Background

[0004] Various therapies are available for treating disease, such as cancer. For example, photoimmunotherapy (PIT) is a method that uses a photosensitizer conjugated to an antibody or other targeting molecule to target a cell surface protein in order to permit the targeted killing of specific cells. In some cases, PIT can selectively target disease cells, such as tumor cells, and thereby selectively kill such cells without damaging healthy cells. Improved strategies are needed to improve photoimmunotherapy methods, for example, to increase the efficacy of treatment. Provided are compositions and methods that meet such needs.

Summary

[0005] Provided in some examples is a method of treating a disease or condition in a subject containing using photoimmunotherapy (PIT). In some examples, the method includes administering to the subject having a disease or condition a conjugate containing a phthalocyanine dye linked to a targeting molecule, such as an antibody or an antigen-binding fragment thereof, that binds to a protein on the surface of a cell present in the microenvironment of a lesion associated with the disease or condition. In some examples, the conjugate is administered to effect a systemic exposure that is no more than 75% of the total therapeutically effective systemic exposure of the antibody or antigen-binding fragment that is not so conjugated for treating the same disease or condition as described at the label approved for commercialization by the regulatory agencies (*e.g.* FDA, EMA, PDMA). In some examples, after administering the conjugate, the lesion is irradiated at a wavelength of 500 to 900 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. In some examples, the wavelength for irradiation is 600 nm to 850 nm, such as 660 nm to 740 nm.

[0005a] In one aspect, the present invention provides use of a pharmaceutical composition comprising a conjugate, the conjugate comprising a phthalocyanine dye linked to a targeting molecule that binds to a protein on the surface of a cell present in the microenvironment of a lesion associated with a disease or condition, for preparation of a medicament formulated for intravenous administration in a dosing schedule for treating a lesion associated with a disease or condition in a subject, wherein the dosing schedule comprises:

a) that the medicament is to be intravenously administered to the subject having a lesion associated with a disease or condition the conjugate in an amount that is between about 160 mg/m^2 and about 2000 mg/m^2; and

b) after administration of the conjugate, the lesion is to be irradiated at a wavelength of 600 nm to 850 nm at a dose from or from about 25 J cm^{-2} to about 400 J cm^{-2} or from or from about 25 J/cm fiber length to about 500 J/cm fiber length,

wherein the disease or condition is a cancer.

[000b] In another aspect, the present invention provides of a pharmaceutical composition comprising a conjugate comprising a phthalocyanine dye linked to cetuximab for preparation of a medicament formulated for intravenous administration in a dosing schedule for treating a tumor in a subject having a head or neck cancer, wherein the dosing schedule comprises:

a) that the medicament is to be intravenously administered, to the subject having a tumor associated with a head or neck cancer, the conjugate in an amount that is between about 160 mg/m^2 and about 2000 mg/m^2; and

b) after administration of the conjugate, the lesion is to be irradiated at a wavelength of or of about 690 ± 50 nm at a dose of at least or about at least or about 50 J cm^{-2}or 100 J/cm of fiber length.

[0006] In some examples, the conjugate is administered in a dosing schedule in which: the administration of the conjugate is performed only one time as a single injection or infusion; or the dosing schedule does not include a subsequent dose of the conjugate; or the dosing schedule does not include a subsequent dose of the targeting molecule, *e.g.*, a macromolecule, that is not so conjugated.

[0007] In some examples, the conjugate is administered systemically. In some examples, the conjugate is administered intravenously.

[0008] In some examples, the conjugate is administered to effect a systemic exposure (AUC) that is no more than 60%, no more than 50%, no more than 40% or no more than 30% of the therapeutically effective systemic exposure of the antibody or antigen-binding fragment that is not so conjugated for treating the same disease or condition.

[0009] In some examples, the disease or condition is a tumor, whereby the antibody or an antigen-binding fragment binds to a molecule on the surface of a cell present in the tumor microenvironment and the tumor is irradiated.

[0010] Provided in some examples is a method of treating a disease or condition in a subject using photoimmunotherapy (PIT) wherein the systemic exposure as measured by the average area under the plasma conjugate concentration-time curve from time 0 to infinity (AUC[0-inf] or $AUC_{0-\infty}$) for a patient population, such as a sample patient population after administration of the conjugate is between or between about 250 μg/mL*h and 100,000 μg/mL*h, between or between about 500 μg/mL*h and 50,000 μg/mL*h, between or between about 500 μg/mL*h and 18,000 μg/mL*h, or between or between about 500 μg/mL*h and 10,000 μg/mL*h. In some examples, the systemic exposure as measured by the average area under the plasma conjugate concentration-time curve from time 0 to infinity (AUC[0-inf] or $AUC_{0-\infty}$) for a patient population, such as a sample patient population after administration of the conjugate is no more than 100,000 μg/mL*h, no more than 75,000 μg/mL*h, no more than 50,000 μg/mL*h, no more than 40,000 μg/mL*h, no more than 30,000 μg/mL*h, no more than 20,000 μg/mL*h, no more than 10,000 μg/mL*h, no more than 5,000 μg/mL*h, or no more than 2,500 μg/mL*h.

[0011] In some examples, the systemic exposure as measured by the average area under the plasma conjugate concentration-time curve from time 0 to 24 hours (AUC[0-24] or AUC_{0-24}) for a patient population, such as a sample patient population after administration of the conjugate is between or between about 100 μg/mL*h and 25,000 μg/mL*h, between or between about 200 μg/mL*h and 10,000 μg/mL*h, between or between about 500 μg/mL*h and 5,000 μg/mL*h; or the systemic exposure as measured by the average area under the plasma conjugate concentration-time curve from time 0 to 24 hours (AUC[0-24] or AUC_{0-24}) for a patient population, such as a sample patient population after administration of the conjugate is no more than 25,000 μg/mL*h, no more than 15,000 μg/mL*h, no more than 10,000 μg/mL*h, no more than 5,000 μg/mL*h, no more than 2,500 μg/mL*h, no more than 1,000 μg/mL*h, or no more than 500 μg/mL*h.

[0012] In some examples, the conjugate is administered in a dosage range that is at least about 10 mg/m^2 (body surface area of the subject), at least about 50 mg/m^2 or at least about 75 mg/m^2 and is no more than 5000 mg/m^2, no more than 2000 mg/m^2, no more than 1000 mg/m^2. In some examples, the conjugate is administered in a dosage range that is no more than 500 mg/m^2, no more than 250 mg/m^2, or no more than 200 mg/m^2. In some examples, the conjugate is administered at a dosage that is between or between about 100 mg/m^2 and 1500 mg/m^2 or 150 mg/m^2 and 750 mg/m^2. In some examples, the conjugate is administered at a dosage that is or is about 160 mg/m^2, 320 mg/m^2, 640 mg/m^2 or 1280 mg/m^2.

[0013] In some examples, the targeting molecule is an antibody or an antigen-binding antibody fragment. In some examples, the antibody is an antigen-binding antibody fragment that is a Fab, a single V_H domain, a single chain variable fragment (scFv), a multivalent scFv, a bispecific scFv or an scFv-CH3 dimer.

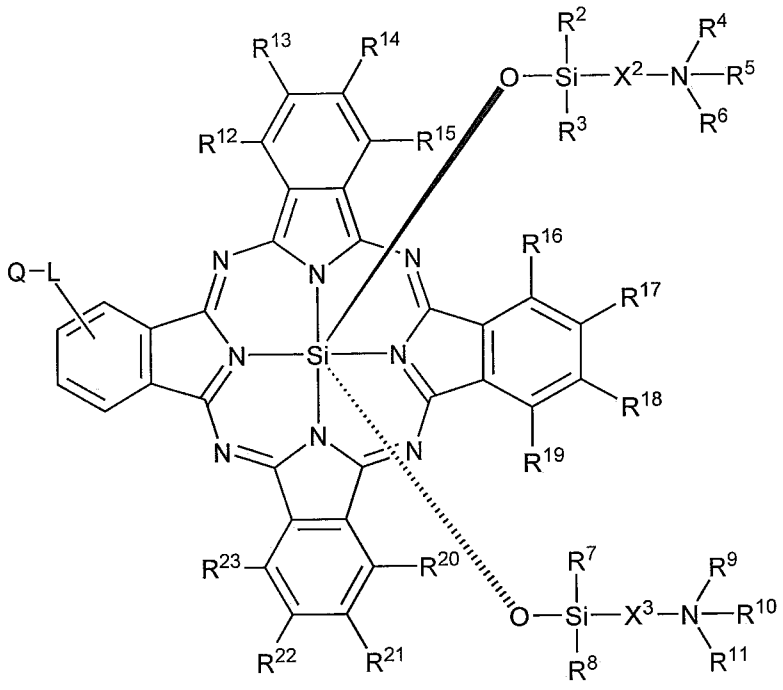
[0014] In some examples, the lesion is irradiated at a wavelength of 690 ± 50 nm or at a wavelength of or about 690 ± 20 nm. In some examples, the lesion is irradiated at a dose of from or from about 2 J cm^{-2} to about 400 J cm^{-2} or from or from about 2 J/cm fiber length to about 500 J/cm fiber length. In some examples, the lesion is irradiated at a dose of at least or at least about 2 J cm^{-2}, 5 J cm^{-2}, 10 J cm^{-2}, 25 J cm^{-2}, 50 J cm^{-2}, 75 J cm^{-2}, 100 J cm^{-2}, 150 J cm^{-2}, 200 J cm^{-2}, 300 J cm^{-2}, 400 J cm^{-2}, or 500 J cm^{-2}; or the lesion is irradiated at a dose of at least or at least about 2 J/cm fiber length, 5 J/cm fiber length, 10 J/cm fiber length, 25 J/cm fiber length, 50 J/cm fiber length, 75 J/cm fiber length, 100 J/cm fiber length, 150 J/cm fiber length, 200 J/cm fiber length, 250 J/cm fiber length, 300 J/cm fiber length, 400 J/cm fiber length or 500 J/cm fiber length.

