biocatalysts, Appl Biochem Biotech 184(2) (2018) 659-672). The wide variety of termination mechanisms leads to the broad molecular weight distributions observed for this lipase-catalyzed copolymerization.

Table 2. Composition, molecular weight, and polydispersity for the lipase-catalyzed copolymerization of EB and DO with varying feed ratios (reactions were all conducted at 80°C).

						
Entry	EB:DO Feed Ratio ^a	Incorporation Ratio ^b	Amount of enzyme (mg enzyme/ mmol monomer)	M_n^c (g/mol)	M_w^c (g/mol)	PDI ^c
1	90:10	91:9	16.7	30,000	117,000	3.9
2	80:20	86:14	16.7	39,000	119,000	2.0
3	70:30	75:25	16.7	46,000	105,000	2.3
4	60:40	66:34	16.7	29,000	81,000	2.8
5	50:50	58:42	16.7	29,000	71,000	2.4
6	40:60	51:49	16.7	30,000	52,000	1.8

^a Total amount of monomer sums to 2 mmol ^b Incorporation ratio determined by ¹H-NMR. ^c M_w , M_n , and PDI determined by GPC in dichloromethane against polystyrene standards.

Table 3. Composition, molecular weight, and polydispersity for the lipase-catalyzed copolymerizations of EB and DO with varying catalyst loading

Entry	EB:DO Feed Ratio ^a	Incorporation Ratio ^b	Amount of enzyme (mg enzyme/ mmol monomer)	M_n^c (g/mol)	M_w^c (g/mol)	PDI ^c
1	50:50	55:45	33.4	27,000	49,000	1.8
2	50:50	58:42	16.7	29,000	71,000	2.4
3	50:50	62:38	11.4	31,000	66,000	2.1
4	50:50	64:36	4.2	25,000	72,000	2.9

^a Total amount of monomer sums to 2 mmol ^b Incorporation ratio determined by ¹H-NMR. ^c M_w , M_n , and PDI determined by GPC in dichloromethane against polystyrene standards.

(ii) *Large-scale synthesis reactions*

Having established suitable polymerization conditions for a small-scale, copolymerizations were carried out at a 25-g scale to explore the feasibility of large-scale production. Reactions were conducted in a nitrogen glove box equipped with a mechanical stirrer. One limitation of the large-scale synthesis was the hardening of the material and loss of stirring as the polymerization progressed when using a magnetic stir bar. Stirring with an overhead mechanical stirrer, however, allowed for continuous mixing of the contents of the flask throughout the two-hour polymerization. A conversion versus time plot for the large-scale reaction suggest a more random copolymerization (**FIGs. 9A** and **9B**). The reaction reaches a plateau in conversion at 250 minutes, after which the molecular weight and PDI remains constant. It is also noted that the %conversion looked constant after 100 mins with slight variations. The large-scale reactions resulted in random copolymers with number average molecular weights (M_n) ranging from 30k to 55k and broad molecular weight distributions (**Table 4**). The material from these large-scale reactions was used for implant fabrication.

Table 4. Composition, molecular weight, and polydispersity for the lipase-catalyzed copolymerization of EB and DO with varying feed ratios for large-scale polymer synthesis.

Polymer	EB:DO Feed Ratio ^a	Incorporation Ratio (EB:DO) ^b	Amount of enzyme (mg)	M_n^c (g/mol)	M_w^c (g/mol)	PDI ^c
1	100:0	100:0	150	52,000	23,000	1.8
2	100:0	100:0	200	40,000	19,000	2.1
3	90:10	93:7	200	45,000	23,000	1.9
4	75:25	80:20	200	37,000	18,000	2.1
5	50:50	60:40	200	32,000	17,000	1.8

^a Total amount of monomer sums to 2 mmol ^b Incorporation ratio determined by ¹H-NMR. ^c M_w , M_n , and PDI determined by GPC in dichloromethane against polystyrene standards.

20 (iii) *Implant fabrication, in vitro release, and polymer degradability*

A series of poly(EB-co-DO) copolymers—with varying DO contents and number average molecular weights (M_n) ranging from 30k to 55k—were

characterized and used for the fabrication of blank or drug-loaded implants (FIGs. 17A, 17B, and 17C). When characterized by thermogravimetric analysis (TGA), polymers with higher DO content degraded faster, with an onset of degradation at 170°C for a copolymer with 40% DO and 290°C for 20% DO. The DSC results showed a nonlinear decrease in the melting point T_m with increasing percentage of DO in the polymer backbone. Multiple melting peaks are seen in the DSC curves, suggesting that these polymers have a large number of crystalline populations that melt at different temperatures. Polymers of EB with $M_w < 90$ kg/mol have been shown to be more heterogeneous (J. Fernandez, et al. J Mech Behav Biomed Mater 64 (2016) 209-219). Furthermore, pycnometry revealed an increase in polymer density with increasing percentage of DO (FIG. 17C).

The poly(EB-co-DO) copolymers were used to produce 1-cm unloaded and drug-loaded implants according to an established melt-molding technique (W. Saltzman, et al, Biodegradable Contraceptive Implants, 2020.). Implants loaded with 28%, 35%, and 40% drug possessed a theoretical loading of 14 mg, 18 mg, and 20 mg, respectively. DEX-loaded implants were fabricated and characterized for polymer degradation, *in vitro* drug release, and overall internal morphology. DEX release was dependent on both drug loading and DO content of the polymer. Higher DEX loading led to increased cumulative and daily drug release rates (FIGs. 10A-10C, FIGs. 18A-18C). The first five days of the daily release profile also revealed a burst release, likely due to rapid release of DEX near the implant surface. In the higher loading implants, the burst release was as much as three times higher than daily release at later times (FIGs. 18A-18C). Higher DO content in the polymer also resulted in faster drug release rate and faster polymer degradation (FIG. 10C and FIGs. 11A-11D). The faster release in higher DO content materials may be a consequence of increased number of ester linkages, which arise due to the increased number of repeating units of DO at a given M_w . Increasing the number of ester linkages would thus result in faster polymer degradation via hydrolysis. Increased DO content in the polymer also results in increased hydrophilicity, which could also enhance the adsorption of water, therefore increasing the rate of hydrolysis (FIG.

11A). The loading of DEX in the implants did not significantly influence the rate of polymer degradation (FIGs. 11B and 11D).

Implants were produced with two alternate agents incorporated: LNG and DTG. Twenty-eight percent LNG-loaded or DTG-loaded implants were
5 fabricated with P4 (37k M_w , 20% DO). *In vitro* release profiles reveal a slower cumulative release for both LNG and DTG compared to DEX from comparable implants as well as a three-fold reduction in burst release rates, despite the same theoretical drug loading (FIGs. 12A-12F). These
differences in release are likely a consequence of the greater hydrophilicity
10 of DEX relative to LNG and DTG as reflected in their log P values: DEX (log P = 1.6-1.9) > DTG (log P = 2.2) > LNG (log P = 3.3) (FIGs. 12C-12F).

A mathematical model was used to better understand drug release profiles, to predict the *in vitro* release kinetics of DEX from poly(EB-co-DO)
15 implants over time periods beyond our experimental measurements, and to reveal the mechanism of controlled release in these implants. SEM images—as well as our experience of the handling implants after *in vitro* and *in vivo* exposure to release media—suggest that the implants remain mechanically strong throughout months of DEX release. Therefore, a stable continuous
20 polymer phase and a homogeneous distribution of drug dissolved in the polymer matrix was adopted; thus DEX release was modeled assuming Fickian diffusion with an effective diffusion coefficient representing DEX diffusion through the polymer matrix (Saltzman WM, Drug Delivery: Engineering principles for drug therapy, Oxford University Press (2001)).
25 Drug release from DEX-loaded implants were measured *in vitro* for 226 days; the models indicated that these implants will continue to release at a constant rate for at least another 275 days. Similar modeling of LNG and DTG release suggest that drug release for these drugs are comparable during the first 100 days but will likely deviate as time progresses. The model
30 suggests that by 500 days less than half of the drug theoretically incorporated into each implant (14 mg) will be released. However, these models do not account for polymer degradation and erosion of the implant matrix: the model is only valid so long as the implant is intact and Fickian diffusion persists. By day 226 of *in vitro* release, it was noticed that 5 of the 36 DEX-

loaded implants had started to physically erode, exposing millimeter-sized pores, with no clear trend with respect to drug loading or DO content.

The effective diffusion coefficients describing DEX release from poly(EB-co-DO) implants with varying drug loadings and DO content
 5 ranged from 1.1×10^{-8} to 9.0×10^{-9} cm²/sec (**Table 5**).

Table 5. Parameters resulting from mathematical diffusion model for *in vitro* release of DEX.

Polymer	Mn (g/mol)	DO incorporation	% Loading	Diffusion Coefficient (cm ² /sec)	RMSE (ug)
P1	52,000	0%	28	5.9×10^{-9}	162.9
P2	40,000	0%	28	1.3×10^{-9}	110.6
P2			35	2.7×10^{-9}	172.0
P2			40	6.3×10^{-9}	669.4
P3	45,000	7%	28	1.8×10^{-9}	233.7
P4	37,000	20%	28	3.7×10^{-9}	247.8
P4			35	6.5×10^{-9}	304.9
P4			40	9.0×10^{-9}	515.7
P5	32,000	40%	28	1.1×10^{-8}	318.0

The diffusion coefficients for DTG and LNG in these implants are similar in order of magnitude (**Table 6**).

10

Table 6. Parameters resulting from mathematical diffusion model for *in vitro* release of DEX, DTG, and LNG.

