dye conjugates for use in such methods, for example, strategies that minimize or avoid photodegradation and improve the activity of the conjugate when used for PIT. Provided are methods and conjugates that meet such needs.

Summary

[0005] Provided in some examples is a method of manufacturing a phthalocyanine dye-conjugate. In some examples, the method includes contacting a targeting molecule, such as a macromolecule, with a phthalocyanine dye, which in some cases contains a reactive chemical group, under conditions to produce a conjugate containing the phthalocyanine dye linked to, such as covalently bound to, the targeting molecule. In some examples, the method includes formulating the conjugate in a pharmaceutically acceptable buffer. In some examples, before, during, and/or after preparation of the conjugate, the only light to which the dye and conjugate are exposed has a wavelength within a range from about 400 nm to about 650 nm. In some examples, before, during, and/or after preparation of the conjugate, such as during the contacting and/or formulating steps, the only light to which the dye and conjugate are exposed has an intensity of less than 500 lux.

[0005a] In one aspect, the present invention provides a method of manufacturing a phthalocyanine dye-targeting molecule conjugate, comprising:

a) contacting a targeting molecule with a phthalocyanine dye under conditions to produce a conjugate comprising the phthalocyanine dye linked to the targeting molecule; and

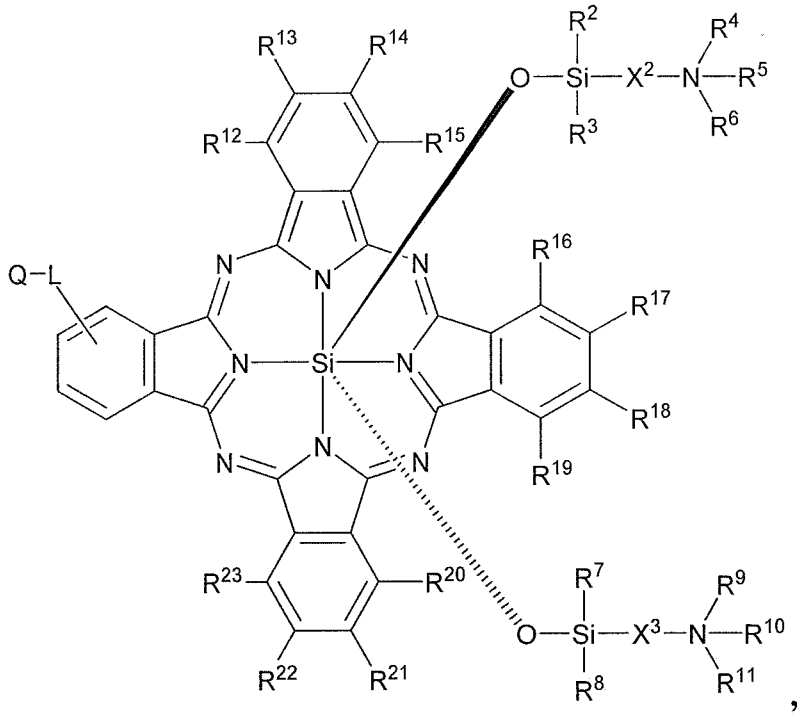
b) formulating the conjugate in a pharmaceutically acceptable buffer,

wherein in each of steps a) – b):

the only light to which the dye and conjugate are exposed has a wavelength within a range from 400 nm to 650 nm, or

the only light to which the dye and conjugate are exposed has an intensity of less than 500 lux.

[0006] In some examples, the method includes contacting a targeting molecule with a phthalocyanine dye at a molar ratio of dye to targeting molecule of from or from about 1:1 to 1000:1. In some examples, the dye includes a reactive chemical group, under conditions to produce a conjugate containing the phthalocyanine dye covalently linked to an attachment group of the targeting molecule. In some examples, the method includes formulating the conjugate in a pharmaceutically acceptable buffer to a concentration from or from about 0.01 mg/mL to 1000.0 mg/mL. In



, wherein:

L is a linker;

Q is a reactive group for attachment of the dye to the targeting molecule;

R^2, R^3, R^7, and R^8 are each independently selected from among optionally substituted alkyl and optionally substituted aryl;

R^4, R^5, R^6, R^9, R^{10}, and R^{11} are each independently selected from among hydrogen, optionally substituted alkyl, optionally substituted alkanoyl, optionally substituted alkoxycarbonyl, optionally substituted alkylcarbamoyl, and a chelating ligand, wherein at least one of R^4, R^5, R^6, R^9, R^{10}, and R^{11} comprises a water soluble group;

R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are each independently selected from among hydrogen, halogen, optionally substituted alkylthio, optionally substituted alkylamino and optionally substituted alkoxy; and

X^2 and X^3 are each independently C_1–C_{10} alkylene, optionally interrupted by a heteroatom.