[0015] In some examples, the irradiation is carried out or effected between or between about 30 minutes and 96 hours after administering the conjugate. In some examples, the conjugate is administered in a dosing schedule in which the administration of the conjugate is performed only one time as a single injection or infusion. In some examples, the conjugate is administered in a dosing schedule in which the dosing schedule does not contain a subsequent dose of the conjugate. In some examples, the conjugate is administered in a dosing schedule in which the dosing schedule does not contain a subsequent dose of the targeting molecule that is not so conjugated. In some examples, the dosing schedule is repeated.

[0016] In some examples, the conjugate is administered systemically. In some examples, the conjugate is administered intravenously.

[0017] In some examples, the phthalocyanine dye has a maximum absorption wavelength from or from about 600 nm to about 850 nm.

[0018] In some examples, the phthalocyanine dye is linked directly or indirectly to the targeting molecule. In some examples, the phthalocyanine dye includes the formula:



, wherein:

L is a linker;

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

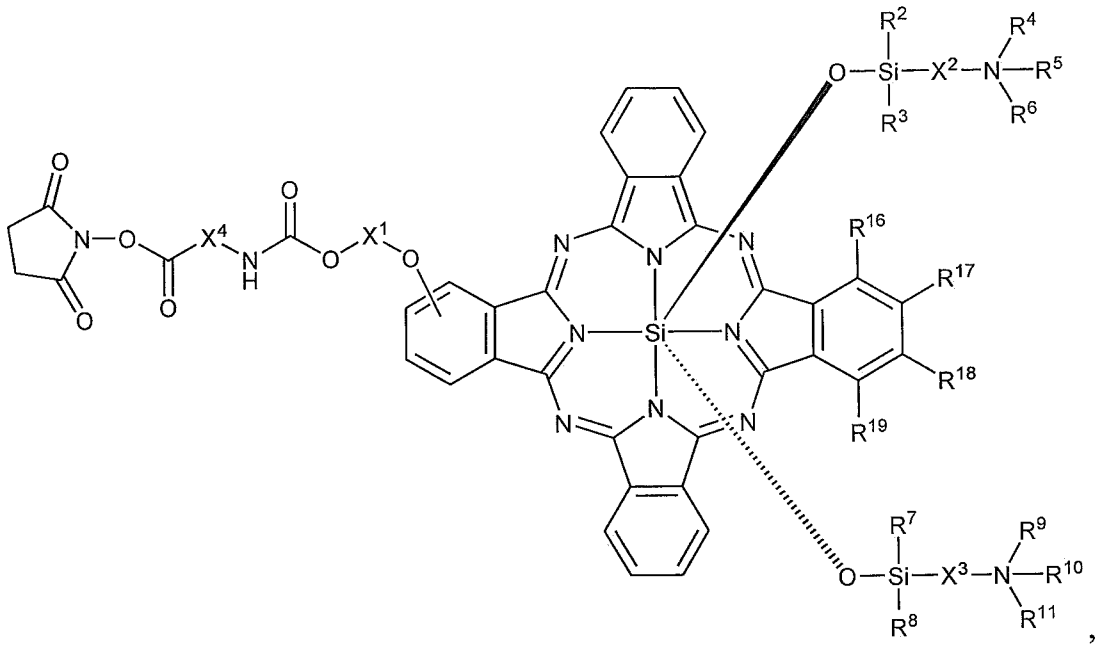
R^2, R^3, R^7, and R^8 are each independently selected from optionally substituted alkyl and optionally substituted aryl;

R^4, R^5, R^6, R^9, R^{10}, and R^{11} are each independently selected from 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} include 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 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.

[0019] In some examples, the phthalocyanine dye includes 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 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} includes a water soluble group; and

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

[0020] In some examples, the phthalocyanine dye includes IRDye 700DX (IR700).

[0021] In some examples, the cell surface protein is selected from among 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, 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, ITGAM, Kalikrien-9, Lewis Y, LH receptor, LHRH-R, LPA1, MAC-1, MAGE 1, MAGE 2, MAGE 3, MAGE 4, MART1, MC1R, Mesothelin, MUC1, MUC16, 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.

[0022] In some examples, the cell surface protein is selected from among HER1/EGFR, HER2/ERBB2, CD20, CD25 (IL-2Rα receptor), CD33, CD52, CD133, CD206, CEA, CEACAM1, CEACAM3, CEACAM5, CEACAM6, cancer antigen 125 (CA125), alpha-fetoprotein (AFP), Lewis Y, TAG72, Caprin-1, mesothelin, PDGF receptor, PD-1, PD-L1, CTLA-4, IL-2 receptor, vascular endothelial growth factor (VEGF), CD30, EpCAM, EphA2, Glypican-3, gpA33, mucins, CAIX, PSMA, folate-binding protein, gangliosides (such as GD2, GD3, GM1 and GM2), VEGF receptor (VEGFR), integrin αVβ3, integrin α5β1, ERBB3, MET, IGF1R, EPHA3, TRAILR1, TRAILR2, RANKL, FAP, tenascin, AFP, BCR complex, CD3, CD18, CD44, CTLA-4, gp72, HLA-DR 10 β, HLA-DR antigen, IgE, MUC-1, nuC242, PEM antigen, metalloproteinases, Ephrin receptor, Ephrin ligands, HGF receptor, CXCR4, CXCR4, Bombesin receptor, and SK-1 antigen.

[0023] In some examples, the cell surface protein is selected from among CD25, PD-1 (CD279), PD-L1 (CD274, B7-H1), PD-L2 (CD273, B7-DC), CTLA-4, LAG3 (CD223), TIM3 (HAVCR2), 4-1BB (CD137, TNFRSF9), CXCR2, CXCR4 (CD184), CD27, CEACAM1, Galectin 9, BTLA, CD160, VISTA (PD1 homologue), B7-H4 (VCTN1), CD80

(B7-1), CD86 (B7-2), CD28, HHLA2 (B7-H7), CD28H, CD155, CD226, TIGIT, CD96, Galectin 3, CD40, CD40L, CD70, LIGHT (TNFSF14), HVEM (TNFRSF14), B7-H3 (CD276), Ox40L (TNFSF4), CD137L (TNFSF9, GITRL), B7RP1, ICOS (CD278), ICOSL, KIR, GAL9, NKG2A (CD94), GARP, TL1A, TNFRSF25, TMIGD2, BTNL2, Butyrophilin family, CD48, CD244, Siglec family, CD30, CSF1R, MICA (MHC class I polypeptide-related sequence A), MICB (MHC class I polypeptide-related sequence B), NKG2D, KIR family (Killer-cell immunoglobulin-like receptor, LILR family (Leukocyte immunoglobulin-like receptors, CD85, ILTs, LIRs), SIRPA (Signal regulatory protein alpha), CD47 (IAP), Neuropilin 1 (NRP-1), a VEGFR, and VEGF.

[0024] In some examples, the antibody or an antigen-binding fragment is selected from among cetuximab, panitumumab, zalutumumab, nimotuzumab, Tositumomab (Bexxar ®), Rituximab (Rituxan, Mabthera), Ibritumomab tiuxetan (Zevalin), Daclizumab (Zenapax), Gemtuzumab (Mylotarg), Alemtuzumab, CEA-scan Fab fragment, OC125 monoclonal antibody, ab75705, B72.3, Bevacizumab (Avastin ®), Basiliximab, nivolumab, pembrolizumab, pidilizumab, MK-3475, BMS-936559, MPDL3280A, ipilimumab, tremelimumab, IMP321, BMS-986016, LAG525, urelumab, PF-05082566, TRX518, MK-4166, dacetuzumab, lucatumumab, SEA-CD40, CP-870, CP-893, MED16469, MEDI6383, MEDI4736, MOXR0916, AMP-224, PDR001, MSB0010718C, rHIgM12B7, Ulocuplumab, BKT140, Varlilumab (CDX-1127), ARGX-110, MGA271, lirilumab (BMS-986015, IPH2101), IPH2201, AGX-115, Emactuzumab, CC-90002 and MNRP1685A or is an antigen-binding fragment thereof.