Drug	% Loading	Diffusion Coefficient (cm ² /sec)	RMSE (ug)
DEX	28	3.7×10^{-9}	247.8
DTG	28	1.7×10^{-9}	112.8
LNG	28	1.0×10^{-9}	98.7

Literature values for the diffusion coefficient of free DEX in in tissues has been found to be substantially higher ($2.0 - 6.8 \times 10^{-6}$ cm²/sec depending on the experimental conditions) (Y. Moussy, et al., Biotechnol
 15 Progr 22(6) (2006) 1715-1719; L. Hersh, Mathematical techniques for the estimation of the diffusion coefficient and elimination constant of agents in subcutaneous tissue, Physics, University of South Florida, 2007, p. 81). In water at 37°C, radiolabeled DEX in saline was found to have a diffusion

coefficient of $5.2 \times 10^{-6} \text{ cm}^2/\text{sec}$, whereas in porous ethylene-vinyl acetate copolymer (EVAc) implants with 35% DEX loading, the diffusion coefficient was four orders of magnitudes lower at $2.0 \times 10^{-10} \text{ cm}^2/\text{sec}$ (W.M. Saltzman, et al, Chem Eng Sci 46(10) (1991) 2429-2444). Results also indicate that the diffusion coefficient of DEX increases with increasing DO content, following an exponential relationship over the measured range of DO content.

(iv) *Mechanical testing*

Mechanical testing of DEX-loaded implants was performed to evaluate their suitability as an implanted medical device. Results from three-point bend tests and compression tests revealed variation in mechanical properties with implant drug loading and polymer composition (**FIGs. 13A-13D**). For both tests, the modulus and maximum force to fracture were not statistically different between unloaded and DEX-loaded implants (**FIGs. 13A-13D** and **FIGs. 19A-19D**). For each drug loading, implants with a greater percentage of DO monomer were mechanically weaker, with reduced flexural and compressive modulus and reduced flexural and compressive maximum force before fracture (**FIGs. 13A-13D** and **FIGs. 19A-19D**). This trend was also observed qualitatively in the polymers prior to implant fabrication, as the 40% DO polymer was noticeably softer and gummier compared to the 0% DO polymer during routine handling.

During compressive testing on 0% and 20% DO implants, higher drug loading increased the compressive modulus but had no statistically significant effect on the compressive maximum force before failure. For three-point testing on 20% DO implants, increasing drug loading had no statistically significant effect on flexural modulus or flexural maximum force before failure. On the other hand, for 0% DO implants, increasing drug loading decreased both the flexural modulus and flexural maximum force before failure. The addition of drug to these implants effects mechanical strength in ways that are not yet predictable.

To examine mechanical strength after a period of degradation, implants from each group were sacrificed at Day 56 and Day 112 of *in vitro* release to determine flexural modulus and maximum force before failure. As expected, the flexural strength generally decreased over time, a feature likely

attributed to increased porosity in implant microstructure as the polymer degrades and drug is released.

The mechanical strength of these implants is relevant as, in a clinical application, the implants must withstand mechanical forces from within the user's tissue on a continual basis. Although the main advantage of biodegradable contraceptive implants compared to commercial implants is the convenience of not needing an excision procedure, implants must remain structurally intact throughout use and they must be mechanically strong enough to survive a removal procedure, if needed during the use period. In clinical trials, the tensile integrity of implants is assessed by comparing implant breaking rates to that of other contraceptive implants. For instance, researchers noted a significantly higher breakage rate of LNG-releasing Sino-implants (II) compared to Jadelle® implants (16.3% vs 3.1%) during removal procedures (M.J. Steiner, et al., Randomized trial to evaluate contraceptive efficacy, safety and acceptability of a two-rod contraceptive implant over 4 years in the Dominican Republic, *Contracept X* 1 (2019) 100006). Determining the ease of implant removal from mice models is an obvious next step to assess implant tensile strength *in vivo*.

(v) *SEM imaging*

To better understand the effect on drug loading and DO content on internal microstructure of the implant during various stages of drug release, SEM images of cross sections of unloaded and DEX-loaded implants were examined. Among unloaded poly(EB-co-DO) implants, cross-sections of implants with 0, 7 or 20% DO appeared brittle and firm, as illustrated by the sharp ridges of the image. On the other hand, cross sections of the 40% DO implant appears softer in texture, as noted by the rounded edges (**FIG. 14**). These images corroborate the mechanical testing results that revealed greater compressive and flexural strength among implants with lower DO content. Cross-sections of DEX-loaded poly(EB-co-DO) implants reveal crystalline drug structures, identified by their distinct, cuboid-shaped protrusions. Compared to month 0, SEM images of cross-sections at months 2 and 4 reveal greater porosity in implants with 0-40% DO, irrespective of drug loading (**FIG. 15**, **FIG. 20**, and **FIG. 21**).

(vi) *Biocompatibility study*

To examine tissue responses and *in vivo* degradation of these implants, unloaded 20% DO implants (P4) were used and examined histological sections and polymer properties over a period of 8 months after subcutaneous implantation. Implants of ~10 to 15 mg were implanted in the subdermal layer of 16 mice. Three implants were extracted every two months; half of the implants were used for histological examination while the other half were used to characterize the polymer using GPC and NMR (**FIGs. 16A and 16B**). Histology results demonstrate an increase in encapsulation thickness to ~75 μm during the first four months, after which the encapsulation thickness remained constant (**FIG. 16A**). This encapsulation layer is much less thick than described in comparable experiments with PLGA and PLA implants: Previous studies with PLGA implants in mice showed an encapsulation thickness of greater than 100 μm within 7 to 60 days of implantation. Another study with PLA implants shows an encapsulation thickness of ~300 μm . GPC results indicate that the Mw of the polymer decreased from 37 kg/mol to 10 kg/mol within a period of 4 months and then remained constant from month 4 to month 8 (**FIG. 16B**). This decrease in Mw (73%) during the first four months is slightly less than observed *in vitro* degradation, where there was an 84% decrease in Mw after four months of incubation in PBS buffer at 37°C. However, these results may not be comparable given that the starting Mw of the *in vitro* degradation study was slightly lower, at 29 kg/mol. This trend can likely be attributed to the highly degradable PDO polymeric segments of the copolymer. In terms of structural integrity of the implants, the implants appeared intact at 8 months and were firm enough to be picked up by tweezers without damage to the implant.

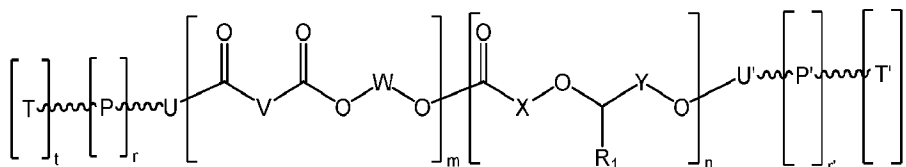
In sum, copolymerization reactions were conducted with EB and DO, resulting in reproducible production of poly(EB-co-DO) by enzyme-catalyzed ROP. These reactions were scaled up to produce an array of polymers with varying DO contents. These copolymers were used for the fabrication of rod-shaped biodegradable implants, which were successfully loaded with either DEX, LNG, and DTG. Drug release rates and implant mechanical properties depended on monomer content, polymer molecular

weight, and drug loading, demonstrating that these implants can be tuned for desired properties of release and degradation. The poly(EB-co-DO) implants are well tolerated after subcutaneous implantation in mice, demonstrating their suitability for safe use for long-term drug release.

- 5 Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

We claim:

1. A polymer having a structure:



Formula I

wherein:

m and n are independently integers from 1 to 1500,

r, r', t, t' are independently integers from 0 to 1500,

P and P' comprise a hydrophilic polymer segment,

T and T' comprise a targeting moiety,

U and U' are independently absent, -O-, -S-, NRu, -C(O)-, -C(O)O-, or -C(O)NRu-,

R₁ and Ru are independently hydrogen, substituted alkyl, unsubstituted alkyl, substituted alkenyl, unsubstituted alkenyl, substituted alkynyl, unsubstituted alkynyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, substituted polyaryl, unsubstituted polyaryl, substituted polyheteroaryl, unsubstituted polyheteroaryl, substituted C₃-C₂₀ cycloalkyl, unsubstituted C₃-C₂₀ cycloalkyl, substituted C₁-C₂₀ heterocyclyl, unsubstituted C₁-C₂₀ heterocyclyl, substituted C₃-C₂₀ cycloalkenyl, unsubstituted C₃-C₂₀ cycloalkenyl, substituted C₃-C₂₀ cycloalkynyl, unsubstituted C₃-C₂₀ cycloalkynyl, substituted polyheteroaralkyl, unsubstituted polyheteroaralkyl, substituted polyaralkyl, unsubstituted polyaralkyl, substituted aralkyl, unsubstituted aralkyl, hydroxyl, substituted carbonyl, unsubstituted carbonyl, substituted thiocarbonyl, unsubstituted thiocarbonyl, substituted alkoxy, unsubstituted alkoxy, substituted phosphoryl, unsubstituted phosphoryl, substituted phosphate, unsubstituted phosphate, substituted phosphonate, unsubstituted phosphonate, substituted phosphinate, unsubstituted phosphinate, substituted amino, unsubstituted amino, substituted amido, unsubstituted amido, substituted amidine, unsubstituted amidine, substituted imine, unsubstituted imine, cyano, nitro, azido, thiol, substituted alkylthio, unsubstituted alkylthio, substituted sulfate, unsubstituted sulfate, substituted

sulfonate, unsubstituted sulfonate, substituted sulfamoyl, unsubstituted sulfamoyl, substituted sulfonamido, unsubstituted sulfonamido, substituted sulfonyl, or unsubstituted sulfonyl,

V, W, X, and Y are independently substituted alkyl, unsubstituted alkyl, unsubstituted alkylene, substituted alkenyl, unsubstituted alkenyl, substituted alkynyl, unsubstituted alkynyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, substituted polyaryl, unsubstituted polyaryl, substituted polyheteroaryl, unsubstituted polyheteroaryl, substituted C₃-C₂₀ cycloalkyl, unsubstituted C₃-C₂₀ cycloalkyl, substituted C₁-C₂₀ heterocyclyl, unsubstituted C₁-C₂₀ heterocyclyl, substituted C₃-C₂₀ cycloalkenyl, unsubstituted C₃-C₂₀ cycloalkenyl, substituted C₃-C₂₀ cycloalkynyl, unsubstituted C₃-C₂₀ cycloalkynyl, substituted polyheteroaryl, unsubstituted polyheteroaryl, substituted polyaralkyl, unsubstituted polyaralkyl, substituted aralkyl, unsubstituted aralkyl, or fused combinations thereof, with the proviso that V, W, X, and Y are each at least divalent (such as bonded to at least two non-hydrogen atoms), and

wherein the polymer is not (i) poly(ethylene brassylate-*co*-D,L-lactide); (ii) poly(ethylene brassylate-*co*-hexalactone) or poly(ethylene brassylate-*co*- δ -hexalactone); (iii) poly(ethylene brassylate-*co*- ϵ -caprolactone); or (iv) poly(ethylene brassylate-*co*-squaric acid).