[0048a] In another aspect, the present invention provides a stable conjugate, comprising the phthalocyanine dye-targeting molecule conjugate manufactured by a method comprising:

a) contacting a targeting molecule with a phthalocyanine dye under conditions to produce a conjugate comprising the phthalocyanine dye linked to the targeting molecule; and

b) formulating the conjugate in a pharmaceutically acceptable buffer,

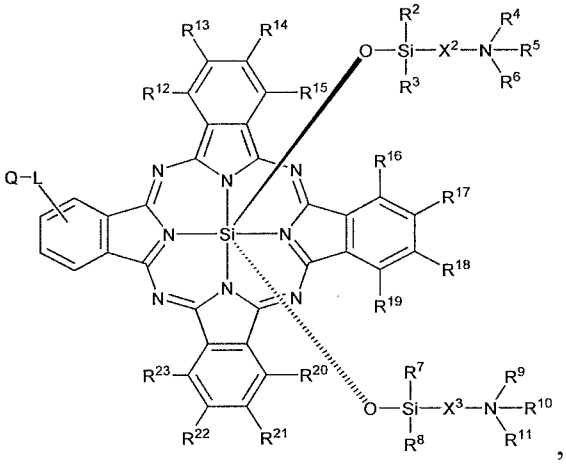
wherein in each of steps a) – b):

the only light to which the dye and conjugate are exposed has a wavelength within a range from 400 nm to 650 nm, or

the only light to which the dye and conjugate are exposed has an intensity of less than 500 lux; and

wherein the conjugate is stable for greater than three months or greater than 6 months or greater than 12 months; and

wherein the phthalocyanine dye comprises the formula:



, wherein:

L is a linker;

Q is a reactive group for attachment of the dye to the targeting molecule;

R^2, R^3, R^7, and R^8 are each independently selected from among optionally substituted alkyl and optionally substituted aryl;

R^4, R^5, R^6, R^9, R^{10}, and R^{11} are each independently selected from among hydrogen, optionally substituted alkyl, optionally substituted alkanoyl, optionally substituted alkoxycarbonyl, optionally substituted alkylcarbamoyl, and a chelating ligand, wherein at least one of R^4, R^5, R^6, R^9, R^{10}, and R^{11} comprises a water soluble group;

R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are each independently selected from among hydrogen, halogen, optionally substituted alkylthio, optionally substituted alkylamino and optionally substituted alkoxy; and

X^2 and X^3 are each independently C_1-C_{10} alkylene, optionally interrupted by a heteroatom.

[0049] In some examples, the stable conjugate containing the phthalocyanine dye includes the formula:

the conjugate, the conjugate is not exposed to an intensity of environmental light greater than 500 lux.

[0094] In some examples, the method is performed *in vitro* or *ex vivo*. In some examples, the *ex vivo* irradiation is method is performed using an extracorporeal device. Provided in some examplesis a method of treating hyperplasia or a tumor in a subject. In some examples, the method includes administering to the subject a therapeutically effective amount of the conjugate or stable conjugate or composition, where prior to and during the administration step the conjugate is not exposed to an intensity of environmental light greater than 500 lux. In some examples, the method further includes irradiating the hyperplasia or the tumor at a wavelength of 660 to 740 nm at a dose of at least 1 J cm^{-2} or 1 J/cm of fiber length, thereby treating the tumor in the subject.

[0094a] In yet another aspect, the present invention provides use of a phthalocyanine dye-targeting molecule conjugate manufactured according to the method described herein for the preparation of a medicament for use in a photoimmunotherapyfor treating a hyperplasia or a tumor in a subject, wherein:

a) a therapeutically effective amount of the phthalocyanine dye-targeting molecule conjugate is to be administered to the subject, wherein prior to and during the administration the conjugate is not exposed to an intensity of environmental light greater than 500 lux; and
b) the photoimmunotherapy comprises irradiation of the hyperplasia or the tumor at a wavelength of 660 to 740 nm at a dose of at least 1 J cm^{-2} or 1 J/cm of fiber length to thereby treat the tumor in the subject

[0095] Provided in some examplesis a method of treating hyperplasia or a tumor in a subject. In some such examples, the method includes administering to the subject a therapeutically effective amount of a conjugate containing IRDye 700DX (IR700) linked to a targeting molecule. In some examples, the conjugate is targeted to the hyperplasia or the tumor and prior to and during the administration step the conjugate is not exposed to an intensity of environmental light greater than 500 lux. In some examples, the method further includes irradiating the tumor at a wavelength of 600 to 800 nm at a dose of at least 1 J cm^{-2} or 1 J/cm of fiber length thereby treating the tumor in the subject.

[0095a] In yet another aspect, the present invention provides use of the stable conjugate described herein for the preparation of a medicament for use in a photoimmunotherapy for treating a hyperplasia or a tumor in a subject, wherein:

a) a therapeutically effective amount of the stable conjugate is to be administered to the subject, wherein prior to and during the administration the conjugate is not exposed to an intensity of environmental light greater than 500 lux; and

b) the photoimmunotherapy comprises irradiation of the hyperplasia or the tumor at a wavelength of 660 to 740 nm at a dose of at least 1 J cm^{-2} or 1 J/cm of fiber length to thereby treat the tumor in the subject.

[0096] Provided in some examplesis a method of treating hyperplasia or a tumor in a sample. In some examples, the method includes administering to the sample a therapeutically effective amount of the conjugate or stable conjugate or composition, where prior to and during the administration step the conjugate is not exposed to an intensity of environmental light greater than 500 lux. In some examples, the method further includes irradiating the hyperplasia or the tumor at a wavelength of 660 to 740 nm at a dose of at least 1 J cm^{-2} or 1 J/cm of fiber length, thereby treating the tumor in the sample.

[0096a] In yet another aspect, the present invention provides a pharmaceutical composition described herein for use in a photoimmunotherapy for treating a hyperplasia or a tumor in a subject, the photoimmunotherapy comprising:

a) a therapeutically effective amount of the phthalocyanine dye-targeting molecule conjugate that is to be administered to the subject, wherein prior to and during the administration the conjugate is not exposed to an intensity of environmental light greater than 500 lux; and

b) the hyperplasia or the tumor is to be irradiated at a wavelength of 660 to 740 nm at a dose of at least 1 J cm^{-2} or 1 J/cm of fiber length to thereby treat the tumor in the subject.

