PHTHALOCYANINE DYE CONJUGATE COMPOSITIONS

Cross-Reference to Related Applications

[0001] This application claims priority from U.S. provisional application No. 62/679,747, filed June 1, 2018, entitled "PHTHALOCYANINE DYE CONJUGATE COMPOSITIONS," the contents of which are incorporated by reference in their entirety.

Field

[0002] The present disclosure relates in some aspects to compositions containing a conjugate containing a phthalocyanine dye and one or more stabilizing agents. In some aspects, the compositions containing the conjugate are more stable and/or less prone to aggregation with the stabilizing agent than compositions that do not contain the stabilizing agent. In some aspects, the disclosure further relates to articles of manufacture containing the compositions and to methods for their administration to subjects for photoimmunotherapy. In some embodiments, the conjugate included in the compositions described herein contains a phthalocyanine dye linked to an antibody, for example an antibody-IR700 conjugate, such as a cetuximab-IR700 conjugate.

Background

[0003] 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 to a cell surface target molecule, *e.g.,* a cell surface receptor, 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 phthalocyanine dye conjugates for use in PIT. Provided are compositions and methods that meet such needs.

Summary

[0004] Provided in some examples is a pharmaceutical composition containing a conjugate, such as an antibody-IR700 conjugate, that exhibits reduced aggregation or reduces or prevents aggregation of the conjugate. In some of any examples, the pharmaceutical composition includes (1) a conjugate including an antibody linked to a phthalocyanine dye such as IR700 and (2) one or more stabilizing agents in an amount effective to reduce or prevent aggregation of the conjugate, wherein the one or more stabilizing agents include a

surfactant, such as a non-ionic surfactant or a zwitterionic surfactant, and/or a protectant.

[0005] In some of any examples, the cell surface molecule is HER1 (also known as epidermal growth factor receptor, ErbB-1, and EGFR) and/or the antibody is cetuximab. In some of any examples, the antibody binds to HER1 (EGFR) or a portion thereof. In some of any examples, the antibody is cetuximab or a biosimilar, interchangeable, or biobetter thereof. In some of any examples, the antibody is cetuximab. In some of any examples, the conjugate is cetuximab-IR700.

[0006] Also provided herein are pharmaceutical compositions that include (1) a conjugate comprising a cetuximab or a biosimilar, interchangeable, or biobetter thereof linked to IR700 and (2) one or more stabilizing agents in an amount effective to reduce or prevent aggregation of the conjugate, wherein the one or more stabilizing agents comprises a surfactant and/or a protectant. In one aspect, the present disclosure refers to a pharmaceutical composition comprising: (1) a conjugate comprising a cetuximab antibody or a biosimilar, interchangeable, or biobetter thereof linked to IR700 and (2) one or more stabilizing agents in an amount effective to reduce or prevent aggregation of the conjugate, wherein the one or more stabilizing agents comprises a surfactant and/or a protectant.

[0007] In some of any examples, the one or more stabilizing agents comprises a surfactant. In some of any examples, the one or more stabilizing agents include a surfactant, such as a non-ionic surfactant. In some of any examples, the non-ionic surfactant is a polysorbate, a lecithin, a polyethylene glycol (PEG), a polyoxyethylene glycol sorbitan alkyl ester, a polyethylene glycol octylphenyl ether, a block copolymer of polyethylene glycol and polypropylene glycol, a polyethylene glycol alkyl ether, or combinations thereof. In some of any examples, the non-ionic surfactant is selected from the group consisting of a polysorbate, a polyethylene glycol (PEG), a block copolymer of polyethylene glycol and polypropylene glycol or a polyethylene glycol octylphenyl ether, or a combination thereof.