[0025] In some examples, the conjugate is selected from among cetuximab-IR700, panitumumab-IR700, zalutumumab-IR700, nimotuzumab-IR700, Tositumomab-IR700, Rituximab-IR700, Ibritumomab tiuxetan-IR700, Daclizumab-IR700, Gemtuzumab-IR700, Alemtuzumab-IR700, CEA-scan Fab fragment-IR700, OC125-IR700, ab75705-IR700, B72.3-IR700, Bevacizumab-IR700, Basiliximab-IR700, nivolumab-IR700, pembrolizumab-IR700, pidilizumab-IR700, MK-3475-IR700, BMS-936559-IR700, MPDL3280A-IR700, ipilimumab-IR700, tremelimumab-IR700, IMP321-IR700, BMS-986016-IR700, LAG525-IR700, urelumab-IR700, PF-05082566-IR700, TRX518-IR700, MK-4166-IR700, dacetuzumab-IR700, lucatumumab-IR700, SEA-CD40-IR700, CP-870-IR700, CP-893-IR700, MED16469-IR700, MEDI6383-IR700, MEDI4736-IR700, MOXR0916-IR700, AMP-224-IR700, PDR001-IR700, MSB0010718C-IR700, rHIgM12B7-IR700, Ulocuplumab-IR700, BKT140-IR700, Varlilumab-IR700, ARGX-110-IR700, MGA271-

IR700, lirilumab-IR700, IPH2201-IR700, AGX-115-IR700, Emactuzumab-IR700, CC-90002-IR700 and MNRP1685A-IR700.

[0026] In some examples, the targeting molecule is an antibody that is cetuximab or is an antigen-binding fragment thereof or the conjugate is cetuximab-IR700.

[0027] In some examples, the average area under the plasma conjugate concentration-time curve from time 0 to infinity (AUC[0-inf] or $AUC_{0-\infty}$) for a patient population, such as a sample patient population after administration of the conjugate is between or between about 500 μg/mL*h and 18,000 μg/mL*h, between or between about 500 μg/mL*h and 10,000 μg/mL*h, between or between about 500 μg/mL*h and 5,000 μg/mL*h, or between or between about 500 μg/mL*h and 2,500 μg/mL*h. In some examples, the average area under the plasma conjugate concentration-time curve from time 0 to 24 hours (AUC[0-24] or AUC_{0-24}) for a patient population, such as a sample patient population after administration of the conjugate is between or between about 500 μg/mL*h and 8,000 μg/mL*h, between or between about 500 μg/mL*h and 5,000 μg/mL*h, between or between about 500 μg/mL*h and 2,000 μg/mL*h or between or between about 1000 μg/mL*h and 4,000 μg/mL*h.

[0028] In some examples, the conjugate is administered in a dosage range that is between or between about 75 mg/m^2 (body surface area of the subject) and 1500 mg/m^2, between or between about 75 mg/m^2 and 1000 mg/m^2, between or between about 75 mg/m^2 and 500 mg/m^2 or between or between about 75 mg/m^2 and 225 mg/m^2. In some examples, the conjugate is administered in a dosage range that is at least about or is about 160 mg/m^2, 320 mg/m^2, 640 mg/m^2 or 1280 mg/m^2.

[0029] Provided in some examples is a method of treating a disease lesion in a subject, that includes: a) intravenously administering to a subject having a lesion associated with a disease or condition a cetuximab-IR700 conjugate, wherein the conjugate is administered in an amount that is or is about 640 mg/m^2; and b) after administering the conjugate, irradiating the lesion at a wavelength of 690 ± 20 nm at a dose of at least or about at least or about 50 J cm^{-2}or 100 J/cm of fiber length, thereby treating the disease or condition in the subject.

[0030] In some examples, the conjugate is administered in a dosing schedule in which: the administration of the conjugate is performed only one time as a single injection or infusion; or the dosing schedule does not include a subsequent dose of the conjugate; or the dosing schedule does not include a subsequent dose of the targeting molecule that is not so conjugated.

[0031] In some examples, the irradiation is carried out 24 hours ± 3 hours, such as 24 hours ± 2 hours, after administering the conjugate.

[0032] In some examples, the lesion is a tumor and the disease or condition is a tumor or a cancer.

[0033] In some examples, the lesion is a tumor that is a superficial tumor. In some examples, the tumor is less than 10 mm thick. In some examples, irradiation is carried out using a microlens-tipped fiber for surface illumination. In some examples, the light irradiation dose is from or from about 5 J/cm^2 to about 200 J/cm^2.

[0034] Provided in some examples is a method for treating a superficial tumor with photoimmunotherapy, that includes illuminating an superficial tumor in a subject with a microlens-tipped fiber for surface illumination with a light dose of from or from about 5 J/cm^2 to about 200 J/cm^2, wherein the tumor is associated with a phototoxic agent that includes a targeting molecule bound to a cell surface molecule of the tumor. In some examples, the light irradiation dose is or is about 50 J/cm^2.

[0035] In some examples, the lesion is a tumor that is an interstitial tumor. In some examples, the tumor is greater than 10 mm deep or is a subcutaneous tumor. In some examples, irradiation is carried out using cylindrical diffusing fibers that includes a diffuser length of 0.5 cm to 10 cm and spaced 1.8 ± 0.2 cm apart. In some examples, the light irradiation dose is from or from about 20 J/cm fiber length to about 500 J/cm fiber length.

[0036] Provided in some examples is a method for treating an interstitial tumor with photommunotherapy, that includes illuminating an interstitial tumor in a subject with cylindrical diffusing fibers that includes a diffuser length of 0.5 cm to 10 cm and spaced 1.8 ± 0.2 cm apart with a light dose of or about 100 J/cm fiber length or with a fluence rate of or about 400 mW/cm, wherein the tumor is associated with a phototoxic agent that includes a targeting molecule bound to a cell surface molecule of the tumor.

[0037] In some examples, the light irradiation dose is from or from about 50 J/cm fiber length to about 300 J/cm fiber length. In some examples, the light irradiation dose is or is about 100 J/cm fiber length.

[0038] In some examples, the tumor is greater than 10 mm deep or is a subcutaneous tumor. In some examples, the cylindrical diffusing fibers are placed in a catheter positioned in the tumor 1.8 ± 0.2 cm apart. In some examples, the catheter is optically transparent.

[0039] In some examples, greater than 6 hours prior to illuminating the tumor, the subject has been administered the phototoxic agent that includes the targeting molecule, wherein the phototoxic agent associates with the tumor. In some examples, the phototoxic agent has been previously administered to the subject greater than or greater than about 12 hours, 24 hours, 26 hours, 48 hours, 72 hours or 96 hours prior to illuminating the tumor. In some examples, the phototoxic agent is a phthalocyanine dye-targeting molecule conjugate. In some examples, the phthalocyanine dye is IR700.

[0040] In some examples, in any of the methods for treating provided herein, the dosing schedule is repeated, whereby steps (a) and (b) are repeated. In some examples, the dosing schedule is repeated if residual lesion remains after a prior treatment with the conjugate. In some examples, the method additionally includes assessing the subject for the presence of a residual lesion and if residual lesion remains repeating the dosing schedule. In some examples, the dosing schedule is repeated if a residual lesion remains at a time that is more than or about or 1 week, 2 weeks, 3 weeks, 4 weeks, 2 months, 6 months or 1 year after initiation of the prior administration of the conjugate. In some examples, the dosing schedule is repeated if a residual lesion remains at or about 4 weeks after initiation of the prior administration of the conjugate.

[0041] In some examples, the conjugate contains 1 to 100, 1 to 10 or 2 to 5 phthalocyanine dye molecules per targeting molecule.

[0042] In some examples, the method does not contain administration of an additional therapeutic agent or anti-cancer treatment. In some examples, the method contains administration of an additional therapeutic agent or anti-cancer treatment. In some examples, the anti-cancer treatment contains radiation therapy.

[0043] In some examples, the additional therapeutic agent is an anti-cancer agent or an immune modulating agent. In some examples, the additional therapeutic agent is an immune modulating agent is an immune checkpoint inhibitor. In some examples, the immune checkpoint inhibitor specifically binds a molecule selected from among CD25, PD-1, PD-L1, PD-L2, CTLA-4, LAG-3, TIM-3, 4-1BB, GITR, CD40, CD40L, OX40, OX40L, CXCR2, B7-H3, B7-H4, BTLA, HVEM, CD28 and VISTA. In some examples, the immune checkpoint inhibitor is and antibody or antigen-binding fragment, a small molecule or a polypeptide. In some examples, the immune checkpoint inhibitor is selected from among nivolumab, pembrolizumab, pidilizumab, MK-3475, BMS-936559, MPDL3280A, ipilimumab, tremelimumab, IMP31, BMS-986016, urelumab, TRX518, dacetuzumab,

lucatumumab, SEQ-CD40, CP-870, CP-893, MED16469, MEDI4736, MOXR0916, AMP-224, and MSB001078C, or is an antigen-binding fragment thereof.

[0044] In some examples, the immune modulating agent is administered prior to irradiating the lesion or tumor. In some examples, the immune modulating agent is administered greater than or greater than about 30 minutes, 1 hour, 2 hours, 6 hours, 12 hours, 24 hours, 48 hours, 96 hours, one week, two weeks, three weeks or one month prior to irradiating the tumor.

[0045] In some examples, the provided methods include continued administration of the immune modulating agent subsequent to the irradiation three times a week, two times a week, once every week, once every two weeks, once every three weeks or once a month.

[0046] Provided in some examples is a method of treating a tumor in a subject that includes: a) administering to a subject an immune modulating agent; b) administering to the subject a therapeutically effective amount of a conjugate that includes a phthalocyanine dye linked to a targeting molecule capable of binding to a molecule on the surface of a cell present in the microenvironment of a tumor; and c) greater than 12 hours after administering the immune modulating agent, irradiating the tumor at a wavelength that renders the conjugate cytotoxic, thereby treating the tumor. In some examples, the immune modulating agent is administered greater than or greater than about 24 hours, 48 hours, 96 hours, one week, two weeks, three weeks or one month prior to irradiating the tumor.