[0097] Provided in some examplesis a method of treating hyperplasia or a tumor in a sample. In some such examples, the method includes administering to the sample a therapeutically effective amount of a conjugate containing IRDye 700DX (IR700) linked to a targeting molecule. In some examples, the conjugate is targeted to the hyperplasia or the tumor and prior to and during the administration step the conjugate is not exposed to an intensity of environmental light greater than 500 lux. In some examples, the method further includes irradiating the tumor at a wavelength of 600 to 800 nm at a dose of at least 1 J cm^{-2} or 1 J/cm of fiber length thereby treating the tumor in the sample.

[0097a] In yet another aspect, the present invention provides use of the pharmaceutical composition described herein for the preparation of a medicament for use in a photoimmunotherapy for treating a hyperplasia or a tumor in a subject, wherein:

a) a therapeutically effective amount of the pharmaceutical composition is to be administered to the subject, wherein prior to and during the administration the conjugate in the pharmaceutical composition is not exposed to an intensity of environmental light greater than 500 lux; and

b) the photoimmunotherapy comprises irradiation of the hyperplasia or the tumor at a wavelength of 660 to 740 nm at a dose of at least 1 J cm^{-2} or 1 J/cm of fiber length to thereby treat the tumor in the subject.

[0097b] In yet another aspect, the present invention provides a method of removing unwanted cells or pathogens in a sample comprising:

a) administering to a sample, the sample comprising unwanted cells or pathogens, a therapeutically effective amount of the conjugate manufactured according to the method described herein, wherein prior to and during the administration step the conjugate is not exposed to an intensity of environmental light greater than 500 lux; and

b) irradiating the unwanted cells or pathogens at a wavelength of 660 to 740 nm at a dose of at least 1 J cm^{-2} or 1 J/cm of fiber length thereby removing the unwanted cells or pathogens in the sample, optionally wherein the method is performed *in vitro* or *ex vivo*.

[0097c] In yet another aspect, the present invention provides use of a phthalocyanine dye-targeting molecule conjugate manufactured according to the method described herein for the preparation of a medicament for use in a photoimmunotherapy for removing unwanted cells or pathogens in a subject, wherein the unwanted cells or pathogens are associated with a disease or condition in the subject, wherein the disease or condition is tumor or cancer, an infection, an inflammatory disease or condition, or a neuronal disease or condition, and wherein:

a) a therapeutically effective amount of the conjugate is to be administered to the subject, wherein prior to and during the administration the conjugate is not exposed to an intensity of environmental light greater than 500 lux; and

b) the photoimmunotherapy comprises irradiation of the unwanted cells or pathogens at a wavelength of 660 to 740 nm at a dose of at least 1 J cm^{-2} or 1 J/cm of fiber length to thereby remove the unwanted cells or pathogens in the subject and treat the disease or condition in the subject.

[0097d] In yet another aspect, the present invention provides a pharmaceutical composition described herein for use in a photoimmunotherapy for removing unwanted cells or pathogens in a subject, wherein the unwanted cells or pathogens are associated with a disease or condition in the subject and the photoimmunotherapy comprises:

a) a therapeutically effective amount of the conjugate that is to be administered to the subject, wherein prior to and during the administration the conjugate is not exposed to an intensity of environmental light greater than 500 lux; and

b) the unwanted cells or pathogens are to be irradiated at a wavelength of 660 to 740 nm at a dose of at least 1 J cm^{-2} or 1 J/cm of fiber length to thereby remove the unwanted cells or pathogens in the subject and treat the disease or condition in the subject.

[0098] In some examples, the method is for treating a tumor, wherein the targeting molecule of the conjugate targets the conjugate to the tumor or a microenvironment of the tumor. In some examples, irradiating the tumor is at a wavelength of 600 to 800 nm and at a dose of at least 1 J cm^{-2} or 1 J/cm of fiber length, thereby treating the tumor, e.g., the tumor in the subject or in the sample.

[0099] In some examples, the targeting molecule is an antibody, an antigen binding fragment, a protein, a glycoprotein, a peptide, a polypeptide, a virus, a viral capsid, or a viral particle. In some examples, the targeting molecule is an antibody or an antibody fragment.

[0100] In some examples, administration is performed under fluorescent lighting or LED lighting and in the absence of direct or indirect sunlight.

[0101] In some examples, any exposure of the conjugate to light less than 500 lux is for less than 20 minutes, less than 15 minutes, less than 10 minutes or less than 5 minutes. In some examples, the exposure of the conjugate to any light is light with an intensity that is not greater than 50 lux.

[0102] In some examples, the tumor is a cancer. In some examples, the cancer is a cancer located at the head and neck, breast, liver, colon, ovary, prostate, pancreas, brain, cervix, bone, skin, eye, bladder, stomach, esophagus, peritoneum, or lung. In some examples, the cancer is a cancer of the blood.

[0103] In some examples, the conjugate is targeted to a protein expressed in the tumor. In some examples, the conjugate is targeted to a protein expressed on the surface of a cell present in the tumor microenvironment. In some examples, the cell is a tumor cell, an immune cell or a cancer stem cell.