[0008] In some of any examples, the surfactant is present at a percentage by weight to volume (w/v) of at least or at least about 0.01%. In some of any examples, the surfactant, e.g., non-ionic surfactant or a zwitterionic surfactant, is present at a percentage by volume (w/v) of at least or at least about 0.001%, 0.002%, 0.005%, 0.010%, 0.020%, 0.030%, 0.035%, 0.04%, 0.045%, 0.05%, 0.055%, 0.060%, 0.065%, 0.070%, 0.075%, 0.080%, 0.085%, 0.090%, 0.095%, or 0.100%. In some of any examples, , the surfactant, e.g., non-ionic surfactant or a zwitterionic surfactant, is present at a percentage by weight to volume (w/v) of between 0.001% and 0.10%, between 0.001% and 0.075%, between 0.001% and 0.05%, between 0.001% and 0.01%, between 0.001% and 0.005%, 0.005% and 0.10%, between 0.005% and 0.075%, between 0.005% and 0.05%, between 0.005% and 0.01%, between 0.01% and 0.10%, between 0.01% and 0.075%, between 0.01% and 0.05%, between 0.05% and 0.1%, between 0.05% and 0.075% and between 0.075% and 0.10%, each

inclusive. In some of any examples, the surfactant, e.g., non-ionic surfactant or a zwitterionic surfactant, is present at a percentage by weight to volume (w/v) of at least or at least about 0.02%, 0.03%, 0.04%, or 0.05%. In some of any examples, the surfactant, e.g., non-ionic surfactant or a zwitterionic surfactant, is present at a percentage by weight to volume (w/v) of between 0.02% and 0.06%, 0.02% and 0.05%, between 0.02% and 0.04%, between 0.02% and 0.03%, between 0.03% and 0.06%, between 0.03% and 0.05%, between 0.03% and 0.04%, between 0.04% and 0.06%, between 0.04% and 0.05%, between 0.05% and 0.06%, each inclusive.

[0009] In some of any examples, the wherein the non-ionic surfactant is a polysorbate. In some of any examples, the polyoxyethylene glycol sorbitan alkyl ester is a polysorbate, such as a polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, or combinations thereof. In some of any examples, the polysorbate is polysorbate 20. In some of any examples, the polysorbate is polysorbate 80. In some of any examples, the polysorbate is present at a percentage by weight to volume (w/v) of at or about or at least or at least about 0.02%, 0.03%, 0.04%, or 0.05%. In some of any examples, the polysorbate is present at a percentage by weight to volume (w/v) of between 0.01% and 0.1%, between 0.1% and 0.5%, between 0.02% and 0.06%, between 0.02% and 0.05%, between 0.02% and 0.04%, between 0.02% and 0.03%, between 0.03% and 0.06%, between 0.03% and 0.05%, between 0.03% and 0.04%, between 0.04% and 0.06%, between 0.04% and 0.05%, between 0.05% and 0.06%, each inclusive.

[0010] In some of any examples, the non-ionic surfactant is polyethylene glycol (PEG). In some of any examples, the polyethylene glycol (PEG) is PEG 300, PEG 400, PEG 600, PEG 1000, PEG 1500, PEG 3000, PEG 3350, PEG 4000, PEG 6000, or PEG 8000. In some of any examples, the PEG is present at a percentage by weight to volume (w/v) of between 0.01% and 10%, between 0.025% and 7.5%, between 0.05% and 5%, between 0.05% and 2.5%, between 0.05% and 1%, between 0.05% and 0.75%, between 0.05% and 0.5%, between 0.05% and 0.25%, between 0.1% and 7.5%, between 0.1% and 5%, between 0.1% and 2.5%, between 0.1% and 1%, between 0.1% and 0.75%, between 0.1% and 0.5%, between 0.1% and 0.25%, between 0.5% and 7.5%, between 0.5% and 5%, between 0.5% and 2.5%, between 0.5% and 1%, between 0.5% and 0.75%, between 1% and 7.5%, between 1% and 5% and between 1% and 2.5%, each inclusive. In some of any examples, the PEG is present at a percentage by weight to volume (w/v) of at or about or at least or at least about 0.05%, 0.5% or 1%.