[0047] In some examples, the conjugate binds to a protein on the surface of a cell present in the microenvironment of the tumor. In some examples of the provided methods, step c) of irradiating the tumor is carried out either i) after administration of the immune modulating agent and after administration of the conjugate or ii) only after administration of the conjugate.

[0048] In some examples, the conjugate is administered prior to, simultaneously or subsequently to administration of the immune-modulating agent. In some examples, the conjugate is administered after administering the immune modulating agent but prior to irradiating the tumor. In some examples, the conjugate is administered from or from about 12 hours to 48 hours prior to irradiating the tumor and the immune modulating agent is administered from or from about 12 hours to about 1 month prior to irradiating the tumor.

[0049] In some examples, the immune modulating agent is an immune checkpoint inhibitor. In some examples, the immune checkpoint inhibitor specifically binds a molecule selected from among CD25, PD-1, PD-L1, PD-L2, CTLA-4, LAG-3, TIM-3, 4-1BB, GITR, CD40, CD40L, OX40, OX40L, CXCR2, B7-H3, B7-H4, BTLA, HVEM, CD28

and VISTA. In some examples, the immune checkpoint inhibitor is and antibody or antigen-binding fragment, a small molecule or a polypeptide. In some examples, the immune checkpoint inhibitor is selected from among nivolumab, pembrolizumab, pidilizumab, MK-3475, BMS-936559, MPDL3280A, ipilimumab, tremelimumab, IMP31, BMS-986016, urelumab, TRX518, dacetuzumab, lucatumumab, SEQ-CD40, CP-870, CP-893, MED16469, MEDI4736, MOXR0916, AMP-224, and MSB001078C, or is an antigen-binding fragment thereof of any of the foregoing.

[0050] In some examples, the immune modulating agent that is a demethylating agent that upregulates expression of a tumor associated antigen (TAA) or is a cytokine.

[0051] In some examples, the provided methods include continued administration of the immune modulating agent subsequent to the irradiation three times a week, two times a week, once every week, once every two weeks, once every three weeks or once a month.

[0052] Provided in some examples is a method of treating a tumor in a subject that includes: a) administering to a subject an immune modulating agent that enhances the expression of a molecule on the surface of a cell present in the microenvironment of the tumor; b) administering to the subject a therapeutically effective amount of a conjugate that includes a phthalocyanine dye linked to a targeting molecule that is capable of binding to the cell surface molecule; and c) greater than 5 minutes after administering the conjugate, irradiating the tumor at a wavelength that renders the conjugate cytotoxic, thereby treating the tumor.

[0053] In some examples, the immune modulating agent is a cytokine or is an agent that induces increased expression of a cytokine in the tumor microenvironment. In some examples, the cytokine is interferon gamma.

[0054] In some examples, the molecule on the surface of the cells is selected from CD25, PD-1, PD-L1, PD-L2, CTLA-4, LAG-3, TIM-3, 4-1BB, GITR, CD40, CD40L, OX40, OX40L, CXCR2, B7-H3, B7-H4, BTLA, HVEM, CD28 and VISTA. In some examples, the molecule on the surface of the cell is PD-L1.

[0055] In some examples, the targeting molecule is an immune checkpoint inhibitor.

[0056] In some examples, the targeting molecule is an antibody or antibody fragment, a small molecule or a polypeptide. In some examples, the targeting molecule is selected from among nivolumab, pembrolizumab, pidilizumab, MK-3475, BMS-936559, MPDL3280A, ipilimumab, tremelimumab, IMP31, BMS-986016, urelumab, TRX518, dacetuzumab, lucatumumab, SEQ-CD40, CP-870, CP-893, MED16469, MED14736,

MOXR0916, AMP-224, and MSB001078C, or is an antigen-binding fragment thereof of any of the foregoing.

[0057] Provided in some examples is a method of treating a tumor in a subject that includes: a) administering to a subject a conjugate that includes a phthalocyanine dye linked to a targeting molecule capable of binding a cell surface molecule on a cell in the microenvironment of the tumor; b) greater than 5 minutes after administering the conjugate, irradiating the tumor at a wavelength that renders the conjugate cytotoxic, wherein the treatment of the tumor with the conjugate followed by light irradiation increases the presence of immunosuppressive cells in the tumor or increases the expression of immunosuppressive markers at the tumor; and c) administering to the subject a therapeutically effective amount of an immune modulating agent capable of reducing the amount or activity of immunosuppressive cells in the tumor or capable of blocking the activity of the immunosuppressive marker or reducing the activity of a tumor promoting cell in the tumor or capable of blocking the activity of the tumor promoting marker.

[0058] In some examples, the phthalocyanine dye is a first dye and the immune modulating agent includes a conjugate that includes a second phthalocyanine dye conjugated to an immune modulating agent capable of binding to the immunosuppressive cell or a tumor promoting cell. In some examples, the first and second phthalocyanine dye is the same or different.

[0059] In some examples, the immune modulating agent is an immune checkpoint inhibitor. In some examples, the immune modulating agent specifically binds a molecule selected from among CD25, PD-1, PD-L1, PD-L2, CTLA-4, LAG-3, TIM-3, 4-1BB, GITR, CD40, CD40L, OX40, OX40L, CXCR2, B7-H3, B7-H4, BTLA, HVEM, CD28 and VISTA.

[0060] In some examples, the immune modulating agent is an antibody or antibody fragment, a small molecule or a polypeptide.

[0061] In some examples, the immune modulating agent is not an anti-CTLA4 antibody.

[0062] In some examples, the immune modulating agent is selected from among nivolumab, pembrolizumab, pidilizumab, MK-3475, BMS-936559, MPDL3280A, ipilimumab, tremelimumab, IMP31, BMS-986016, urelumab, TRX518, dacetuzumab, lucatumumab, SEQ-CD40, CP-870, CP-893, MED16469, MED14736, MOXR0916, AMP-224, and MSB001078C, or is an antigen-binding fragment thereof of any of the foregoing.

[0063] Provided in some examples is a method of treating a tumor in a subject that includes: a) administering to a subject a conjugate that includes a phthalocyanine dye linked to a targeting targeting molecule capable of binding to a molecule on the surface of a cell present in the microenvironment of the tumor; b) greater than 5 minutes after administering the conjugate, irradiating the tumor at a wavelength that renders the conjugate cytotoxic, wherein the treatment of the tumor with the conjugate followed by light irradiation primes activation of immune cells; and c) administering to the subject a therapeutically effective amount of an immune modulating agent capable of increasing the activity of the immune cell.

[0064] In some examples, the immune cell is an antigen presenting cell. In some examples, the immune cell is a dendritic cell. In some examples, the immune modulating agent is selected from among GM-CSF, CpG-ODN (CpG oligodeoxynucleotides), lipopolysaccharide (LPS), monophosphoryl lipid A (MPL), alum, recombinant Leishmania polyprotein, imiquimod, MF59, poly I:C, poly A:U, type 1 IFN, Pam3Cys, Pam2Cys, complete freund's adjuvant (CFA), alpha-galactosylceramide, RC-529, MDF2β, Loxoribine, anti-CD40 agonist, SIRPa antagonist, AS04, AS03, Flagellin, Resiquimod, DAP (diaminopimelic acid), MDP (muramyl dipeptide) and CAF01(cationic adjuvant formulation-01). In some examples, the immune modulating agent is a Toll-like receptor (TLR) agonist, an adjuvant or a cytokine. In some examples, the immune modulating agent is a TLR agonist and the TLR agonist is TLR agonist is a TLR4 agonist, a TLR7 agonist, a TLR8 agonist, or a TLR9 agonist. In some examples, the TLR agonist is selected from among triacylated lipoprotein, diacylated lipopeptide, lipoteichoic acid, peptidoglycan, zymosan, Pam3CSK4, dsRNA, polyI:C, Poly G10, Poly G3, CpG, 3M003, flagellin, lipopolysaccharide (LPS) Leishmania homolog of eukaryotic ribosomal elongation and initiation factor 4a (LeIF), MEDI9197, SD-101, and imidazoquinoline TLR agonists.

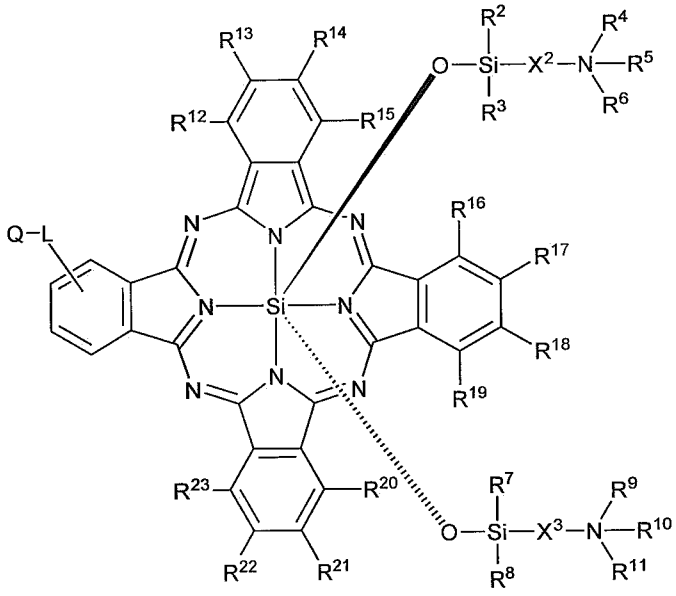
[0065] In some examples, the immune modulating agent is a cytokine and the cytokine is IL-4, TNF-α, GM-CSF or IL-2. In some examples, the immune modulating agent is administered prior to, simultaneously with or after the irradiation. In some examples, the immune modulating agent is administered no more than 5 minutes, 30 minutes, 60 minutes, 2 hours, 6 hours, 12 hours or 24 hours after the irradiation. In some examples, the immune modulating agent is administered no more than 5 minutes, 30 minutes, 60 minutes, 2 hours, 6 hours, 12 hours or 24 hours before the irradiation.