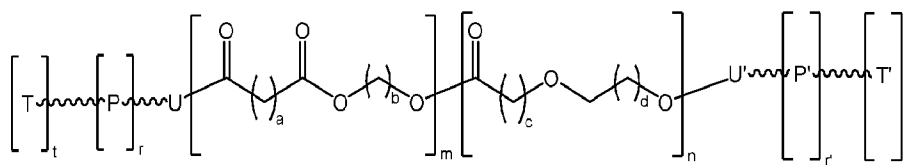
2. The polymer of claim 1, wherein Ru, when present, and R₁ are independently hydrogen, substituted alkyl, unsubstituted alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, substituted polyaryl, unsubstituted polyaryl, substituted polyheteroaryl, unsubstituted polyheteroaryl, substituted C₃-C₂₀ cycloalkyl, or unsubstituted C₃-C₂₀ cycloalkyl.

3. The polymer of claim 1 or 2, wherein Ru, when present, and R₁ are independently hydrogen, substituted alkyl, unsubstituted alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, substituted polyaryl, unsubstituted polyaryl, substituted polyheteroaryl, or unsubstituted polyheteroaryl.

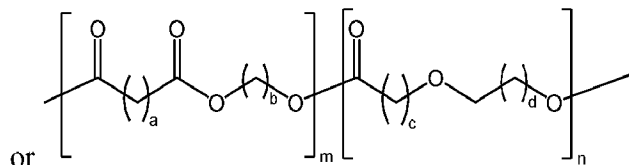
4. The polymer of any one of claims 1 to 3, wherein Ru, when present, and R₁ are independently hydrogen, substituted alkyl, or unsubstituted alkyl.

5. The polymer of any one of claims 1 to 4, wherein Ru, when present, and R₁ are hydrogen.
6. The polymer of any one of claims 1 to 5, wherein V, W, X, and Y are independently substituted alkyl, unsubstituted alkyl, unsubstituted alkylene, substituted alkenyl, unsubstituted alkenyl, substituted alkynyl, unsubstituted alkynyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, substituted C₃-C₂₀ cycloalkyl, unsubstituted C₃-C₂₀ cycloalkyl, substituted C₁-C₂₀ heterocyclyl, unsubstituted C₁-C₂₀ heterocyclyl, substituted C₃-C₂₀ cycloalkenyl, unsubstituted C₃-C₂₀ cycloalkenyl, substituted C₃-C₂₀ cycloalkynyl, unsubstituted C₃-C₂₀ cycloalkynyl, or fused combinations thereof, with the proviso that V, W, X, and Y are each at least divalent (such as bonded to at least two non-hydrogen atoms).
7. The polymer of any one of claims 1 to 6, wherein V, W, X, and Y are independently substituted alkyl, unsubstituted alkyl, unsubstituted alkylene, substituted alkenyl, unsubstituted alkenyl, substituted alkynyl, unsubstituted alkynyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, or fused combinations thereof, with the proviso that V, W, X, and Y are each at least divalent (such as bonded to at least two non-hydrogen atoms).
8. The polymer of any one of claims 1 to 7, wherein V, W, X, and Y are independently substituted alkyl, unsubstituted alkyl, unsubstituted alkylene, substituted alkenyl, unsubstituted alkenyl, substituted alkynyl, unsubstituted alkynyl, with the proviso that V, W, X, and Y are each at least divalent (such as bonded to at least two non-hydrogen atoms).
9. The polymer of any one of claims 1 to 8, wherein V, W, X, and Y are independently substituted alkyl, unsubstituted alkyl, unsubstituted alkylene, with the proviso that V, W, X, and Y are each at least divalent (such as bonded to at least two non-hydrogen atoms).

10. The polymer of any one of claims 1 to 9, having a structure:



Formula II



Formula II'

wherein:

a, b, c, and d are independently integers from 1 to 20, such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, preferably a is an integer from 1 to 15, 5 to 15, or 10 to 15, such as 11, b is an integer from 1 to 10, or 1 to 5, such as 2, c is an integer from 1 to 10, or 1 to 5, such as 1, and d is an integer from 1 to 10, or 1 to 5, such as 2.

11. The polymer of any one of claims 1 to 10, wherein P and P' when present, independently comprise comprises polyalkylene glycols and polyalkylene oxides such as poly(ethylene glycol); polysaccharides such as celluloses, alginates, glucosaminoglycans, and dextrans; hydrophilic polypeptides and poly(amino acids) such as poly-L-glutamic acid, gamma-polyglutamic acid, poly-L-aspartic acid, and poly-L-serine; poly(oxyethylated polyol); poly(olefinic alcohol) such as poly(vinyl alcohol) and aminoacetalized poly(vinyl alcohol); poly(N-vinylpyrrolidone); acrylic or acrylate, and alkacrylic or alkacrylate polymers such as poly(acrylic acid), poly(methacrylic acid), poly(hydroxyethyl acrylate); poly(N,N-dimethylaminoethyl methacrylate), poly(hydroxyalkyl methacrylate) e.g. poly(hydroxyethyl methacrylate); acrylamide polymers such as poly(acrylamide), poly(hydroxyalkyl methacrylamide), e.g., poly(hydroxyethyl methacrylamide); and poly(4-vinylpyridine); and copolymers thereof.

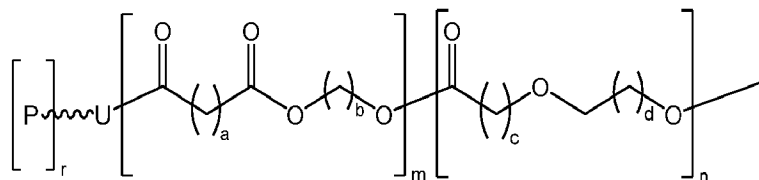
12. The polymer of any one of claims 1 to 11, wherein P and P' when present, independently comprise polyalkylene glycols and polyalkylene oxides such as PEG.

13. The polymer of any one of claims 1 to 12, wherein T and T' when present are independently a protein, peptide, glycoprotein, aptamer, carbohydrate, or small molecule.

14. The polymer of any one of claims 1 to 13, wherein:

- (i) U' is absent,
- (ii) P' is absent,
- (iii) T' is absent, or
- (iv) U', P', and T' are absent.

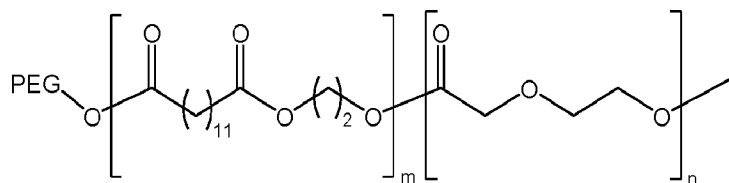
15. The polymer of any one of claims 1 to 14, having a structure:



Formula III

16. The polymer of any one of claims 1 to 15, wherein U is -O-.

17. The polymer of claim 16, having a structure:



Formula IV

18. The polymer of any one of claims 1 to 17, having a weight-average molecular weight between about 2 kDa and about 1 Mda, between about 2 kDa and about 750 kDa, between about 2 kDa and about 500 kDa, between about 2 kDa and about 250 kDa, or between about 2 kDa and about 100 kDa, between about 2 kDa and about 60 kDa, between about 5 kDa and about 60 kDa, between about 10 kDa and about 60 kDa, between about 2 kDa and about 25 kDa, between about 5 kDa and about 25 kDa, between about 10 kDa and about 25 kDa, or between about 15 kDa and about 25 kDa, such as about 20 kDa, as measured using gel permeation chromatography.

19. The polymer of any one of claims 1 to 17, having a weight-average molecular weight between about 10 kDa and about 150 kDa, between about 10 kDa and about 130 kDa, or between about 10 kDa and about 125 kDa, as measured using gel permeation chromatography, such as between about 15

kDa and about 25 kDa, between about 45 kDa and about 72 kDa, and between about 50 kDa and about 125 kDa.

20. The polymer of any one of claims 1 to 18, having a mole ratio of ethylene brassylate:dioxanone residues between about 95:5 and about 5:95, or between about 95:5 and about 50:50, as determined using ¹H-NMR.

21. Particles or macroimplants comprising the polymers of any one of claims 1 to 20 and one or more therapeutic, prophylactic, or diagnostic agents.

22. The particles or macroimplants of claim 21, wherein:

- (i) the particles are nanoparticles, or
- (ii) the macroimplants have a dimension between 1 mm and 5 cm.

23. The particles or macroimplants of claim 21 or 22, wherein:

- (i) the particles have an average diameter from about 50 nm to about 500 nm, about 50 nm to about 400 nm, about 50 nm to about 300 nm, or about 50 nm to about 250 nm, preferably between about 50 nm and about 250 nm as measured using dynamic light scattering or scanning electron microscopy, or
- (ii) the macroimplants have a length between 0.5 cm and 2 cm, and a diameter between 1 mm and 2.5 mm.

24. The particles or macroimplants of any one of claims 21 to 23, wherein the one or more therapeutic, prophylactic, or diagnostic agents comprise small molecule drugs (such as small molecule chemotherapeutic drugs; anti-inflammatories (*e.g.*, dexamethasone), progestins (*e.g.*, levonorgestrel), or integrase inhibitors (*e.g.*, dolutegravir), between 100 Da and 2,500 Da); proteins; nucleic acids, such as mRNAs, siRNAs, miRNAs, ribozymes, triplex forming molecules, sgRNAs, or DNAs; ribonucleoproteins; or a combination thereof.

25. The particles or macroimplants of any one of claims 21 to 24, wherein the therapeutic agents comprise chemotherapeutic agents.