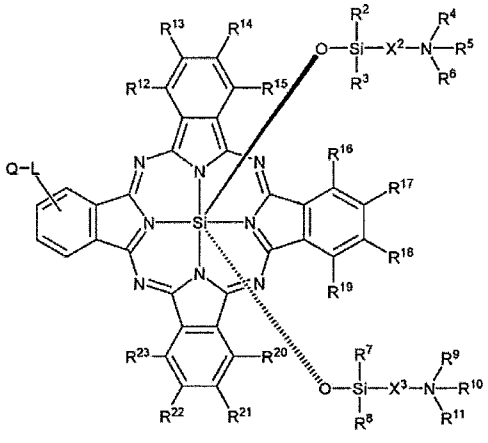
[0104] In some examples, the protein expressed in the tumor is ACTHR, endothelial cell Anxa-1, aminopetidase N, anti-IL-6R, alpha-4-integrin, alpha-5-beta-3 integrin, alpha-5-beta-5 integrin, alpha-fetoprotein (AFP), ANPA, ANPB, APA, APN, APP, 1AR, 2AR, AT1, B1, B2, BAGE1, BAGE2, B-cell receptor BB1, BB2, BB4, calcitonin receptor, cancer antigen 125 (CA 125), CCK1, CCK2, CD5, CD10, CD11a, CD13, CD14,

[0115] In some examples, the ACPP comprises the structure: A-X1-B-, wherein B is a peptide portion of about 5 to about 20 basic amino acid residues, which is suitable for cellular uptake; A is a peptide portion of about 2 to about 20 acidic amino acid residues, which when linked with portion B is effective to inhibit or prevent cellular uptake of portion B; X1 is a cleavable linker of about 2 to about 100 atoms; and one or more of L-Y is linked to the C-terminus of peptide portion B.

[0116] In some examples, the homing peptide has a sequence as set forth in any of SEQ ID NOs: 1-52. In some examples, the dye is IR700.

[0116a] In another aspect, the present invention provides a pharmaceutical composition comprising a conjugate of a phthalocyanine dye and a targeting molecule; wherein:

the phthalocyanine dye comprises the formula:



, wherein:

L is a linker;

Q is a reactive group for attachment of the dye to the targeting molecule;

R^2, R^3, R^7, and R^8 are each independently selected from among optionally substituted alkyl and optionally substituted aryl;

R^4, R^5, R^6, R^9, R^{10}, and R^{11} are each independently selected from among hydrogen, optionally substituted alkyl, optionally substituted alkanoyl, optionally substituted alkoxycarbonyl, optionally substituted alkylcarbamoyl, and a chelating ligand, wherein at least one of R^4, R^5, R^6, R^9, R^{10}, and R^{11} comprises a water soluble group;

R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are each independently selected from among hydrogen, halogen, optionally substituted alkylthio, optionally substituted alkylamino and optionally substituted alkoxy; and

X^2 and X^3 are each independently C_1-C_{10} alkylene, optionally interrupted by a heteroatom; and

the pharmaceutical composition has two or more features selected from the group consisting of (a) less than or equal to 3% free dye, (b) high molecular weight species less than or equal to 5%, (c) low molecular weight species less than or equal to 5%, and (d) greater than or equal to 92% monomer.

Brief Description of the Drawings

[0117] **FIG.1A** displays the relative amounts of high molecular weight species (aggregates) and monomer form of the Cetuximab-IRDye 700DX as assessed by High Pressure Liquid Chromatography using a Size Exclusion column (HPLC-SEC) of a sample in a clear vial before 24 hours of light exposure.

CLAIMS

1. A method of manufacturing a phthalocyanine dye-targeting molecule conjugate, comprising:

a) contacting a targeting molecule with a phthalocyanine dye under conditions to produce a conjugate comprising the phthalocyanine dye linked to the targeting molecule; and

b) formulating the conjugate in a pharmaceutically acceptable buffer,

wherein in each of steps a) – b):

the only light to which the dye and conjugate are exposed has a wavelength within a range from 400 nm to 650 nm, or

the only light to which the dye and conjugate are exposed has an intensity of less than 500 lux.

2. The method of claim 1, further comprising a quenching step subsequent to step (a) and before step (b), wherein, during the quenching step:

the only light to which the conjugate is exposed has a wavelength within a range from about 400 nm to about 650 nm, or

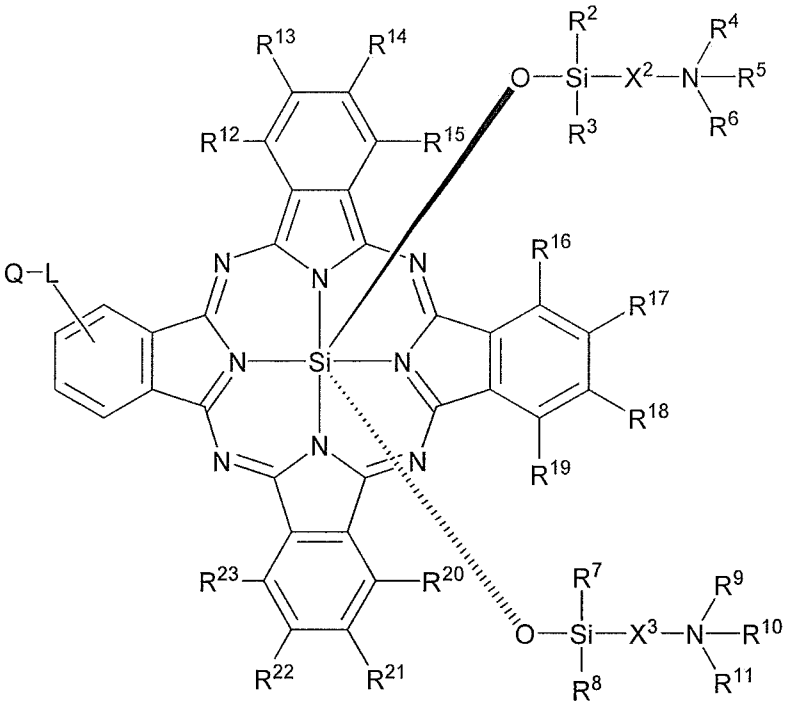
the only light to which the conjugate are exposed has an intensity of less than 500 lux.