[0066] In some examples, the targeting molecule binds to molecule or protein directly or indirectly. In some examples, the targeting molecule is a second binding molecule that binds to a first binding molecule, said first binding molecule being capable of binding to the molecule or protein. In some examples, the targeting molecule is a secondary antibody.

[0067] In some examples, the phthalocyanine dye has a maximum absorption wavelength from or from about 600 nm to about 850 nm.

[0068] In some examples, the phthalocyanine dye is covalently or non-covalently linked to the targeting molecule. In some examples, the phthalocyanine dye includes a linker that includes a reactive group for attachment of the dye to the targeting molecule.

[0069] In some examples, the phthalocyanine dye includes the formula:



, wherein:

L is a linker;

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

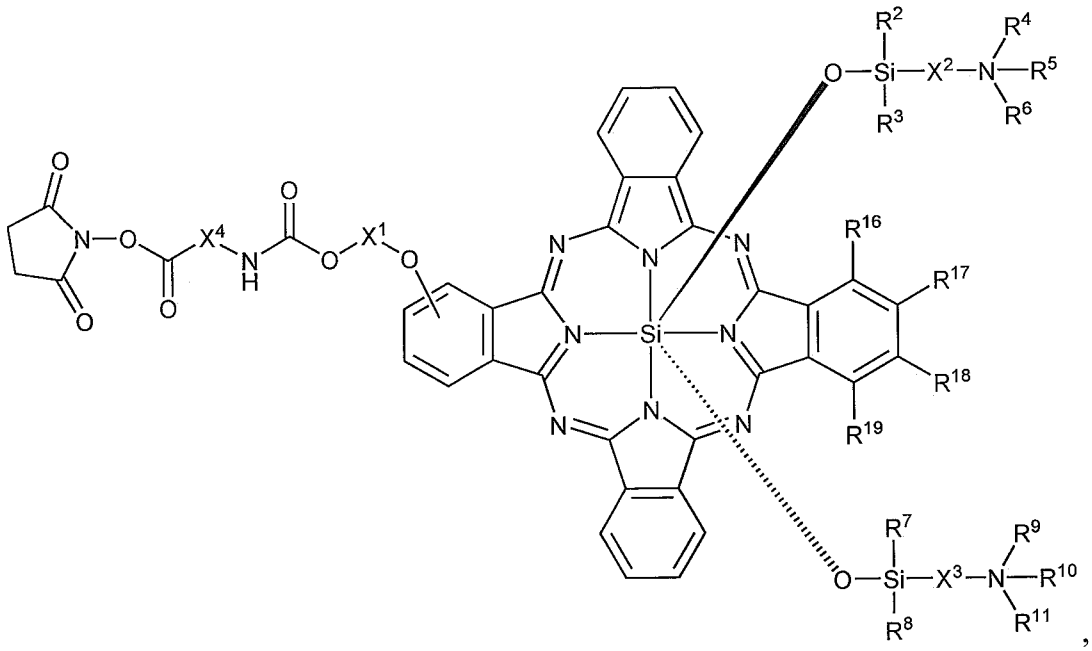
R^2, R^3, R^7, and R^8 are each independently selected from optionally substituted alkyl and optionally substituted aryl;

R^4, R^5, R^6, R^9, R^{10}, and R^{11} are each independently selected from 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} includes 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 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.

[0070] In some examples, the phthalocyanine dye includes 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 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} includess a water soluble group; and

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

[0071] In some examples, the phthalocyanine dye includes IRDye 700DX (IR700).

[0072] In some examples, the conjugate is administered at a dose from or from about 50 mg/m^2 to about 5000 mg/m^2, from about 250 mg/m^2 to about 2500 mg/m^2, from about 750 mg/m^2 to about 1250 mg/m^2 or from about 100 mg/m^2 to about 1000 mg/m^2.

[0073] 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 tumor is a sarcoma or carcinoma. In some examples, the tumor is a carcinoma that is a squamous cell carcinoma, basal cell carcinoma or adenocarcinoma. In some examples, the tumor is a carcinoma that is a carcinoma of the bladder, pancreas, colon, ovary, lung, breast, stomach, prostate, cervix, esophagus or head and neck.

[0074] In some examples, the tumor is irradiated at a wavelength of 600 nm to 850 nm at a dose of at least 1 J cm^{-2} or at least 1 J/cm fiber length. In some examples, the tumor is irradiated at a wavelength of 690 nm ± 50 nm or at a wavelength of or about 690 ± 20 nm.

[0075] In some examples, the method reduces the size or volume of the tumor by at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80% at least 90 % or more within one month of the irradiation compared to the size or volume of the tumor prior to the administration and irradiation.

[0076] In some examples, the method of PIT treatment using the phthalocyanine dye conjugate, such as in accord with any of the methods above or provided herein, results in an improvement of a disorder- or cancer-related parameter in a population of treated subjects compared to a similarly situated population of subjects treated with the antibody or antigen-binding antibody fragment that is not conjugated. In some examples, the parameter is selected from one or more of: a) objective response rate (ORR); b) progression free survival (PFS); c) overall survival (OS); d) reduction in toxicity; e) tumor response; or f) quality of life.

[0077] In some examples, the parameter is improved by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100% or more.

[0078] In some examples, the method of PIT treatment using the phthalocyanine dye conjugate, such as in accord with any of the methods above or provided herein, results in an objective response rate (ORR) that is at least 15%, at least 25%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or more in a population of treated subjects.

[0079] In some examples, the conjugate contains a phthalocyanine dye as a first dye and further contains a second fluorescent dye linked to the targeting molecule that is different than the first dye. In some examples, the second fluorescent dye exhibits one or more spectral properties selected from among fluorescent quantum yield in water, extinction coefficient, Stokes shift, absorption and emission at long wavelength and photostability that is greater compared to the corresponding spectral property of the first dye. In some

examples, the lesion or tumor emits a fluorescence signal from the second fluorescent dye to effect detection of the presence of the conjugate at the lesion or tumor in the subject. In some examples, the provided method further includes imaging the lesion or tumor in the subject by irradiating or illuminating the tumor at a wavelength capable of being absorbed by the second dye.

[0080] In some examples, the first dye is IR700. In some examples, the second dye is not IR700. In some examples, the second dye is selected from among hydroxycoumarin, Cascade Blue, Dylight 405, Pacific Orange, Alexa Fluor 430, Fluorescein, Oregon Green, Alexa Fluor 488, BODIPY 493, 2.7-Diochlorofluorescien, ATTO 488, Chromeo 488, Dylight 488, HiLyte 488, Alexa Fluor 555, ATTO 550, BODIPY TMR-X, CF 555, Chromeo 546, Cy3, TMR, TRITC, Dy547, Dy548, Dy549, HiLyte 555, Dylight 550, BODIPY 564, Alexa Fluor 568, Alexa Fluor 594, Rhodamine, Texas Red, Alexa Fluor 610, Alexa Fluor 633, Dylight 633, Alexa Fluor 647, APC, ATTO 655, CF633, CF640R, Chromeo642, Cy5, Dylight 650, Alexa Fluor 680, IRDye 680, Alexa Fluor 700, Cy 5.5, ICG, Alexa Fluor 750, Dylight 755, IRDye 750, Cy7, Cy7.5, Alexa Fluor 790, Dylight 800, IRDye 800, Qdot® 525, Qdot® 565, Qdot® 605, Qdot® 655, Qdot® 705 and Qdot® 800.

[0081] In some examples, the first dye is IR700 and the conjugate contains 1 to 10 or 1 to 5 second dye molecules per targeting molecule.

[0082] In some examples, the second dye exhibits a Stokes shift that is greater than 15 nm, greater than 20 nm, greater than 30 nm, greater than 40 nm, greater than 50 nm, greater than 60 nm, greater than 70 nm, greater than 80 nm, greater than 90 nm or greater than 100 nm.

[0083] In some examples, the second dye has a quantum yield in water that is greater than 10%, greater than 15%, greater than 20% or greater than 25%, greater than 30%, greater than 40%, greater than 50% or greater.

[0084] In some examples, the second dye has an absorption and emission wavelength in the spectrum between or between about 650 nm and 950 nm, between or between about 700 nm and 1000 nm, or between or between about 1000 nm and 1700 nm.

[0085] In some examples, the first dye and second dye do not exhibit an overlapping emission and absorption spectra. In some examples, the second dye is selected from among ICG, IRDye 680, Alexa Fluor 750, Dylight 755, IRDye 750, Cy7.5, Alexa Fluor 790, Dylight 800 and IRDye 800. In some examples, the second dye is Alexa Fluor 488, IRDye 680, IRDye 800 or Dylight 755.