26. The particles or macroimplants of claim 25, wherein the chemotherapeutic agents comprise alkylating agents (*e.g.*, DNA alkylators), DNA damage response inhibitors, antimetabolites, anthracyclines, plant alkaloids, topoisomerase inhibitors, monoclonal antibodies, antitumor

antibiotics, biologic response modifiers, histone deacetylase inhibitors, hormonal agents, protein kinase inhibitors, taxanes, or combinations thereof.

27. The particles or macroimplants of claim 25 or 26, wherein the chemotherapeutic agent comprises alkylating agents (*e.g.*, DNA alkylators); DNA damage response inhibitors (such as PARP inhibitors or analogs thereof, ATR inhibitors or analogs thereof); or combinations thereof.

28. The particles or macroimplants of any one of claims 21 to 27, constituting from about 0.01% wt/wt to about 60% wt/wt, about 0.01% wt/wt to about 55% wt/wt, about 0.01% wt/wt to about 50% wt/wt, about 0.01% wt/wt to about 45% wt/wt, about 0.01% wt/wt to about 40% wt/wt, about 0.01% wt/wt to about 35% wt/wt, about 0.01% wt/wt to about 30% wt/wt, about 0.01% wt/wt to about 25% wt/wt, about 0.01% wt/wt to about 20% wt/wt, about 0.01% wt/wt to about 10% wt/wt, about 0.01% wt/wt to about 5% wt/wt, about 0.5% wt/wt to about 5% wt/wt, the therapeutic, prophylactic, or diagnostic agents.

29. The particles of any one of claims 21 to 28, having a zeta potential between about -50 mV and +10 mV.

30. A pharmaceutical composition comprising the particles or macroimplants of any one of claims 21 to 29 and a pharmaceutically acceptable carrier.

31. A method of administering one or more therapeutic, prophylactic, or diagnostic agents to a subject in need thereof, the method comprising administering the particles or macroimplants of any of claims 21 to 29, or the composition of claim 30 to the subject.

32. The method of claim 31, wherein the particles, macroimplants, or composition are administered parenterally (such as intracranially such as intracranial convection enhanced delivery of the particles) or enterally.

33. The method of claim 31 or 32, wherein the particles, macroimplants, or composition are co-administered with a second therapeutic agent, prophylactic agent, diagnostic agent, or a combination thereof.

34. The method of claim 33, wherein co-administration is concurrently, sequentially, or a combination thereof.

35. The method of claim 33 or 34, wherein the second therapeutic agent, prophylactic agent, diagnostic agent, or a combination thereof, is not encapsulated, encapsulated, or a combination thereof.

36. The method of any one of claims 33 to 35, wherein the second therapeutic agent comprises chemotherapeutic agents comprising alkylating agents, DNA damage response inhibitors, antimetabolites, anthracyclines, plant alkaloids, topoisomerase inhibitors, monoclonal antibodies, antitumor antibiotics, biologic response modifiers, histone deacetylase inhibitors, hormonal agents, protein kinase inhibitors, taxanes, or combinations thereof.