3. The method of claim 2, wherein the quenching step comprises contacting the conjugate with glycine.

4. The method of any one of claims 1-3, wherein the contacting step a) further comprises contacting the targeting molecule with the phthalocyanine dye at a molar ratio of dye to targeting molecule of from 1:1 to 100:1, and wherein the conjugate is formulated to a concentration from 0.1 mg/mL to 200.0 mg/mL.

5. The method of any one of claims 1-4, wherein the conjugate is formulated to a concentration from 0.5 mg/mL to 10.0 mg/mL.

6. The method of any one of claims 1-5, wherein the phthalocyanine dye comprises the formula:



, wherein:

L is a linker;

Q is a reactive group for attachment of the dye to the targeting molecule;

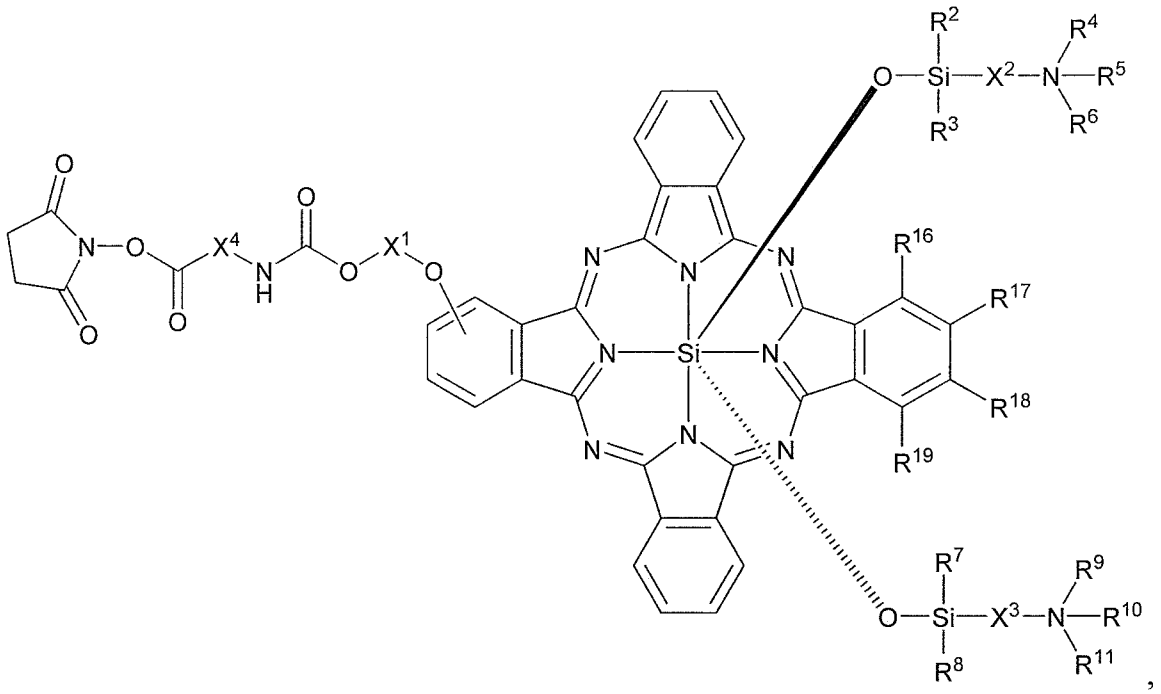
R^2, R^3, R^7, and R^8 are each independently selected from among optionally substituted alkyl and optionally substituted aryl;

R^4, R^5, R^6, R^9, R^{10}, and R^{11} are each independently selected from among hydrogen, optionally substituted alkyl, optionally substituted alkanoyl, optionally substituted alkoxycarbonyl, optionally substituted alkylcarbamoyl, and a chelating ligand, wherein at least one of R^4, R^5, R^6, R^9, R^{10}, and R^{11} comprises a water soluble group;

R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are each independently selected from among hydrogen, halogen, optionally substituted alkylthio, optionally substituted alkylamino and optionally substituted alkoxy; and

X^2 and X^3 are each independently C_1-C_{10} alkylene, optionally interrupted by a heteroatom.

7. The method of any one of claims 1-6, wherein the phthalocyanine dye comprises the formula:



wherein:

X^1 and X^4 are each independently a C_1-C_{10} alkylene optionally interrupted by a heteroatom;

R^2, R^3, R^7, and R^8 are each independently selected from optionally substituted alkyl and optionally substituted aryl;

R^4, R^5, R^6, R^9, R^{10}, and R^{11} are each independently selected from among hydrogen, optionally substituted alkyl, optionally substituted alkanoyl, optionally substituted alkoxycarbonyl, optionally substituted alkylcarbamoyl, and a chelating ligand, wherein at least one of R^4, R^5, R^6, R^9, R^{10}, and R^{11} comprises a water soluble group; and

R^{16}, R^{17}, R^{18} and R^{19} are each independently selected from among hydrogen, halogen, optionally substituted alkylthio, optionally substituted alkylamino and optionally substituted alkoxy.