[0086] In some examples, the method further includes irradiating or illuminating the tumor at a wavelength capable of being absorbed by the second dye, thereby imaging the subject. In some examples, the irradiation or illumination of the tumor is performed with a device selected from among a hand-held ultraviolet lamp, a mercury lamp, a xenon lamp, a laser, a laser diode or an imaging device. In some examples, the LED imaging device contains a near-infrared (NIR) diode.

[0087] Provided in some examples is a composition containing a conjugate containing a phthalocyanine dye linked to an antibody or antigen-binding antibody fragment that binds to a molecule on the surface of a cell present in the microenvironment of a lesion, such as the tumor microenvironment. In some examples, the composition is formulated for single dosage administration of the conjugate in an amount that is between or between about 100 mg and 1200 mg. In some examples, the composition is formulated for single dosage administration of an amount between or between about 100 mg and 500 mg or between or between about 200 mg and 400 mg. In some examples, the composition is formulated for single dosage administration of an amount between or between about 500 mg and 1500 mg, 800 mg and 1200 mg or 1000 mg and 1500 mg.

[0088] In some examples, the volume of the composition is between or between about 10 mL and 500 mL or 50 mL and 250 mL. In some examples, the volume of the composition is at least 10 mL, 20 mL, 30 mL, 40 mL, 50 mL, 75 mL, 100 mL, 150 mL, 200 mL, 250 mL, 300 mL, 400 mL or 500 mL. In some examples, the volume of the composition is between or between about 10 mL and 1000 mL or 50 mL and 500 mL; or the volume of the composition is at least 10 mL, 20 mL, 30 mL, 40 mL, 50 mL, 75 mL, 100 mL, 150 mL, 200 mL, 250 mL, 300 mL, 400 mL, 500 mL or 1000 mL.

[0089] Provided in some examples is an article of manufacture, including a plurality of sealable containers, each individually containing a fraction of a single administration dose of a composition containing a conjugate containing a phthalocyanine dye linked to an antibody or antigen-binding antibody fragment that binds to a molecule on the surface of a cell present in the microenvironment of a lesion, such as the tumor microenvironment. In some examples, the combined amount of the conjugate in the plurality of sealable containers is between or between about 100 mg and 1500 mg, or 100 mg and 1200 mg. In some examples, the article of manufacture contains packaging material and a label or package insert containing instructions for combining the contents of the plurality of vials to prepare a single dosage formulation of the composition.

[0090] In some examples, the combined amount of the conjugate in the plurality of sealable containers is between or between about 100 mg and 1200 mg. In some examples, the combined amount of the conjugate in the plurality of sealable container is between or between about 100 mg and 500 mg, between or between about 200 mg and 400 mg, between or between about 500 mg and 1500 mg, between or between about 800 mg and 1200 mg or between or between about 1000 mg and 1500 mg.

[0091] In some examples, the lesion is a tumor.

[0092] Provided in some examples is a conjugate, that includes a phthalocyanine dye linked to an antibody or antigen-binding fragment that is an immune modulating agent. In some examples, the immune modulating agent is an immune checkpoint inhibitor.

[0093] In some examples, the immune modulating agent is an antibody or antigen binding fragment that binds to the surface of a tumor, tumor cell or cancer cell. In some examples, the immune modulating agent specifically binds a molecule selected from among CD25, PD-1, PD-L1, PD-L2, CTLA-4, LAG-3, TIM-3, 4-1BB, GITR, CD40, CD40L, OX40, OX40L, CXCR2, B7-H3, B7-H4, BTLA, HVEM, CD28 and VISTA. In some examples the immune modulating agent is selected from among nivolumab, pembrolizumab, pidilizumab, MK-3475, BMS-936559, MPDL3280A, ipilimumab, tremelimumab, IMP31, BMS-986016, urelumab, TRX518, dacetuzumab, lucatumumab, SEQ-CD40, CP-870, CP-893, MED16469, MED14736, MOXR0916, AMP-224, and MSB001078C, or is an antigen-binding fragment thereof of any of the foregoing. In some examples, the immune modulating agent is an antibody or antibody fragment that binds to PD-L1.

[0094] In some examples, the immune modulating agent is an antibody selected from BMS-935559, MEDI4736, MPDL3280A and MSB0010718C, or an antigen-binding fragment thereof.

[0095] Provided in some examples is a conjugate that contains a targeting molecule linked to at least a first and second fluorescent dye. In some examples, the first fluorescent dye is a phthalocyanine dye capable of exhibiting phototoxicity.

[0096] In some examples, the conjugate has the formula:

$[D_1\text{-}(L_1)_n]_p - A - [(L_2)_m\text{-}D_2]_o$, wherein:

A is a targeting molecule that can bind to a molecule on the surface of a cell;

L_1 and L_2 are each an independently selected linker, which can be the same or different;

n and m are independently 1 or 2;

D_1 is a first dye that is the phthalocyanine dye capable of exhibiting phototoxicity;

D_2 is a second dye that is a fluorescent dye, wherein D_2 is different than D_1;

p is 1 to 10; and

o is 1 to 10.

[0097] In some examples, the targeting molecule is an antibody or an antigen-binding antibody fragment.

[0098] In some examples, the cell surface molecule contains an antigen, a polypeptide, a lipid, or a carbohydrate or a combination of these molecules.

[0099] In some examples, the cell surface molecule is selected from among 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, 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, ITGAM, Kalikrien-9, Lewis Y, LH receptor, LHRH-R, LPA1, MAC-1, MAGE 1, MAGE 2, MAGE 3, MAGE 4, MART1, MC1R, Mesothelin, MUC1, MUC16, 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.

[0100] In some examples, the cell surface molecule is selected from among HER1/EGFR, HER2/ERBB2, CD20, CD25 (IL-2Rα receptor), CD33, CD52, CD133, CD206, CEA, CEACAM1, CEACAM3, CEACAM5, CEACAM6, cancer antigen 125 (CA125), alpha-fetoprotein (AFP), Lewis Y, TAG72, Caprin-1, mesothelin, PDGF receptor, PD-1, PD-L1, CTLA-4, IL-2 receptor, vascular endothelial growth factor (VEGF), CD30, EpCAM, EphA2, Glypican-3, gpA33, mucins, CAIX, PSMA, folate-binding protein, gangliosides (such as GD2, GD3, GM1 and GM2), VEGF receptor (VEGFR), integrin αVβ3, integrin α5β1, ERBB3, MET, IGF1R, EPHA3, TRAILR1, TRAILR2, RANKL, FAP, tenascin, AFP, BCR complex, CD3, CD18, CD44, CTLA-4, gp72, HLA-DR 10 β, HLA-DR antigen, IgE, MUC-1, nuC242, PEM antigen, metalloproteinases, Ephrin receptor, Ephrin ligands, HGF receptor, CXCR4, CXCR4, Bombesin receptor, and SK-1 antigen.

[0101] In some examples, the cell surface molecule is selected from among CD25, PD-1 (CD279), PD-L1 (CD274, B7-H1), PD-L2 (CD273, B7-DC), CTLA-4, LAG3 (CD223), TIM3 (HAVCR2), 4-1BB (CD137, TNFRSF9), CXCR2, CXCR4 (CD184), CD27, CEACAM1, Galectin 9, BTLA, CD160, VISTA (PD1 homologue), B7-H4 (VCTN1), CD80 (B7-1), CD86 (B7-2), CD28, HHLA2 (B7-H7), CD28H, CD155, CD226, TIGIT, CD96, Galectin 3, CD40, CD40L, CD70, LIGHT (TNFSF14), HVEM (TNFRSF14), B7-H3 (CD276), Ox40L (TNFSF4), CD137L (TNFSF9, GITRL), B7RP1, ICOS (CD278), ICOSL, KIR, GAL9, NKG2A (CD94), GARP, TL1A, TNFRSF25, TMIGD2, BTNL2, Butyrophilin family, CD48, CD244, Siglec family, CD30, CSF1R, MICA (MHC class I polypeptide-related sequence A), MICB (MHC class I polypeptide-related sequence B), NKG2D, KIR family (Killer-cell immunoglobulin-like receptor, LILR family (Leukocyte immunoglobulin-like receptors, CD85, ILTs, LIRs), SIRPA (Signal regulatory protein alpha), CD47 (IAP), Neuropilin 1 (NRP-1), a VEGFR, and VEGF.