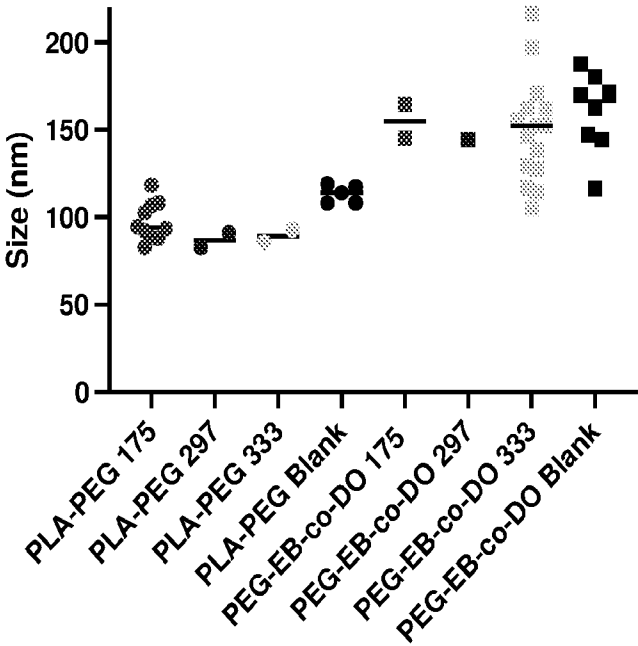


FIG. 1A

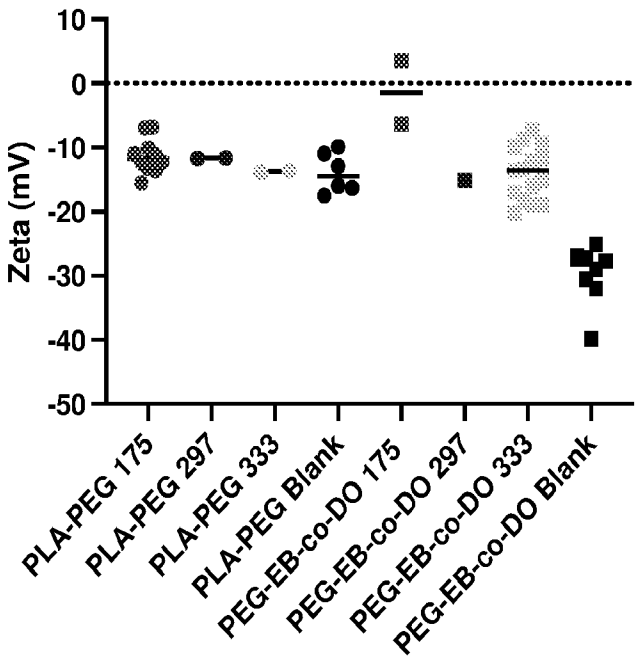


FIG. 1B

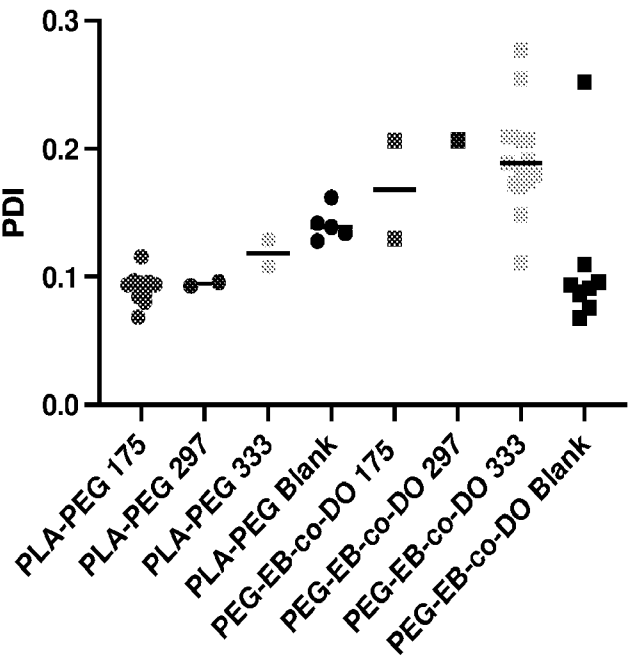


FIG. 1C

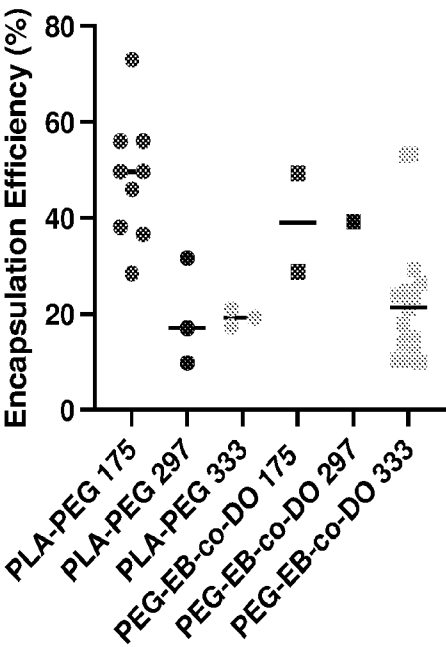


FIG. 2A

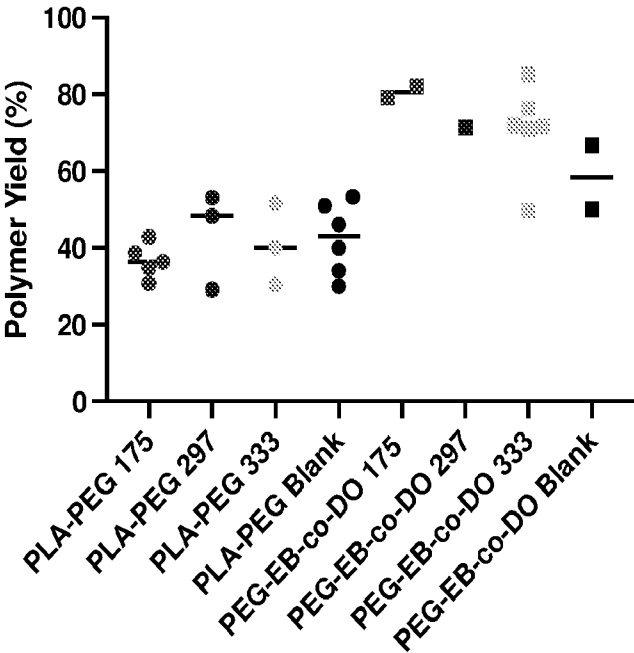


FIG. 2B

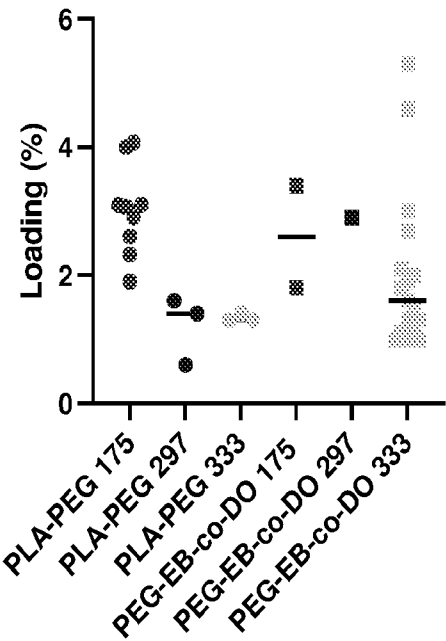


FIG. 2C

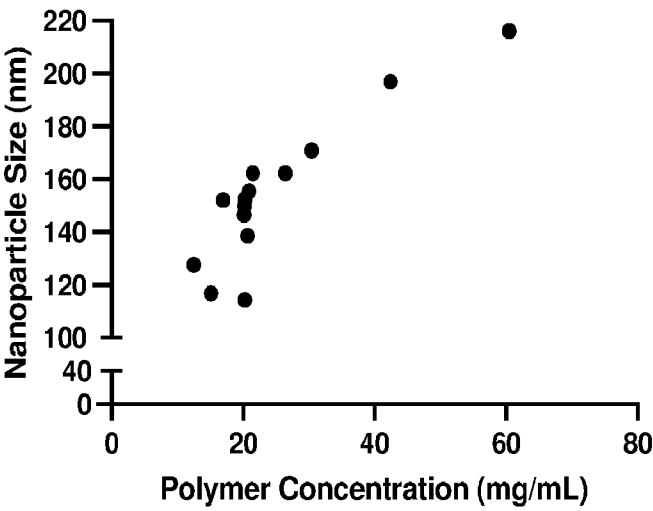


FIG. 3

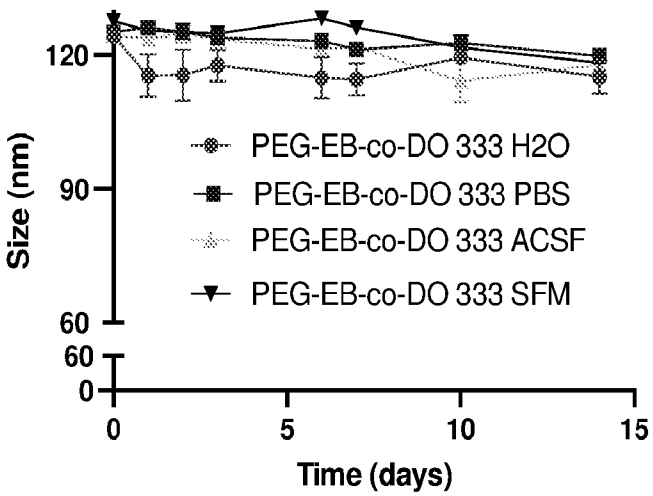


FIG. 4A

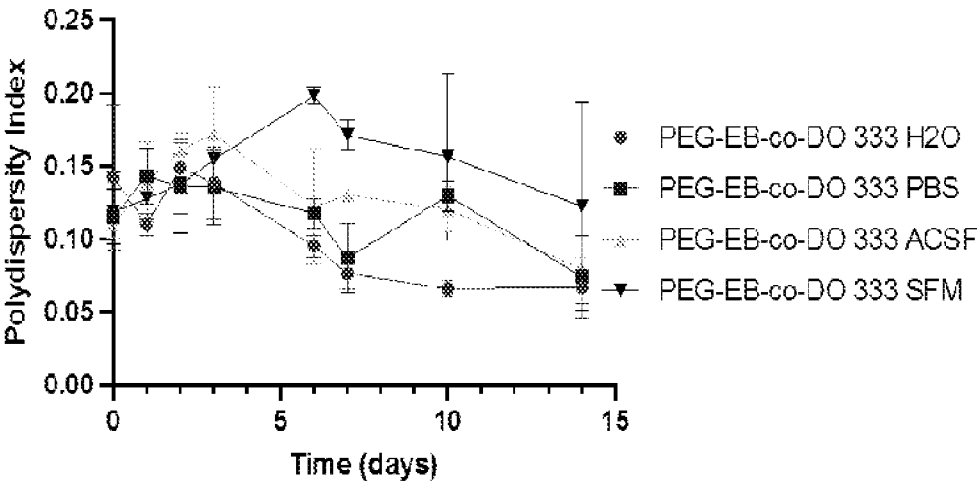
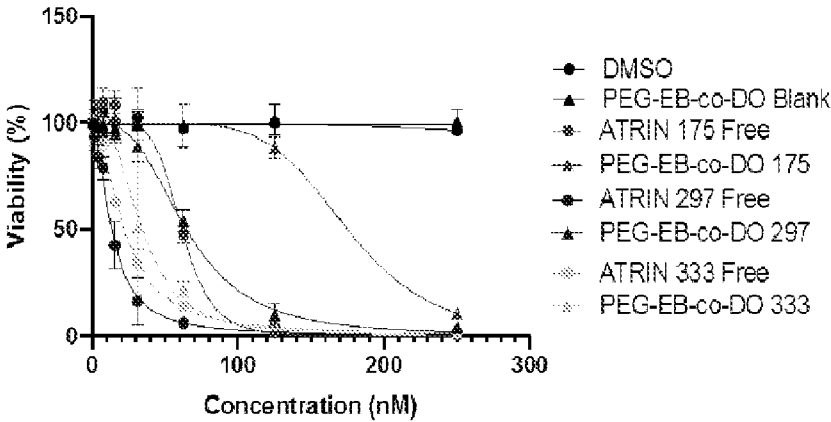


FIG. 4B



Drug	LogP	MW	Free Drug IC50 (nM)	NP LD50 (nM)
175	3.3	552.69	61.55	175.1
297	2.4	567.71	13.54	64.64
333	2.8	593.74	22.16	34.48