8. The method of any one of claims 1-7, wherein the phthalocyanine dye comprises IRDye 700DX-NHS (IR700-NHS).

9. The method of any one of claims 1-8, wherein the targeting molecule binds to an antigen, protein or cell surface target molecule.

10. The method of claim 9, wherein the cell surface target molecule is selected from among cell membrane phospholipids, prokaryotic peptidoglycans, bacterial cell envelop

proteins, viral capsid proteins, ACTHR, endothelial cell Anxa-1, aminopetidase N, anti-IL-6R, alpha-4-integrin, alpha-5-beta-3 integrin, alpha-5-beta-5 integrin, alpha-fetoprotein (AFP), ANPA, ANPB, APA, APN, APP, 1AR, 2AR, AT1, B1, B2, BAGE1, BAGE2, B-cell receptor BB 1, BB2, BB4, calcitonin receptor, cancer antigen 125 (CA 125), CCK1, CCK2, CD5, CD10, CD11a, CD13, CD14, CD19, CD20, CD22, CD25, CD30, CD33, CD38, CD45, CD52, CD56, CD68, CD90, CD133, CD7, CD15, CD34, CD44, CD206, CD271, CEA (CarcinoEmbryonic Antigen), CGRP, chemokine receptors, cell-surface annexin-1, cell-surface plectin-1, Cripto-1, CRLR, CXCR2, CXCR4, DCC, DLL3, E2 glycoprotein, EGFR, EGFRvIII, EMR1, Endosialin, EP2, EP4, EpCAM, EphA2, ET receptors, Fibronectin, Fibronectin ED-B, FGFR, frizzled receptors, GAGE1, GAGE2, GAGE3, GAGE4, GAGE5, GAGE6, GLP-1 receptor, G-protein coupled receptors of the Family A (Rhodopsin-like), G-protein coupled receptors of the Family B (Secretin receptor-like) like), G-protein coupled receptors of the Family C (Metabotropic Glutamate Receptor-like), GD2, GP100, GP120, Glypican-3, hemagglutinin, Heparin sulfates, HER1, HER2, HER3, HER4, HMFG, HPV 16/18 and E6/E7 antigens, hTERT, IL11-R, IL-13R, IL-2 receptor, CTLA-4, PD-L1, ITGAM, Kalikrien-9, Lewis Y, LH receptor, LHRH-R, LPA1, MAC-1, MAGE 1, MAGE 2, MAGE 3, MAGE 4, MART1, MC 1R, Mesothelin, MUC 1, MUC 16, Neu (cell-surface Nucleolin), Neprilysin, Neuropilin-1, Neuropilin-2, NG2, NK1, NK2, NK3, NMB-R, Notch-1, NY-ESO-1, OT-R, mutant p53, p97 melanoma antigen, NTR2, NTR3, p32 (p32/gC1q-R/HABP1), p75, PAC1, PAR1, Patched (PTCH), PDGFR, PDFG receptors, PDT, Protease-cleaved collagen IV, proteinase 3, prohibitin, protein tyrosine kinase 7, PSA, PSMA, purinergic P2X family (*e.g.* P2X1-5), mutant Ras, RAMP1, RAMP2, RAMP3 patched, RET receptor, plexins, smoothened, sst1, sst2A, sst2B, sst3, sst4, sst5, substance P, TEMs, T-cell CD3 Receptor, TAG72, TGFBR1, TGFBR2, Tie-1, Tie-2, Trk-A, Trk-B, Trk-C, TR1, TRPA, TRPC, TRPV, TRPM, TRPML, TRPP (*e.g.* TRPV1-6, TRPA1, TRPC1-7, TRPM1-8, TRPP1-5, TRPML1-3), TSH receptor, VEGF receptors (VEGFR1 or Flt-1, VEGFR2 or FLK-1/KDR, and VEGF-3 or FLT-4), voltage-gated ion channels, VPAC1, VPAC2, Wilms tumor 1, Y1, Y2, Y4, and Y5.

11. The method of any one of claims 1-10, wherein the targeting molecule is an antibody or an antibody fragment.

12. The method of any one of claims 1-11, wherein the targeting molecule is cetuximab.

13. A stable conjugate, comprising the phthalocyanine dye-targeting molecule conjugate manufactured by the method of any one of claims 1-12, wherein the conjugate is stable for greater than three months or greater than 6 months or greater than 12 months.

14. The stable conjugate of claim 13, wherein the conjugate is stable if it retains greater than 30%, 40%, 50%, 60%, 70%, 80%, 90% or more of its potency, activity or purity for greater than 3 months of storage compared to the conjugate's potency, activity or purity prior to storage.