[0011] In some of any examples, the non-ionic surfactant is a polyethylene glycol octylphenyl ether. In some of any examples, the polyethylene glycol octylphenyl ether includes polyethylene glycol p-(1,1,3,3-tetramethylbutyl)-phenyl ether (Triton X-100®). In some of any examples, the Triton X-100® is present at a percentage by weight to volume (w/v) of between 0.01% and 5%, between 0.025% and 2.5%, between 0.05% and 2.5%, between 0.05% and 1%, between 0.05% and 0.75%, between 0.05% and 0.5%, between 0.05% and 0.25%, between 0.1% and 5%, between 0.1% and 2.5%, between 0.1% and 1%, between 0.1% and 0.75%, between 0.1% and 0.5%, between 0.1% and 0.25%, between 0.5% and 5%, between 0.5% and 2.5%, between 0.5% and 1% and between 0.5% and 0.75%, each inclusive. In some of any examples, the Triton X-100 is present at a percentage by weight to volume (w/v) of at or about or at least or at least about 0.05%, 0.5% or 1%.

[0012] In some of any examples, the non-ionic surfactant is a block copolymer of polyethylene glycol and polypropylene glycol. In some of any examples, the block copolymer of polyethylene glycol and polypropylene glycol includes polyoxyethylene-polyoxypropylene block copolymer (Pluronic® F-68), poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol) (Pluronic® L-121), poloxamer 407 (Pluronic® F127), or combinations thereof. In some of any examples, the block copolymer of polyethylene glycol and polypropylene glycol is polyoxyethylene-polyoxypropylene block copolymer (Pluronic® F-68). In some of any examples, the Pluronic® F-68 is present at a percentage by weight to volume (w/v) of between 0.01% and 5%, between 0.025% and 2.5%, between 0.05% and 2.5%, between 0.05% and 1%, between 0.05% and 0.75%, between 0.05% and 0.5%, between 0.05% and 0.25%, between 0.1% and 5%, between 0.1% and 2.5%, between 0.1% and 1%, between 0.1% and 0.75%, between 0.1% and 0.5%, between 0.1% and 0.25%, between 0.5% and 5%, between 0.5% and 2.5%, between 0.5% and 1% and between 0.5% and 0.75%, each inclusive. In some of any examples, the Pluronic® F-68 is present at a percentage by weight to volume (w/v) of at or about or at least or at least about 0.05%, 0.5% or 1%.

[0013] In some of any examples, the polyethylene glycol alkyl ether includes polyethylene glycol dodecyl ether (Brij® 35).

[0014] In some of any examples, the one or more stabilizing agents include a surfactant that is a zwitterionic surfactant. In some of any examples, the zwitterionic surfactant is 3-[(3-Cholamidopropyl) dimethylammonio]-1-propanesulfonate (CHAPS). In some of any examples, the surfactant is a zwitterionic detergent, such as zwittergent®. In some of any examples, the CHAPS is present at a percentage by weight to volume (w/v)

of between 0.01% and 5%, between 0.025% and 2.5%, between 0.05% and 2.5%, between 0.05% and 1%, between 0.05% and 0.75%, between 0.05% and 0.5%, between 0.05% and 0.25%, between 0.1% and 5%, between 0.1% and 2.5%, between 0.1% and 1%, between 0.1% and 0.75%, between 0.1% and 0.5%, between 0.1% and 0.25%, between 0.5% and 5%, between 0.5% and 2.5%, between 0.5% and 1% and between 0.5% and 0.75%, each inclusive. In some of any examples, the CHAPS is present at a percentage by weight to volume (w/v) of at or about or at least or at least about 0.05%, 0.5% or 1%.

[0015] In some of any examples, the one or more stabilizing agents include a protectant such as a tonicity agent. In some of any examples, the protectant is trehalose, sorbitol, sucrose, mannitol, xylitol or glycerol. In some examples, the protectant is trehalose. In some of any examples, the protectant is present at a percentage by weight to volume (w/v) of between 1% and 20%, between 1% and 5%, between 1% and 10%, and between 5% and 9%. In some of any examples, the protectant is present at a percentage by weight to volume (w/v) of at or at about or at least or at least about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14% or 15% by weight to volume (w/v).

[0016] In some of any examples, the one or more stabilizing agents include a protectant and a surfactant, e.g., a non-ionic surfactant or a zwitterionic surfactant.