FIG. 5

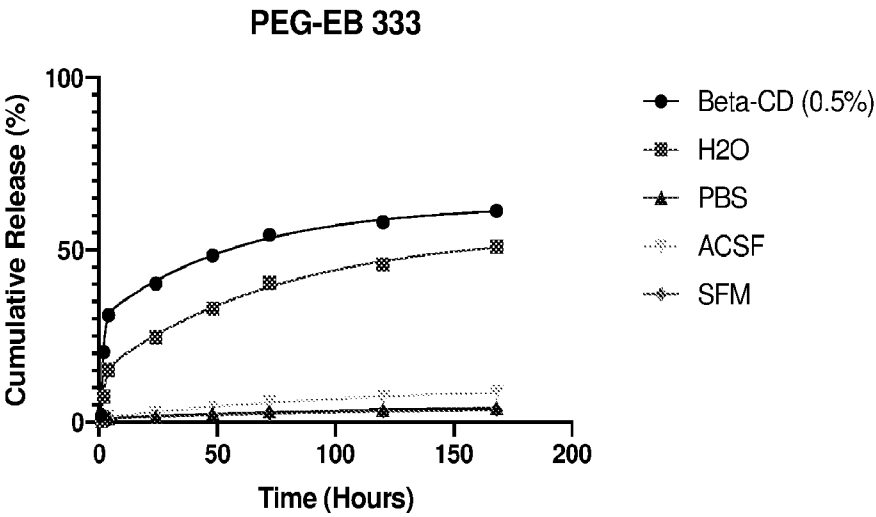


FIG. 6

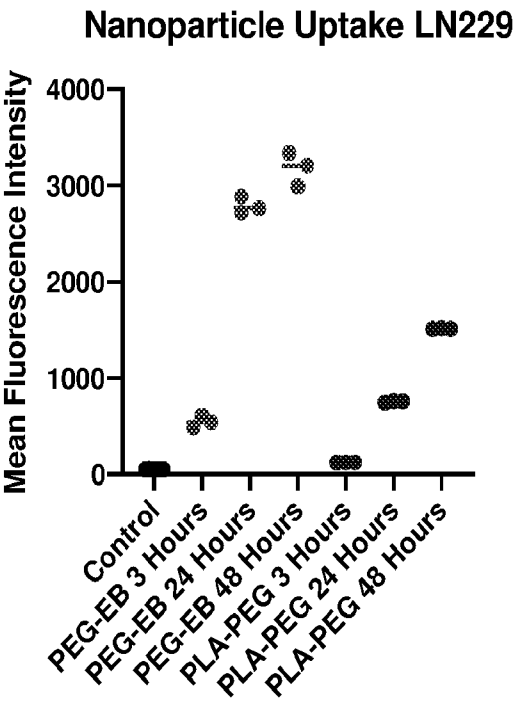


FIG. 7A

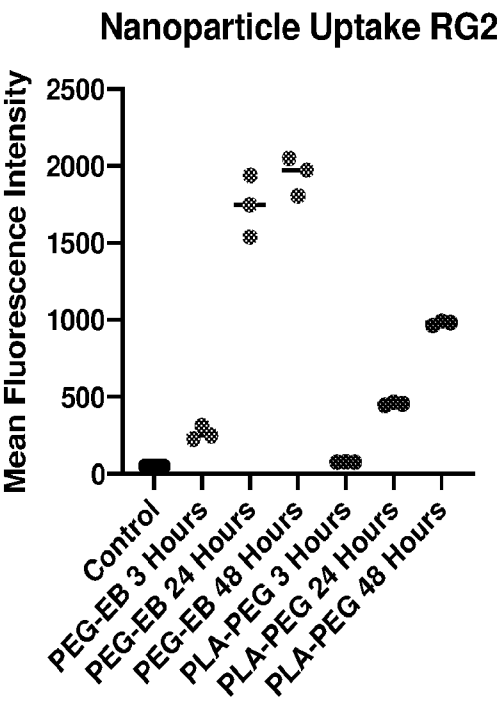


FIG. 7B

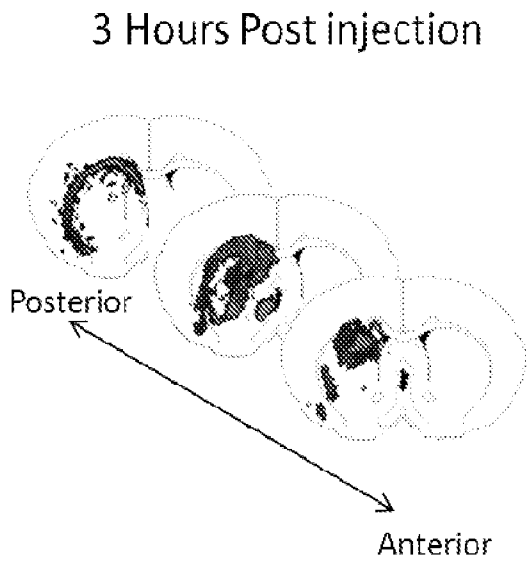


FIG. 8A

24 Hours Post injection

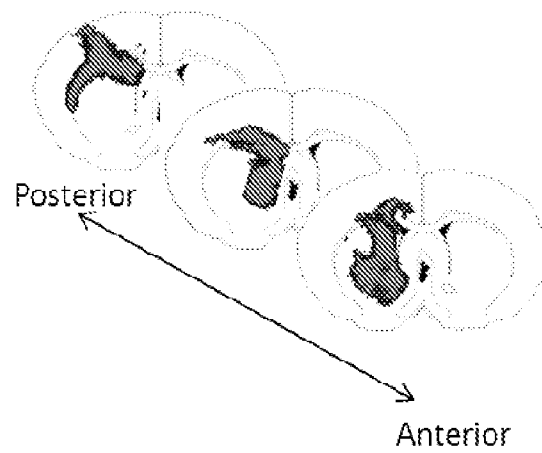


FIG. 8B

5 Days Post injection

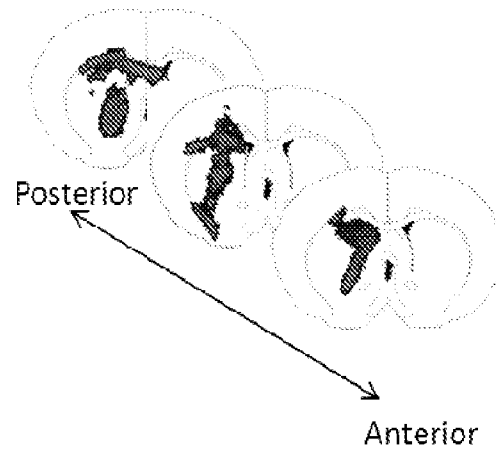


FIG. 8C

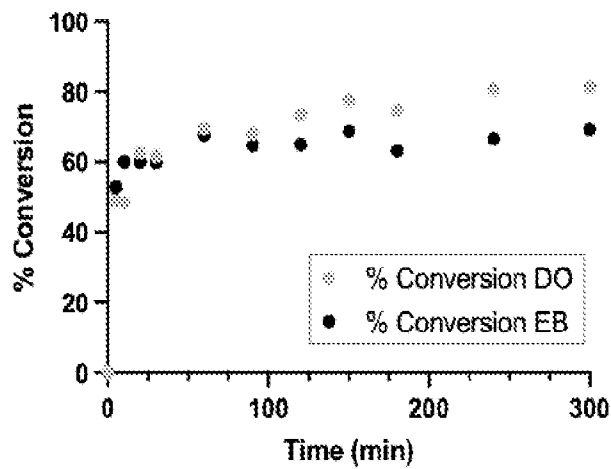


FIG. 9A

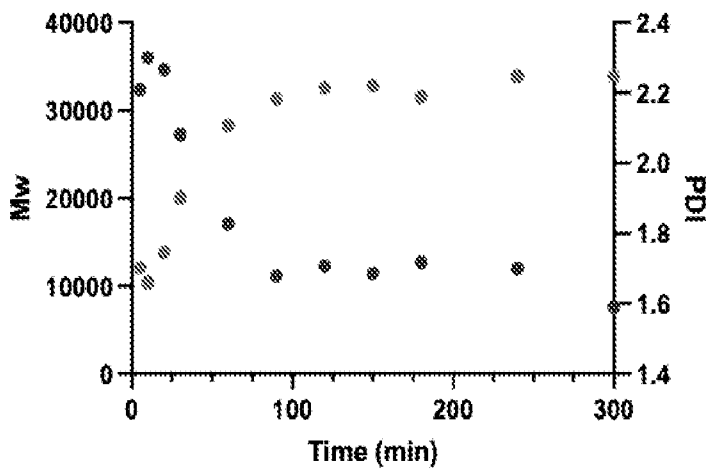


FIG. 9B

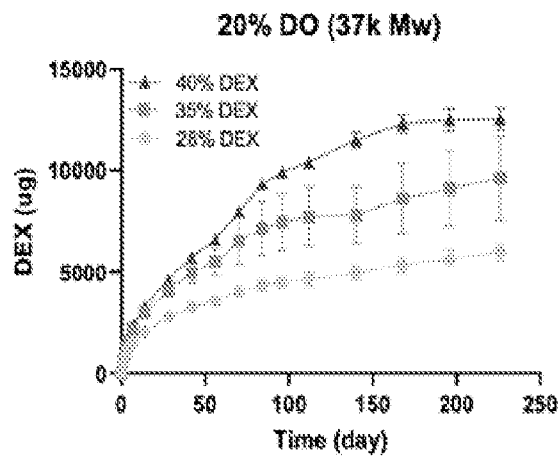


FIG. 10A

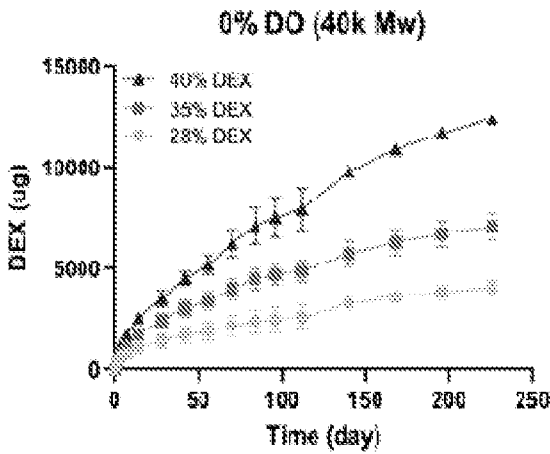


FIG. 10B

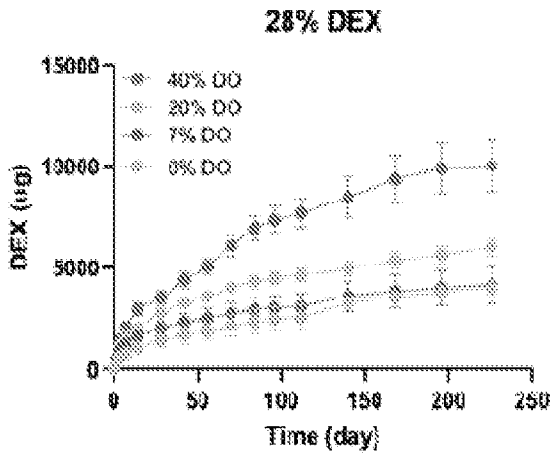
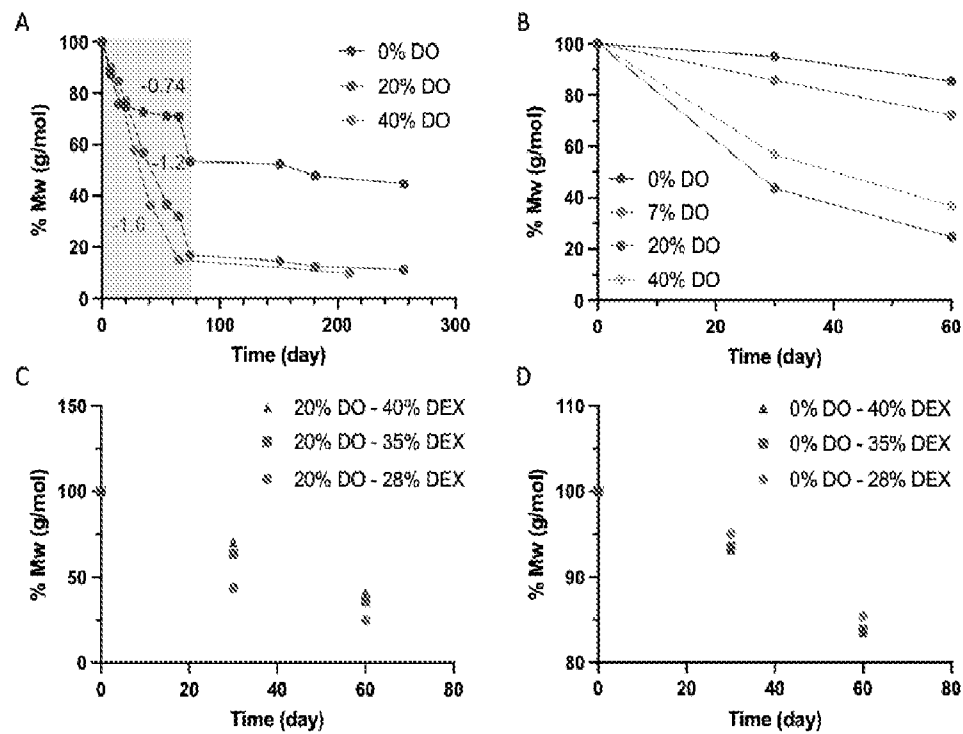
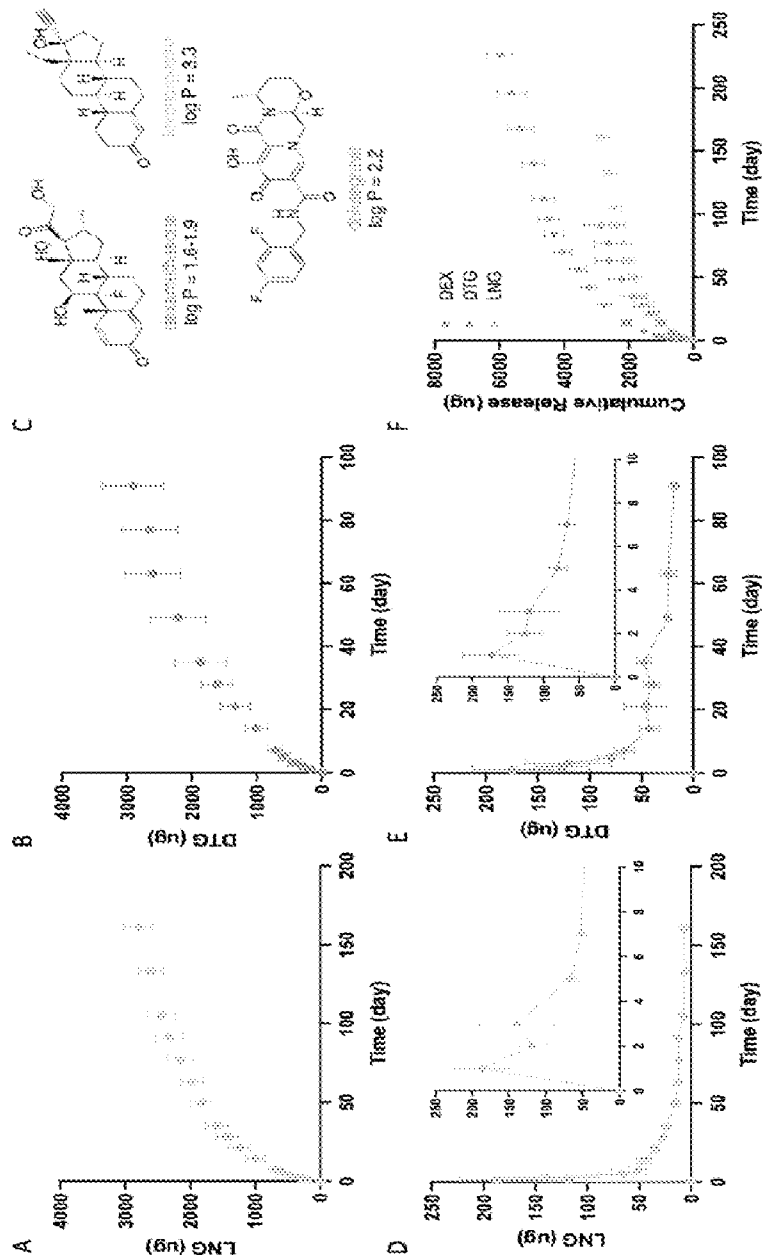