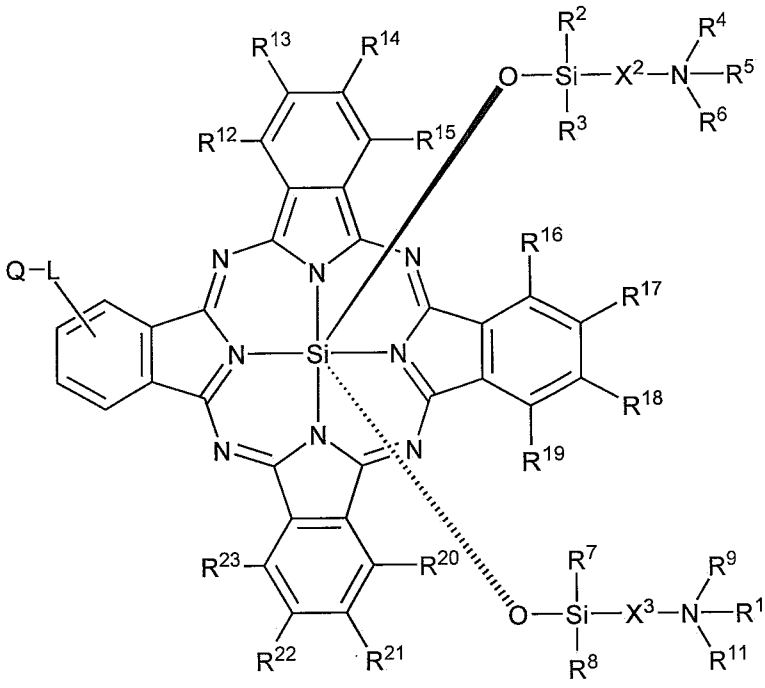
[0102] In some examples, the targeting molecule is an antibody or an antigen-binding fragment that is selected from among cetuximab, panitumumab, zalutumumab, nimotuzumab, Tositumomab (Bexxar ®), Rituximab (Rituxan, Mabthera), Ibritumomab tiuxetan (Zevalin), Daclizumab (Zenapax), Gemtuzumab (Mylotarg), Alemtuzumab, CEA-scan Fab fragment, OC125 monoclonal antibody, ab75705, B72.3, Bevacizumab (Avastin ®), Basiliximab, nivolumab, pembrolizumab, pidilizumab, MK-3475, BMS-936559, MPDL3280A, ipilimumab, tremelimumab, IMP321, BMS-986016, LAG525, urelumab, PF-05082566, TRX518, MK-4166, dacetuzumab, lucatumumab, SEA-CD40, CP-870, CP-893, MED16469,

MEDI6383, MEDI4736, MOXR0916, AMP-224, PDR001, MSB0010718C, rHIgM12B7, Ulocuplumab, BKT140, Varlilumab (CDX-1127), ARGX-110, MGA271, lirilumab (BMS-986015, IPH2101), IPH2201, AGX-115, Emactuzumab, CC-90002 and MNRP1685A or is an antigen-binding fragment thereof.

[0103] In some examples, the targeting molecule is not or does not include a nanocarrier. In some examples, the targeting molecule is not or does not include a virus-like particle, a nanoparticle, a liposome, a quantum dot, or a combination thereof.

[0104] In some examples, the first dye that is a phthalocyanine dye that has a maximum absorption wavelength from or from about 600 nm to about 850 nm.

[0105] In some examples, the first dye that is a phthalocyanine dye contains the formula:



, wherein:

L is a linker;

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

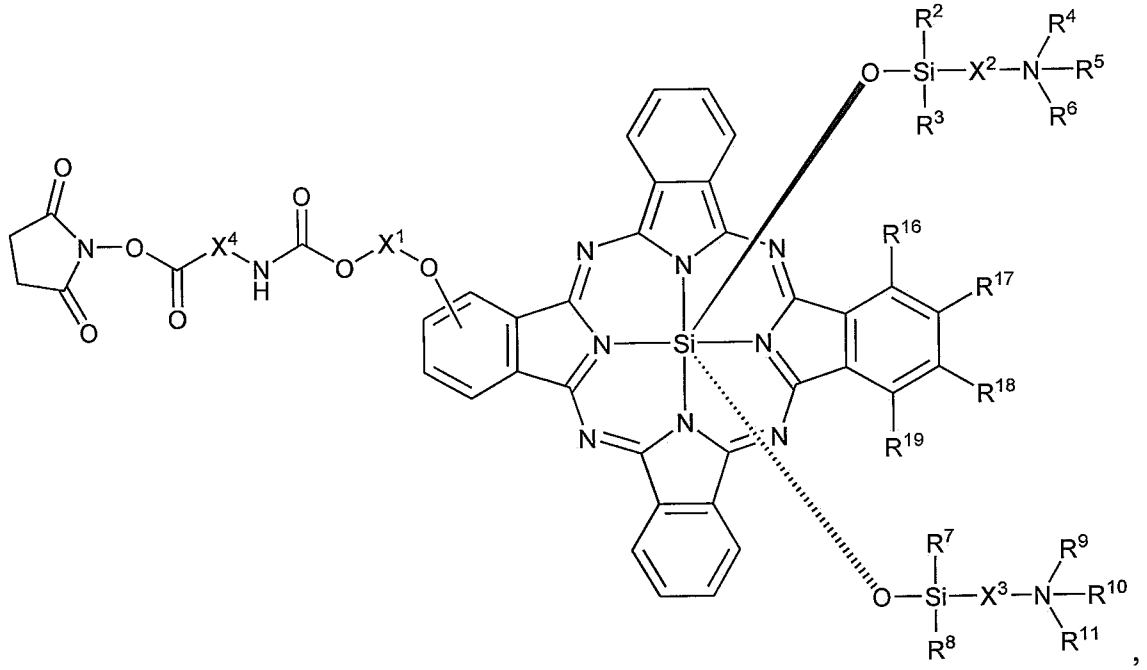
R^2, R^3, R^7, and R^8 are each independently selected from optionally substituted alkyl and optionally substituted aryl;

R^4, R^5, R^6, R^9, R^{10}, and R^{11} are each independently selected from 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} contains 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 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.

[0106] In some examples, the first dye that is a phthalocyanine dye contains 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 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} contains a water soluble group; and

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

[0107] In some examples, the first dye that is a phthalocyanine dye contains IRDye 700DX (IR700).

[0108] In some examples, the second fluorescent dye exhibits one or more spectral properties selected from among fluorescent quantum yield in water, extinction coefficient, Stokes shift, absorption and emission at long wavelength and photostability that is greater compared to the corresponding spectral property of the first dye.

[0109] In some examples, the second dye is not IR700. In some examples, the second dye is selected from among hydroxycoumarin, Cascade Blue, Dylight 405, Pacific Orange, Alexa Fluor 430, Fluorescein, Oregon Green, Alexa Fluor 488, BODIPY 493, 2.7-Diochlorofluorescien, ATTO 488, Chromeo 488, Dylight 488, HiLyte 488, Alexa Fluor 555, ATTO 550, BODIPY TMR-X, CF 555, Chromeo 546, Cy3, TMR, TRITC, Dy547, Dy548, Dy549, HiLyte 555, Dylight 550, BODIPY 564, Alexa Fluor 568, Alexa Fluor 594, Rhodamine, Texas Red, Alexa Fluor 610, Alexa Fluor 633, Dylight 633, Alexa Fluor 647, APC, ATTO 655, CF633, CF640R, Chromeo642, Cy5, Dylight 650, Alexa Fluor 680, IRDye 680, Alexa Fluor 700, Cy 5.5, ICG, Alexa Fluor 750, Dylight 755, IRDye 750, Cy7, Cy7.5, Alexa Fluor 790, Dylight 800, IRDye 800, Qdot® 525, Qdot® 565, Qdot® 605, Qdot® 655, Qdot® 705 and Qdot® 800.

[0110] In some examples, the first dye is IR700 and the conjugate contains 1 to 10 or 1 to 5 second dye molecules per targeting molecule.

[0111] In some examples, the second dye exhibits a Stokes shift that is greater than 15 nm, greater than 20 nm, greater than 30 nm, greater than 40 nm, greater than 50 nm, greater than 60 nm, greater than 70 nm, greater than 80 nm, greater than 90 nm or greater than 100 nm.

[0112] In some examples, the second dye has a quantum yield in water that is greater than 10%, greater than 15%, greater than 20% or greater than 25%, greater than 30%, greater than 40%, greater than 50% or greater.

[0113] In some examples, the second dye has an absorption and emission wavelength in the spectrum between or between about 650 nm and 950 nm, between or between about 700 nm and 1000 nm, between or between about 1000 nm and 1700 nm.

[0114] In some examples, the first dye and second dye do not exhibit an overlapping emission and absorption spectra.

[0115] In some examples, the second dye is selected from among ICG, IRDye 680, Alexa Fluor 750, Dylight 755, IRDye 750, Cy7.5, Alexa Fluor 790, Dylight 800 and IRDye 800. In some examples, the second dye is Alexa Fluor 488, IRDye 680, IRDye 800 or Dylight 755.

[0116] Provided in some examples is a composition, containing any of the conjugates described herein. In some examples, the composition further contains a pharmaceutically acceptable excipient.

[0117] Provided in some examples is a method of treating a disease or condition in a subject that includes: a) administering to the subject a therapeutically effective amount of any of the conjugates or compositions described herein, wherein the conjugate binds to a cell present in the microenvironment of a lesion associated with a disease or condition; and b) after administering the conjugate, irradiating the lesion at one or more wavelengths to induce phototoxic activity of the conjugate, thereby treating the disease or condition.

[0118] Provided in some examples is a method of treating a disease or a condition, such as a tumor in a subject using photoimmunotherapy (PIT), that includes administering to the subject a therapeutically effective amount of any of the conjugates or compositions described herein. In some examples, the method includes irradiating the tumor at a wavelength of 660 nm to 740 nm at a dose of at least 1 J cm^{-2} or 1 J/cm of fiber length, thereby treating the disease or condition in the subject.