[0017] In some of any examples, the conjugate is formulated as a concentrate and the protectant is present at a percentage by weight to volume (w/v) at or at about 20%, 25%, 30%, 35%, 40% or 50%.

[0018] Also provided are pharmaceutical compositions that include (1) a conjugate comprising an anti-HER1 (EGFR) antibody linked to IR700, (2) polysorbate 80, and (3) trehalose. In one aspect, the present dislcosure refers to a pharmaceutical composition comprising (1) a conjugate comprising a cetuximab antibody linked to IR700, (2) polysorbate 80, and (3) trehalose.

[0019] In some of any examples, the conjugate is formulated to a concentration that is from or from about 1.0 to or to about 5.0 mg/mL, from or from about 2.0 to or to about 10.0 mg/mL, from or from about 5.0 to or to about 50 mg/mL, or from or from about 20 to or to about 50 mg/mL. In some of any examples, the conjugate is formulated to a concentration of between 2 mg/mL and 10 mg/mL, inclusive. In some of any examples, the conjugate is formulated to a concentration of, of about, or of least at or about 5 mg/mL.

[0020] In some of any examples, the polysorbate 80 is present at between 0.01% and 0.1%, between 0.1% and 0.5%, or between 0.02% and 0.04% by weight to volume (w/v), each inclusive. In some of any examples, the polysorbate 80 is present at or at about 0.02% by weight to volume (w/v).

[0021] In some of any examples, the trehalose is present in amount between 1% and 20%, 3% and 12%, or 5% and 9% by weight to volume (w/v), each inclusive. In some of any examples, the trehalose is present in amount of between 5% and 9% by weight to volume (w/v), inclusive.

[0022] In some of any examples, the composition is formulated in a pharmaceutically acceptable buffer. In some of any examples, the pharmacologically acceptable buffer has a pH from or from about pH 6.0 to or to about pH 8.0, inclusive. In some of any examples, the pharmaceutically acceptable buffer has a pH of from or from about pH 6.8 to or to pH 7.4, inclusive. In some of any examples, the pharmaceutically acceptable buffer has a pH of or of about pH 7.1.

[0023] In some of any examples, the pharmaceutically acceptable buffer is sodium phosphate. In some of any examples, the sodium phosphate is present at a concentration of between 1 mM and 200 mM, between 1 mM and 50 mM, or between 5 mM and 25 mM, each inclusive.

[0024] Also provided herein are pharmaceutical compositions that include (1) between 2 mg/mL and 10 mg/mL of a conjugate comprising an anti-HER1 (EGFR) antibody linked to IR700, (2) between 0.1% and 0.5% polysorbate 80 by weight to volume (w/v), (3) between 5% and 9% trehalose by weight to volume (w/v), and (4) between 5 mM and 25 mM sodium phosphate, each inclusive. In some of any examples, the composition comprises polysorbate 80 at or at about 0.02% w/v. In some of any examples, the composition comprises trehalose at or at about 9% w/v.

[0025] In some of any examples, the antibody is cetuximab or a biosimilar, interchangeable, or biobetter thereof. In some of any examples, the antibody is cetuximab. In some of any examples, the conjugate comprises a cetuximab-IR700 conjugate.

[0026] Also provided herein are pharmaceutical compositions that include 5 mg/mL cetuximab-IR700 conjugate in a formulation that include 10 mM sodium phosphate, 0.02% (w/v) polysorbate 80 and 9% (w/v) trehalose at a pH of or of about pH 7.1.

[0027] In some of any examples, the composition is a liquid ready to use composition. In some of any examples, the composition is lyophilized or is formulated for lyophilization or is reconstituted from a lyophilized composition. In some of any examples, the composition is sterile. In some of any examples, the composition is stable at 2ºC to 8ºC for greater than 6 months, 12 months or 18 months.

[0028] In some of any examples, the conjugate is present in at least or at least about 70%, 80%, 85%, 90%, 95%, or 98% monomeric form. In some of any examples, the percentage of monomeric form is assessed by size-exclusion chromatography.