15. A stable conjugate, comprising the phthalocyanine dye-targeting molecule conjugate manufactured by a method comprising:

a) contacting a targeting molecule with a phthalocyanine dye under conditions to produce a conjugate comprising the phthalocyanine dye linked to the targeting molecule; and

b) formulating the conjugate in a pharmaceutically acceptable buffer,

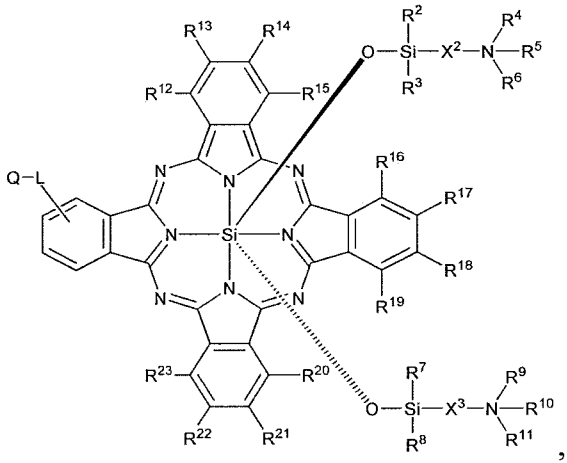
wherein in each of steps a) – b):

the only light to which the dye and conjugate are exposed has a wavelength within a range from 400 nm to 650 nm, or

the only light to which the dye and conjugate are exposed has an intensity of less than 500 lux; and

wherein the conjugate is stable for greater than three months or greater than 6 months or greater than 12 months; and

wherein the phthalocyanine dye comprises the formula:



, wherein:

L is a linker;

Q is a reactive group for attachment of the dye to the targeting molecule;

R^2, R^3, R^7, and R^8 are each independently selected from among optionally substituted alkyl and optionally substituted aryl;

R^4, R^5, R^6, R^9, R^{10}, and R^{11} are each independently selected from among hydrogen, optionally substituted alkyl, optionally substituted alkanoyl, optionally substituted alkoxycarbonyl, optionally substituted alkylcarbamoyl, and a chelating ligand, wherein at least one of R^4, R^5, R^6, R^9, R^{10}, and R^{11} comprises a water soluble group;

R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are each independently selected from among hydrogen, halogen, optionally substituted alkylthio, optionally substituted alkylamino and optionally substituted alkoxy; and

X^2 and X^3 are each independently C_1-C_{10} alkylene, optionally interrupted by a heteroatom.

16. The stable conjugate of claim 15, wherein the phthalocyanine dye comprises IRDye 700DX-NHS (IR700-NHS).

17. The stable conjugate of claim 15 or claim 16, wherein the targeting molecule is cetuximab.

18. A pharmaceutical composition comprising the stable conjugate of any one of claims 13-17 and a pharmaceutically acceptable excipient.

19. The pharmaceutical composition of claim 18, wherein greater than 90% of the conjugate is present as a main monomer component.

20. A packaging system comprising the stable conjugate of any one of claims 13-17, and further comprising a container, wherein the container protects from transmission of light such that the percentage of transmission of light is less than 50%.

21. The packaging system of claim 20, wherein the percentage of transmission of light is less than 10%.

22. The packaging system of claim 20 or claim 21, wherein the container protects from transmission of light having a wavelength from 250 nm to 800 nm.

23. Use of a phthalocyanine dye-targeting molecule conjugate manufactured according to the method of any one of claims 1-12 for the preparation of a medicament for use in a photoimmunotherapy for treating a hyperplasia or a tumor in a subject, wherein:

a) a therapeutically effective amount of the phthalocyanine dye-targeting molecule conjugate is to be administered to the subject, wherein prior to and during the administration the conjugate is not exposed to an intensity of environmental light greater than 500 lux; and

b) the photoimmunotherapy comprises irradiation of the hyperplasia or the tumor at a wavelength of 660 to 740 nm at a dose of at least 1 J cm^{-2} or 1 J/cm of fiber length to thereby treat the tumor in the subject.

24. Use of the stable conjugate of any one of claims 13-17 for the preparation of a medicament for use in a photoimmunotherapy-for treating a hyperplasia or a tumor in a subject, wherein:

a) a therapeutically effective amount of the stable conjugate is to be administered to the subject, wherein prior to and during the administration the conjugate is not exposed to an intensity of environmental light greater than 500 lux; and

b) the photoimmunotherapy comprises irradiation of the hyperplasia or the tumor at a wavelength of 660 to 740 nm at a dose of at least 1 J cm^{-2} or 1 J/cm of fiber length to thereby treat the tumor in the subject.

25. A pharmaceutical composition of claim 18 or claim 19 for use in a photoimmunotherapy for treating a hyperplasia or a tumor in a subject, the photoimmunotherapy comprising:

a) a therapeutically effective amount of the phthalocyanine dye-targeting molecule conjugate that is to be administered to the subject, wherein prior to and during the administration the conjugate is not exposed to an intensity of environmental light greater than 500 lux; and

b) the hyperplasia or the tumor is to be irradiated at a wavelength of 660 to 740 nm at a dose of at least 1 J cm^{-2} or 1 J/cm of fiber length to thereby treat the tumor in the subject.

26. Use of the pharmaceutical composition of claim 18 or claim 19 for the preparation of a medicament for use in a photoimmunotherapy for treating a hyperplasia or a tumor in a subject, wherein:

a) a therapeutically effective amount of the pharmaceutical composition is to be administered to the subject, wherein prior to and during the administration the conjugate in the pharmaceutical composition is not exposed to an intensity of environmental light greater than 500 lux; and

b) the photoimmunotherapy comprises irradiation of the hyperplasia or the tumor at a wavelength of 660 to 740 nm at a dose of at least 1 J cm^{-2} or 1 J/cm of fiber length to thereby treat the tumor in the subject.

27. A method of removing unwanted cells or pathogens in a sample comprising:

a) administering to a sample, the sample comprising unwanted cells or pathogens, a therapeutically effective amount of the conjugate manufactured according to the method of any one of claims 1-12, wherein prior to and during the administration step the conjugate is not exposed to an intensity of environmental light greater than 500 lux; and

b) irradiating the unwanted cells or pathogens at a wavelength of 660 to 740 nm at a dose of at least 1 J cm^{-2} or 1 J/cm of fiber length thereby removing the unwanted cells or pathogens in the sample, optionally wherein the method is performed *in vitro* or *ex vivo*.