[0119] Provided in some examples is a method of treating a disease or condition in a subject that includes: a) administering to the subject a therapeutically effective amount of of any of the conjugates or compositions described herein, wherein the conjugate binds to a cell present in the microenvironment of a lesion associated with a disease or condition; and b) after administering the conjugate, irradiating the lesion at one or more wavelengths to induce phototoxic activity of the first dye of the conjugate and a fluorescent signal of the second dye of the conjugate.

[0120] In some examples, the provided methods include irradiating the lesion at a wavelength that is from or from about 400 to about 900 nm at a dose of at least 1 J cm^{-2}or 1 J/cm of fiber length. In some examples, the provided methods include irradiating the lesion with a single wavelength. In some examples, the provided methods include irradiating the lesion at two different wavelengths, simultaneously or sequentially, wherein one wavelength induces the phototoxic activity and the other wavelength induces the fluorescent signal.

[0121] In some examples, the disease or condition is a tumor.

[0122] In some examples, the provided methods include irradiating the tumor at a wavelength of 660 nm to 740 nm and at a dose of at least 1 J cm^{-2}, thereby treating the tumor in the subject.

[0123] 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 tumor is a sarcoma or carcinoma. In some examples, the tumor is a carcinoma that is a squamous cell carcinoma, basal cell carcinoma or adenocarcinoma. In some examples, the tumor is a carcinoma that is a carcinoma of the bladder, pancreas, colon, ovary, lung, breast, stomach, prostate, cervix, esophagus or head and neck.

[0124] In some examples, prior to administration of the conjugate, the targeting molecule is administered to the subject. In some examples, the targeting molecule is administered up to 96 hours prior to administration of the conjugate. In some examples, the targeting molecule is administered at a dose within a range from or from about 10 mg/m^2 to about 500 mg/m^2. In some examples, the targeting molecule is an antibody or antigen binding fragment, such as cetuximab. In some examples, cetuximab is administered to the subject prior to the administration of the conjugate.

Brief Description of the Drawings

[0125] **FIG. 1** shows the dose response curves of cetuximab and cetuximab-IRDye 700DX conjugate for the inhibition of EGFR phosphorylation in A431 cells.

[0126] **FIG. 2** shows the dose response curve for photoimmunotherapy (PIT) with the cetuximab-IRDye 700DX conjugate using 8 J/cm^2 of 690 nm light on A431 cells.

[0127] **FIG. 3** shows the comparison of dose response curves for the photoimmunotherapy (PIT) with the cetuximab-IRDye 700DX conjugate using 16 J/cm^2 versus 32 $J/cm^2$of 690 nm light on BxPC3 cells.

[0128] **FIG. 4** shows the schematic structure for the dual-labeled panitumumab-IR700DX-Alexa-488 conjugate.

[0129] **FIGS. 5A and 5B** show the progression of cell death after photoimmunotherapy (PIT) induced by different conjugates at various light dosages (0–16 J/cm^2) on BxPC3 pancreatic cancer cells. FIG. 5A shows cells death after PIT using single-labeled panitumumab-IR700 conjugate. FIG. 5B shows cell death after PIT using a dual-labeled panitumumab-IR700-Alexa-488 conjugate.

[0130] **FIG. 6A** shows the duration of exposure of Cetuximab-IRDye 700DX to 500 Lux white fluorescent light or green LED light and its effect on soluble aggregate formation.

[0131] **FIG. 6B** shows the effect of pre-exposure of Cetuximab-IRDye 700DX to white fluorescent light or green LED light on BxPC3 PIT activity.

CLAIMS

1. Use of a pharmaceutical composition comprising a conjugate, the conjugate comprising a phthalocyanine dye linked to a targeting molecule that binds to a protein on the surface of a cell present in the microenvironment of a lesion associated with a disease or condition, for preparation of a medicament formulated for intravenous administration in a dosing schedule for treating a lesion associated with a disease or condition in a subject, wherein the dosing schedule comprises:

a) that the medicament is to be intravenously administered to the subject having a lesion associated with a disease or condition the conjugate in an amount that is between about 160 mg/m^2 and about 2000 mg/m^2; and

b) after administration of the conjugate, the lesion is to be irradiated at a wavelength of 600 nm to 850 nm at a dose from or from about 25 J cm^{-2} to about 400 J cm^{-2} or from or from about 25 J/cm fiber length to about 500 J/cm fiber length,

wherein the disease or condition is a cancer.

2. The use of claim 1, wherein the targeting molecule is an antibody or an antigen-binding antibody fragment.

3. The use of claim 1 or 2, wherein the protein on the surface of the cell is selected from among 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, 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, CTLA-4, 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, ITGAM, Kalikrien-9, Lewis Y, LH receptor, LHRH-R, LPA1, MAC-1, MAGE 1, MAGE 2, MAGE 3, MAGE 4, MART1, MC1R, Mesothelin, MUC1, MUC16, 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, PD-1, PD-L1, 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.

4. The use of any one of claims 1-3, wherein the antibody or the antigen-binding antibody fragment is selected from among cetuximab, panitumumab, zalutumumab, nimotuzumab, Tositumomab (Bexxar ®), Rituximab (Rituxan, Mabthera), Ibritumomab tiuxetan (Zevalin), Daclizumab (Zenapax), Gemtuzumab (Mylotarg), Alemtuzumab, CEA-scan Fab fragment, OC125 monoclonal antibody, ab75705, B72.3, Bevacizumab (Avastin ®), Basiliximab, nivolumab, pembrolizumab, pidilizumab, MK-3475, BMS-936559, MPDL3280A, ipilimumab, tremelimumab, IMP321, BMS-986016, LAG525, urelumab, PF-05082566, TRX518, MK-4166, dacetuzumab, lucatumumab, SEA-CD40, CP-870, CP-893, MED16469, MEDI6383, MEDI4736, MOXR0916, AMP-224, PDR001, MSB0010718C, rHIgM12B7, Ulocuplumab, BKT140, Varlilumab (CDX-1127), ARGX-110, MGA271, lirilumab (BMS-986015, IPH2101), IPH2201, AGX-115, Emactuzumab, CC-90002 and MNRP1685A or is an antigen-binding antibody fragment thereof.

5. The use of any one of claims 1-4, wherein the antibody or antigen-binding antibody fragment is cetuximab.

6. The use of claim 5, wherein the disease or condition is a head or neck cancer.

7. The use of any one of claims 1-6, wherein the irradiation is to be carried out between about 30 minutes and 96 hours after administration of the conjugate.

8. The use of any one of claims 1-7, wherein the irradiation is to be carried out 24 hours ± 4 hours after administration of the conjugate.

9. The use of any one of claims 1-8, wherein the phthalocyanine dye is IR700.

10. The use of any one of claims 1-9, wherein the lesion is to be irradiated at a wavelength of 690 ± 50 nm or at a wavelength of or about 690 ± 20 nm.

11. The use of any one of claims 1-10, wherein the lesion is to be irradiated at a dose of or of about 50 J cm^{-2} or 100 J/cm of fiber length.

12. The use of any one of claims 1-11, wherein the dosing schedule is to be repeated, whereby steps (a) and (b) are to be repeated.

13. The use of claim 12, wherein the dosing schedule is to be repeated if a residual lesion remains at a time that is more than or about 2 weeks, 3 weeks, 4 weeks, 2 months, 6 months or 1 year after initiation of the prior administration of the conjugate.

14. The use of claim 13, wherein the dosing schedule is to be repeated if a residual lesion remains at or about 4 weeks after initiation of the prior administration of the conjugate.

15. The use of any one of claims 1-14, wherein the lesion is a tumor that is a superficial tumor.

16. The use of claim 15, wherein the irradiation step comprises illumination of the superficial tumor with a microlens-tipped fiber for surface illumination.

17. The use of any one of claims 1-16, wherein the lesion is a tumor that is a subcutaneous tumor.

18. The use of claim 17, wherein the irradiation step is to be carried out using cylindrical diffusing fibers

19. The use of claim 18, wherein the cylindrical diffusing fibers comprise a diffuser length of 0.5 cm to 10 cm and spaced 1.8 ± 0.2 cm apart.

20. Use of a pharmaceutical composition comprising a conjugate comprising a phthalocyanine dye linked to cetuximab for preparation of a medicament formulated for intravenous administration in a dosing schedule for treating a tumor in a subject having a head or neck cancer, wherein the dosing schedule comprises:

a) that the medicament is to be intravenously administered, to the subject having a tumor associated with a head or neck cancer, the conjugate in an amount that is between about 160 mg/m^2 and about 2000 mg/m^2; and

b) after administration of the conjugate, the lesion is to be irradiated at a wavelength of or of about 690 ± 50 nm at a dose of at least or about at least or about 50 J cm^{-2}or 100 J/cm of fiber length.

21. The use of claim 20, wherein the conjugate is to be administered in an amount that is or is about 640 mg/m^2.

22. The use claim 20 or 21, wherein the irradiation is to be carried out at a wavelength of or about 690 ± 20 nm.

23. The use of any one of claims 20-22, wherein the irradiation is to be carried out 24 hours ± 4 hours after administration of the conjugate.

24. The use of any one of claims 20-23, wherein the dosing schedule is to be repeated if a residual lesion remains at or about 4 weeks after initiation of the prior administration of the conjugate.

25. The use of any one of claims 1-24, wherein the dosing schedule further comprises administration of an additional therapeutic agent or anti-cancer treatment.