[0029] In some of any examples, aggregation of the conjugate is reduced by 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, or more compared to aggregation in a composition including the conjugate but lacking the surfactant, e.g., non-ionic surfactant or zwitterionic surfactant, and/or the protectant. In some of any examples, the reduced aggregation is present after sheer stress and/or agitation; after exposure to a pH of less than or less than about pH 6.0; after 3 months at a temperature greater than or greater than about 25 ºC; and/or after exposure for 1 week at a temperature greater than or greater than about 40 ºC, or combinations thereof.

[0030] In some of any examples, the reduced aggregation is characterized by percent recovery, the percentage of the conjugate in monomeric form, the percentage of the conjugate contained in a mean peak, potency of the composition, activity of the composition, purity or the composition, or combinations thereof.

[0031] In some of any examples, the recovery of the conjugate is greater than 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or 100% after sheer stress and/or agitation; after exposure to a pH less than or less than about pH 6.0; after 3 months at a temperature greater than or greater than about 25 ºC; and/or after exposure for 1 week at a temperature greater than or greater than about 40 ºC, or a combination thereof. In some of any examples, the percentage of the conjugate in monomeric form in the composition is at least 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% after sheer stress and/or agitation; after exposure to a pH less than or less than about pH 6.0; after 3 months at a temperature greater than or greater than about 25 ºC; and/or after exposure for 1 week at a temperature greater than or greater than about 40 ºC, or a combination thereof. In some of any examples, the percentage of the conjugate contained in a mean peak as determined by high performance liquid chromatography (HPLC) is greater than 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% after sheer stress and/or agitation; after exposure to a pH less than or less than about pH 6.0; after 3 months at a temperature greater than or greater than about 25 ºC; and/or after exposure for 1 week at a temperature greater than or greater than about 40 ºC, or a combination thereof. In some of any examples, the HPLC is size exclusion HPLC (SE-HPLC). In some of any examples, the composition retains greater than or greater than about 30%, 40%, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9% or

100% of its potency, activity or purity after sheer stress and/or agitation; after exposure to a pH less than or less than about pH 6.0; after 3 months at a temperature greater than or greater than about 25 ºC; and/or after exposure for 1 week at a temperature greater than or greater than about 40 ºC, or a combination thereof.

[0032] In some of any examples, the shear stress and/or agitation is caused by shaking, freeze-thaw, transportation, drawing into a syringe, manufacturing procedures including, but not limited to, purification procedures and finish/fill procedures. In some of any examples, the shaking includes shaking on an orbital shaker. In some of any examples, the shaking is at a speed greater than 25 rpm, greater than 50 rpm, greater than 75 rpm, greater than 100 rpm, greater than 125 rpm, greater than 150 rpm, greater than 175 rpm, greater than 200 rpm, greater than 225 rpm, greater than 250 rpm, greater than 275 rpm, or greater than 300 rpm. In some of any examples, the shaking is carried out for a period of time is greater than 1 minute, greater than 5 minutes, greater than 10 minutes, greater than 15 minutes, greater than 20 minutes, greater than 25 minutes, greater than 30 minutes, greater than 45 minutes, greater than 60 minutes, greater than 90 minutes, greater than 120 minutes, greater than 150 minutes, greater than 180 minutes, greater than 210 minutes, greater than 240 minutes, greater than 270 minutes, greater than 300 minutes, greater than 330 minutes, greater than 360 minutes, greater than 390 minutes, greater than 420 minutes, greater than 450 minutes, greater than 480 minutes, greater than 510 minutes, greater than 540 minutes, greater than 570 minutes, or greater than 600 minutes.

[0033] In some of any examples, the exposure for more than or about 3 months is at a temperature greater than or greater than about 30 °C, 35 °C, 37 °C, or 40 °C. In some of any examples, the exposure for more than 1 week at a temperature greater than or greater than about 40 °C is for more than at or about 1 week, more than at or about 2 weeks or more than at or about 1 month.

[0034] In some of any examples, the phthalocyanine dye has a maximum absorption wavelength from or from about 600 nm to about 850 nm. In some of any examples, the phthalocyanine dye has a maximum absorption wavelength from or from about 650 nm to about 850 nm. In some of any examples, the phthalocyanine dye has a maximum absorption wavelength from or from about 680 nm to about 850 nm. In some of any examples, the phthalocyanine dye includes IR700.