28. Use of a phthalocyanine dye-targeting molecule conjugate manufactured according to the method of any one of claims 1-12 for the preparation of a medicament for use in a photoimmunotherapy for removing unwanted cells or pathogens in a subject, wherein the unwanted cells or pathogens are associated with a disease or condition in the subject, wherein the disease or condition is tumor or cancer, an infection, an inflammatory disease or condition, or a neuronal disease or condition, and wherein:

a) a therapeutically effective amount of the conjugate is to be administered to the subject, wherein prior to and during the administration the conjugate is not exposed to an intensity of environmental light greater than 500 lux; and

b) the photoimmunotherapy comprises irradiation of the unwanted cells or pathogens at a wavelength of 660 to 740 nm at a dose of at least 1 J cm^{-2} or 1 J/cm of fiber length to thereby remove the unwanted cells or pathogens in the subject and treat the disease or condition in the subject.

29. A pharmaceutical composition of claim 18 or claim 19 for use in a photoimmunotherapy for removing unwanted cells or pathogens in a subject, wherein the

unwanted cells or pathogens are associated with a disease or condition in the subject and the photoimmunotherapy comprises:

a) a therapeutically effective amount of the conjugate that is to be administered to the subject, wherein prior to and during the administration the conjugate is not exposed to an intensity of environmental light greater than 500 lux; and

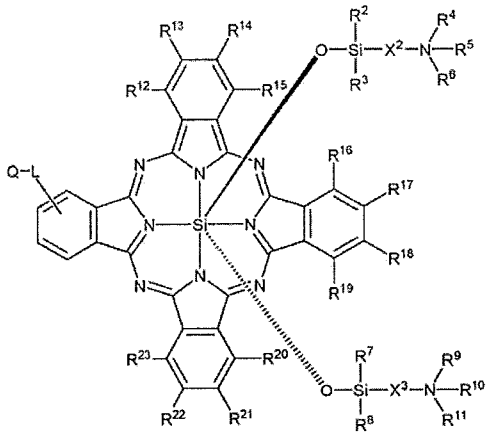
b) the unwanted cells or pathogens are to be irradiated at a wavelength of 660 to 740 nm at a dose of at least 1 J cm^{-2} or 1 J/cm of fiber length to thereby remove the unwanted cells or pathogens in the subject and treat the disease or condition in the subject.

30. The pharmaceutical composition for use of claim 29, wherein disease or condition is a hyperplasia or tumor, an infection, an inflammatory disease or condition, or a neuronal disease or condition.

31. A conjugate, comprising a phthalocyanine dye and a targeting molecule, wherein the targeting molecule is selected from among a tissue-specific homing peptide, an RGD polypeptide, an iRGD polypeptide, a Lyp-1 polypeptide, a cripto-1 binding polypeptide, a somatostatin receptor binding polypeptide, a prohibitin binding polypeptide, a NGR polypeptide, an iNGR polypeptide, an activatable cell penetrating peptide (ACPP) comprised of a polycationic cell penetrating peptide (CPP) connected via a cleavable linker to a neutralizing polyanion, and an antibody selected from Ado-trastuzumab emtansine, Afatinib, Axitinib, Bosutinib, Cabozantinib, Ceritinib, Crizotinib, Dabrafenib, Dasatinib, Everolimus, Ibrutinib, Imatinib, Lenvatinib, Nilotinib, Olaparib, Palbociclib, Pazopanib, Ramucirumab, Regorafenib, Ruxolitinib, Sorafenib, Sunitinib, Temsirolimus, Trametinib, Vandetanib, Vemurafenib, Vismodegib, Ipilimumab, Nivolumab, pembrolizumab, pidilizumab, lambrolizumab, BMS-935559, MPDL3280A, Pidilizumab (CT-011), AMP-224, MSB001078C, or MEDI4736, or an antigen-binding fragment thereof.

32. A pharmaceutical composition comprising a conjugate of a phthalocyanine dye and a targeting molecule; wherein:

the phthalocyanine dye comprises the formula:



, wherein:

L is a linker;

Q is a reactive group for attachment of the dye to the targeting molecule;

R^2, R^3, R^7, and R^8 are each independently selected from among optionally substituted alkyl and optionally substituted aryl;

R^4, R^5, R^6, R^9, R^{10}, and R^{11} are each independently selected from among hydrogen, optionally substituted alkyl, optionally substituted alkanoyl, optionally substituted alkoxycarbonyl, optionally substituted alkylcarbamoyl, and a chelating ligand, wherein at least one of R^4, R^5, R^6, R^9, R^{10}, and R^{11} comprises a water soluble group;

R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are each independently selected from among hydrogen, halogen, optionally substituted alkylthio, optionally substituted alkylamino and optionally substituted alkoxy; and

X^2 and X^3 are each independently C_1-C_{10} alkylene, optionally interrupted by a heteroatom; and

the pharmaceutical composition has two or more features selected from the group consisting of (a) less than or equal to 3% free dye, (b) high molecular weight species less than or equal to 5%, (c) low molecular weight species less than or equal to 5%, and (d) greater than or equal to 92% monomer.

33. The pharmaceutical composition of claim 32, wherein the phthalocyanine dye comprises IRDye 700DX-NHS (IR700-NHS).

34. The pharmaceutical composition of claim 32 or claim 33, wherein the targeting molecule is cetuximab.