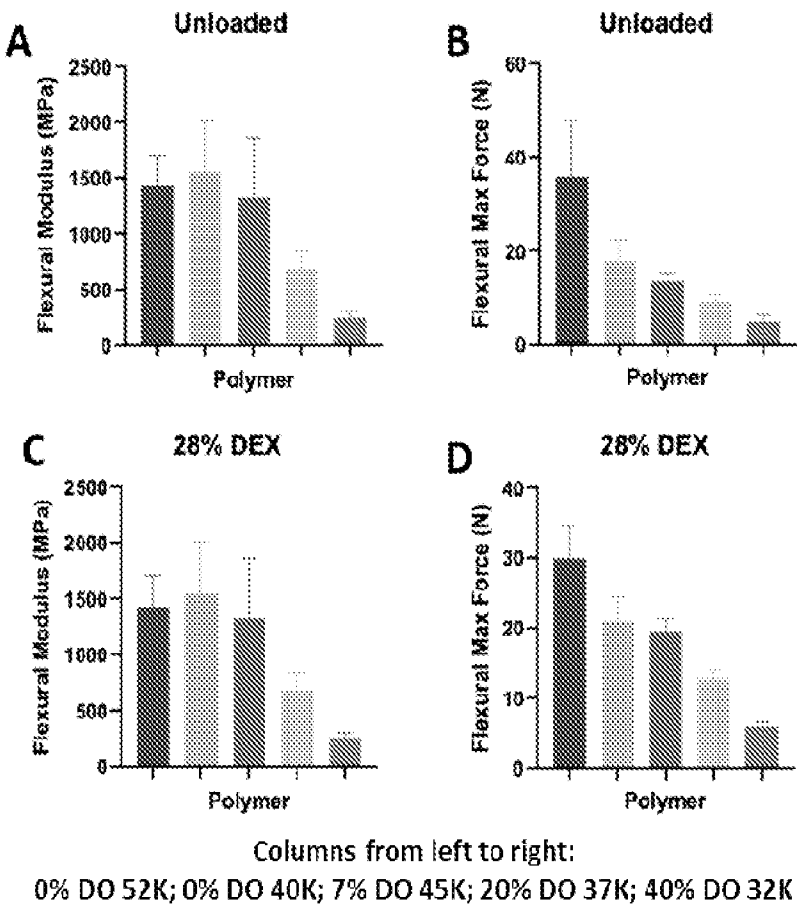
FIG. 10C



FIGs. 11A-11D



FIGS. 12A-12F



FIGs. 13A-13D

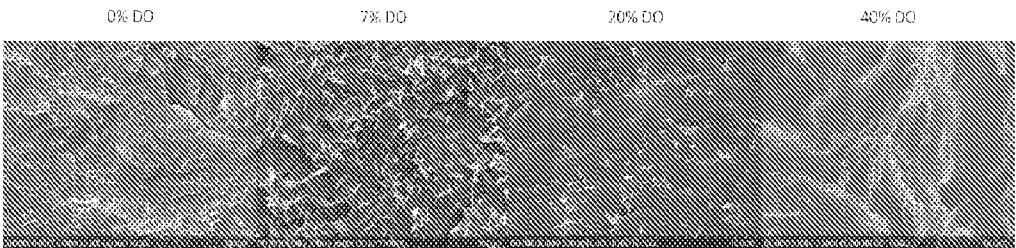


FIG. 14

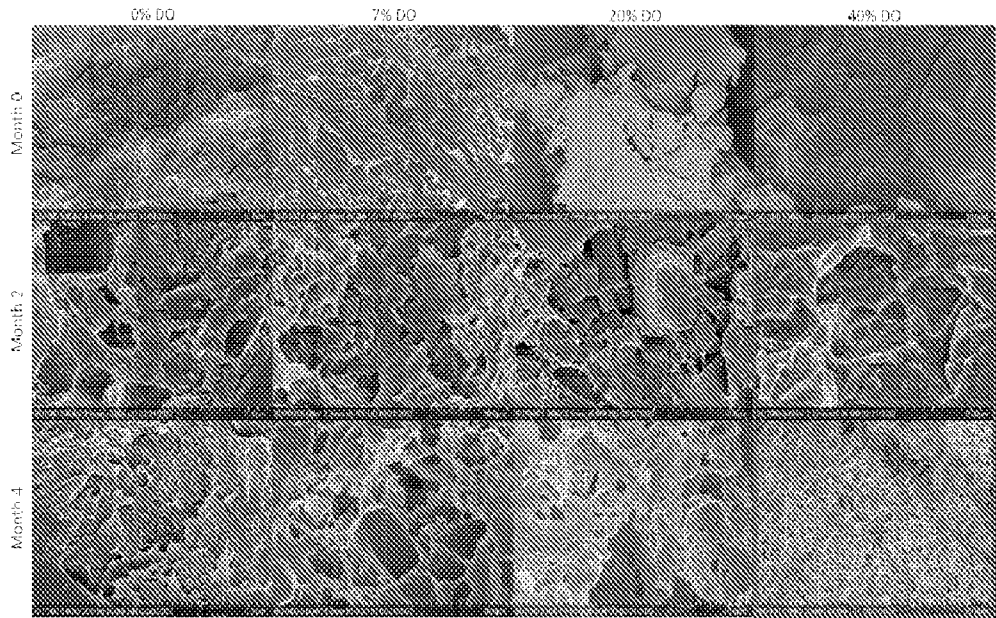


FIG. 15

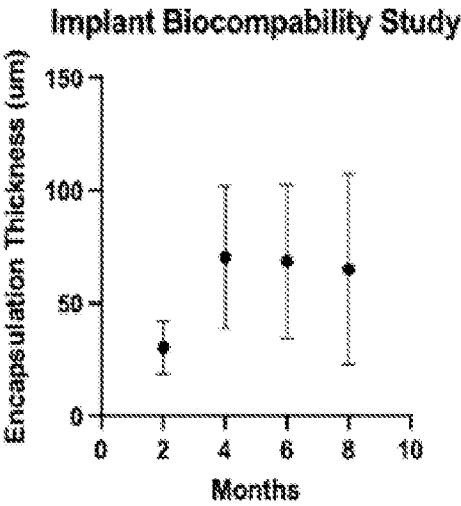


FIG. 16A

Month	M_w (g/mol)	PDI
0	37,000	2.1
2	N/A	N/A
4	9,940	2.4
6	9,216	1.8
8	8,997	1.7

FIG. 16B

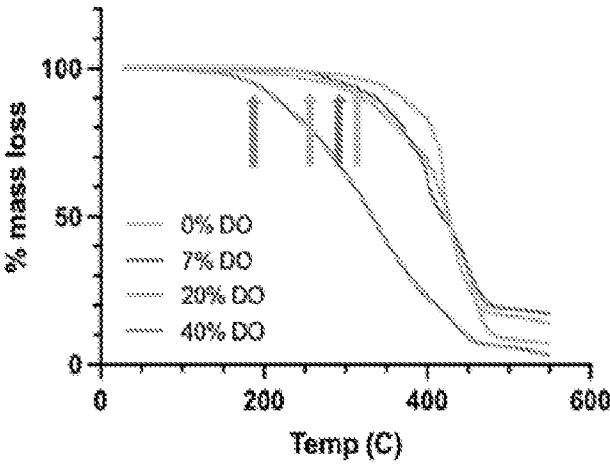


FIG. 17A

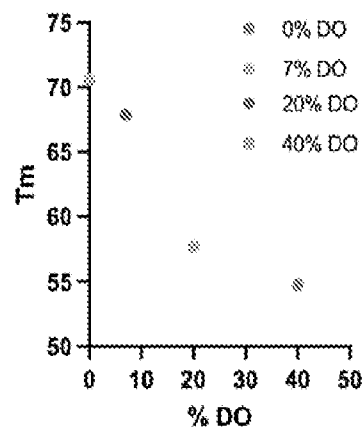


FIG. 17B

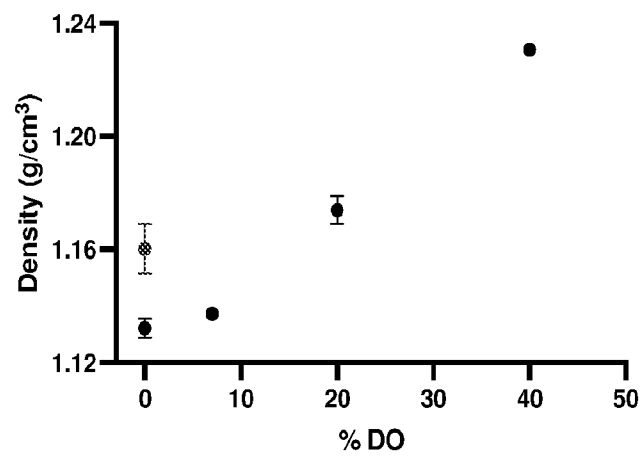
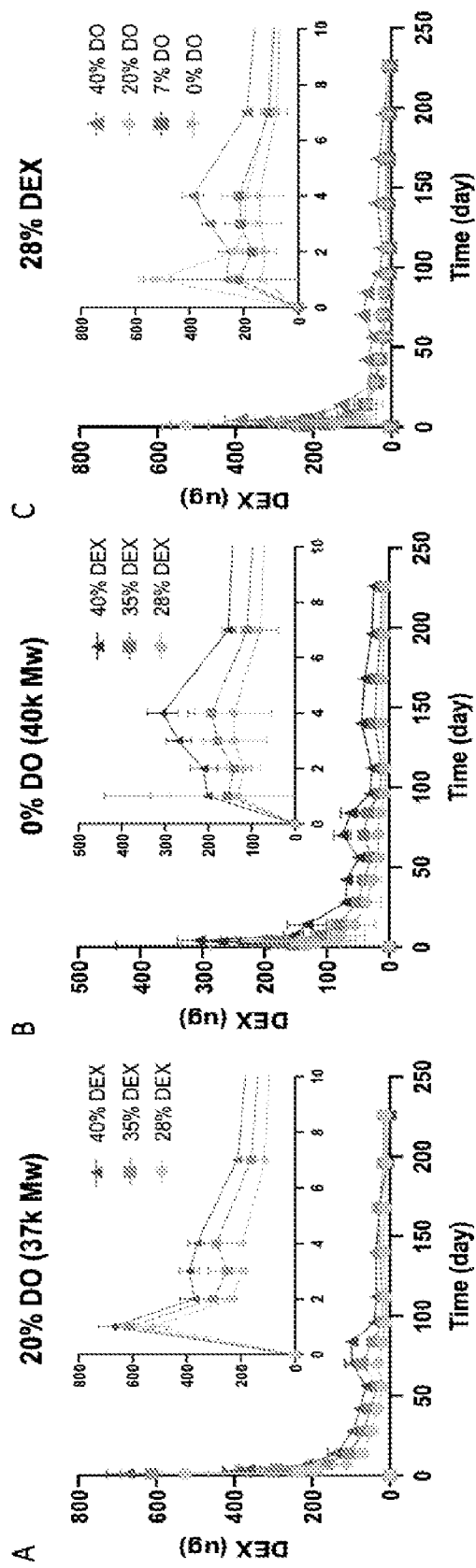
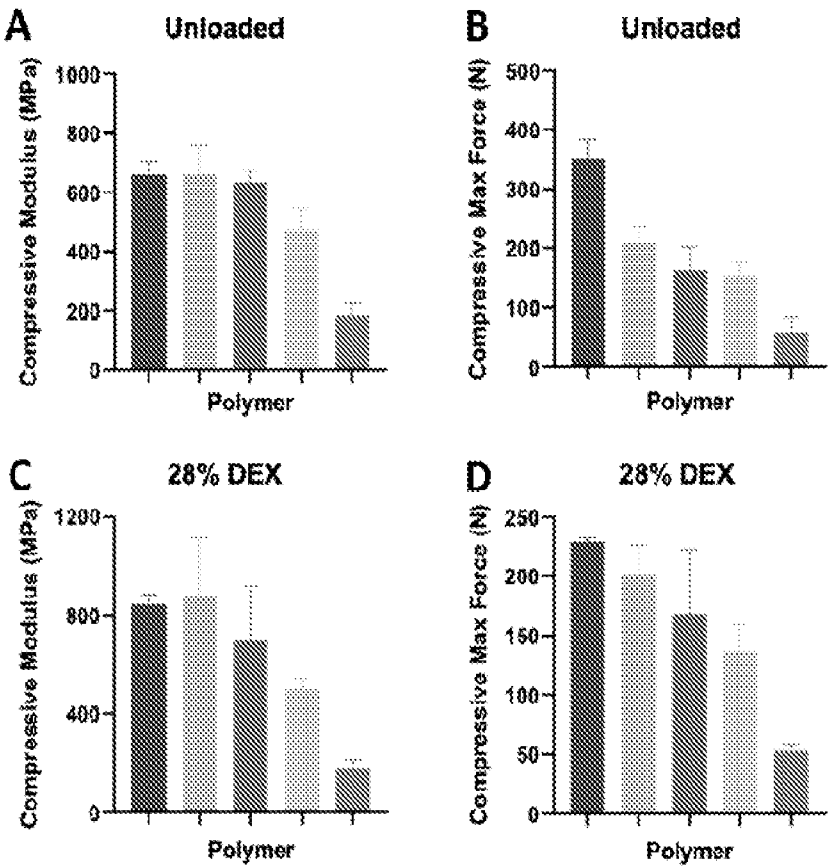


FIG. 17C



FIGs. 18A-18C



Columns from left to right:
0% DO 52K; 0% DO 40K; 7% DO 45K; 20% DO 37K; 40% DO 32K

FIGs. 19A-19D

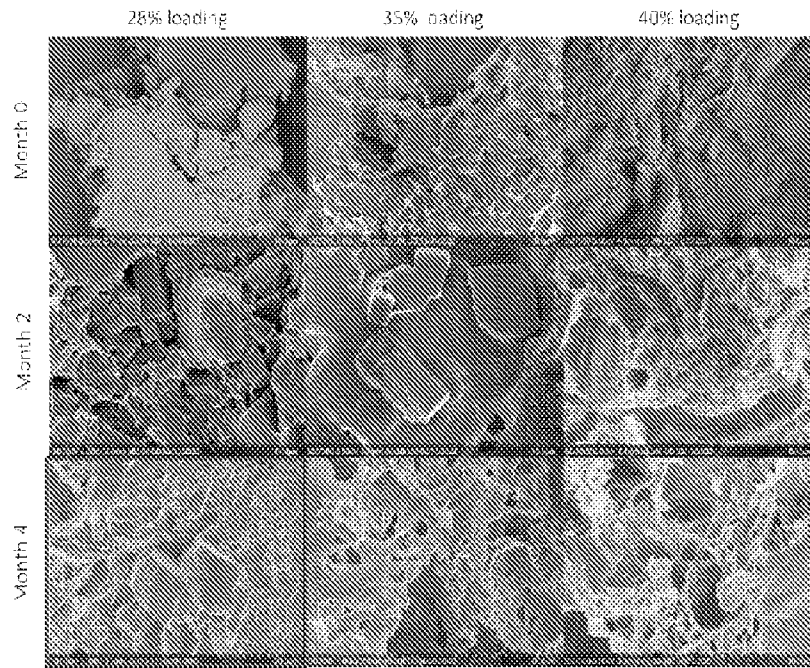


FIG. 20

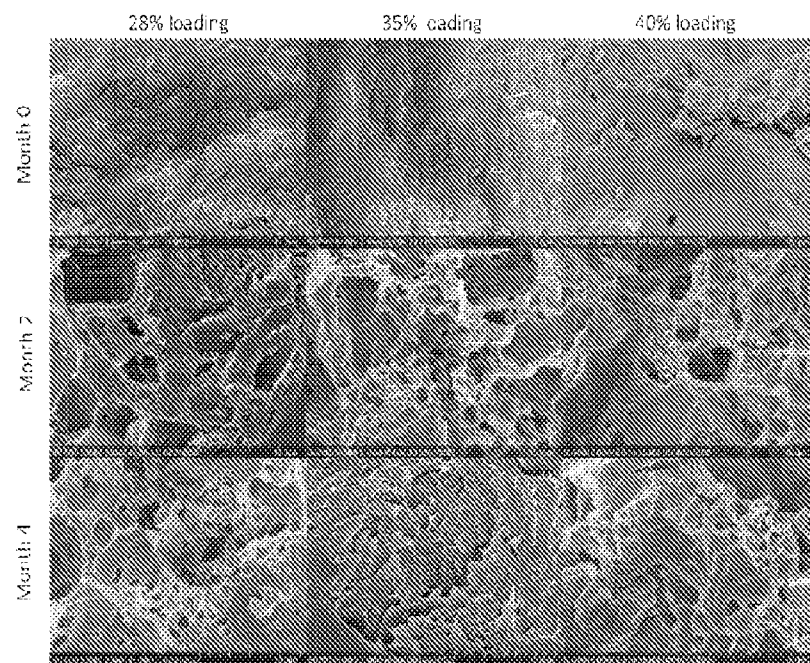


FIG. 21

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2024/019927

A. CLASSIFICATION OF SUBJECT MATTER

INV. C08G63/02

ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C08G

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

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

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/019178 A1 (GROSS RICHARD A [US] ET AL) 29 January 2004 (2004-01-29) claims 29-61; example 3 -----	1 - 30



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

17 July 2024

Date of mailing of the international search report

06/08/2024

Name and mailing address of the ISA/

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Authorized officer

Scheunemann, Sven

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/019927

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

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

1. ☒ Claims Nos.: 31 - 36
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 31-36

The subject-matter of claims 31-36 appears to constitute a treatment procedure on the human body, and therefore under Rule 39.1(iv) PCT (Method for treatment of the human or animal body by surgery), these claims have not been searched. For the same reason, the claims do not require preliminary examination, Rule 67.1 (iv) PCT.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2024/019927

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2004019178 A1	29-01-2004	NONE	