[0035] In some of any examples, the molar ratio of dye to antibody is at least or at least about 1:1, at least or at least about 4:1 or is at least or at least about 10:1. In some of any examples, the molar ratio of dye to antibody is from or from about 1:1 to 10:1. In

some of any examples, the conjugate is formulated to a concentration that is from or from about 1.0 to about 5.0 mg/mL.

[0036] In some of any examples, the composition is formulated in a pharmaceutically acceptable buffer. In some of any examples, the pharmaceutically acceptable buffer is sodium phosphate. In some of any examples, the pharmaceutically acceptable buffer is phosphate buffered saline. In some of any examples, the pharmacologically acceptable buffer has a pH from or from about pH 6.0 to about pH 8.0. In some of any examples, the pharmaceutically acceptable buffer has a pH of from or from about pH 6.8 to pH 7.4. In some of any examples, the pharmaceutically acceptable buffer has a pH of from or from about pH 7.1 to pH 7.3. In some of any examples, the pharmaceutically acceptable buffer has a pH of or of about pH 6.8, 6.9, 7.0, 7.1, 7.2, 7.3 or 7.4.

[0037] Also provided in some examples are containers containing any of the pharmaceutical compositions described herein. In some of any examples, the container is a vial, a tube, a syringe, a bag, a pouch or a box. In some of any examples, the container protects from transmission of light having a wavelength from or from about 250 nm to about 800 nm, from about 250 nm to about 450 nm, from about 400 nm to about 800 nm, from about 450 nm to about 650 nm, or from about 600 nm to about 720 nm. In some of any examples, the container protects from transmission of light such that the percentage of light transmission is less than 50%, less than 40%, less than 30%, less than 20%, less than 10% or less than 5%. In some of any examples, the container is green, blue, amber, translucent, opaque, or is covered by a material with light transmission of less than 50%, less than 40%, less than 30%, less than 20%, less than 10% or less than 5%. In one aspect, the present disclosure refers to a container comprising the pharmaceutical composition as defined herein, wherein the container is green, blue, amber, translucent, opaque, or is covered by a material with light transmission of less than less than 30%.

[0038] Also provided in some examples are methods of treating a lesion in a subject that involves administering to the subject a therapeutically effective amount of any of the compositions provided herein; and after administering the conjugate, irradiating the lesion at a wavelength to induce phototoxic activity of the conjugate.

[0039] In some of any examples, irradiating the lesion is carried out at a wavelength of 500 nm to 900 nm, inclusive, at a dose of at least 1 J cm^{-2}or 1 J/cm of fiber length. In some of any examples, irradiating the lesion is carried out at wavelength of 600 nm to 850 nm. In some of any examples, irradiating the lesion is carried out at a wavelength of 690 ± 50 nm or at a wavelength of or about 690 ± 20 nm. In some of any examples, the irradiating step is carried out at a wavelength of about 690 nm. In some of any examples, irradiating the lesion is carried out 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 of

any examples, irradiating of the lesion is carried out 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 irradiating of the lesion is carried out 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.

[0040] In some of any examples, the irradiating step is carried out at a dose of from or from about 25 J/cm^2 to about 100 J/cm^2. In some of any examples, the irradiating step is carried out with a frontal light diffuser at a dose of or of about 50 J/cm^2. In some of any examples, the irradiating step is carried out with a frontal light diffuser or by superficial illumination. In some of any examples, the irradiating step is carried out with a cylindrical light diffuser at a dose of from or from about 50 J/cm fiber length to about 150 J/cm fiber length. In some of any examples, the irradiating step is carried out with a cylindrical light diffuser at a dose of or of about 100 J/cm fiber length. In some of any examples, the irradiating step is carried out with a cylindrical light diffuser or by interstitial illumination.

[0041] In some of any examples, the lesion is fibrosis, premalignant dysplasia, carcinoma in situ, hyperplasia, neoplasm, a tumor, or a tumor that is associated with a cancer. In some of any examples, the tumor is a sarcoma or carcinoma. In some of any examples, the tumor is a carcinoma that is a squamous cell carcinoma, basal cell carcinoma or adenocarcinoma. In some of any 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. In some of any 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.

[0042] In some of any of the methods provided herein, the conjugate is IR700-cetuximab. In some of any examples, the cancer is a cancer located at the head and neck, and the conjugate is IR700-cetuximab.

[0043] In some of any examples, irradiating of the lesion is carried out between or between about 30 minutes and about 96 hours after administering the conjugate. In some of any examples, the irradiating step is carried out between or between or between about 10 and about 40 hours after administering the conjugate. In some of any examples, the irradiating step is carried out between or between or between about 20 and about 28 hours

after administering the conjugate. In some of any examples, the irradiating step is carried out at about 24 hours after administering the conjugate. In some of any examples, the irradiating step is carried out at about 24 ± 4 hours after administering the conjugate.

[0044] In some of any 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, from about 160 mg/m^2 to 640 mg/m^2, from about 160 mg/^{2} to 1000 mg/^{2}, from about 500 mg/m^2 to about 1000 mg/m^2, from about 500 mg/m^2 to about 750 mg/m^2or from about 100 mg/m^2 to about 1000 mg/m^2. In some of any examples, the conjugate is administered at a dose of about 500 mg/m^2, 550 mg/m^2, 600 mg/m^2, 620 mg/m^2, 640 mg/m^2, 660 mg/m^2, 680 mg/m^2, or 700 mg/m^2. In some of any examples, the conjugate is administered at a dose of or of about 160 mg/$m^{2,}$ 320 mg/$m^{2,}$ 640 mg/m^2, or 1280 mg/m^2. In some of any examples, the conjugate is administered at a dose of or of about 640 mg/m^2.

[0045] In some of any examples, the method further includes administering an additional therapeutic agent or anti-cancer treatment. In some of any examples, the anti-cancer treatment includes radiation therapy. In some of any examples, the additional therapeutic agent comprises an immune modulating agent. In some of any examples, the immune modulating agent is an immune checkpoint inhibitor.

[0046] Also provided herein are methods of treating a tumor or cancer in a subject that involves (a) intravenously administering to a subject having a tumor or cancer a composition comprising a cetuximab-IR700 conjugate in a formulation comprising 10 mM sodium phosphate, 0.02% (w/v) polysorbate 80 and 9% (w/v) trehalose at pH 7.1, wherein the conjugate is administered in an amount that is or is about 640 mg/m2; and (b) after administering the conjugate, irradiating the lesion at about 24 ± 4 hours at a wavelength of 690 ± 20 nm at a dose of at least or about at least 50 J cm^{-2} or 100 J/cm of fiber length, thereby treating the tumor or cancer in the subject.

[0047] Also provided herein are methods of treating a tumor or cancer in a subject that involves (a) intravenously administering to a subject having a head or neck cancer a composition comprising a cetuximab-IR700 conjugate in a formulation comprising 10 mM sodium phosphate, 0.02% (w/v) polysorbate 80 and 9% (w/v) trehalose at pH 7.1, 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 about 24 ± 4 hours at a wavelength of 690 ± 20 nm at a dose of at least or about at least 50 J cm^{-2} or 100 J/cm of fiber length, thereby treating the cancer in the subject.

[0048] In some of any examples of the provided methods, the composition comprises 5 mg/mL cetuximab-IR700 conjugate.

[0048a] In one aspect, the present disclosure refers to use of the pharmaceutical composition as disclosed herein in the manufacture of a medicament for the treatment of a tumor or cancer, wherein: (a) the pharmaceutical composition is to be administered to the subject in a therapeutically effective amount; and (b) after the pharmaceutical composition is administered, the cancer or tumor is to be irradiated at a wavelength to induce phototoxic activity of the conjugate.

[0048b] In one aspect, the present disclosure refers to use of a pharmaceutical composition comprising a cetuximab-IR700 conjugate in a formulation comprising 10 mM sodium phosphate, 0.02% (w/v) polysorbate 80 and 9% (w/v) trehalose at pH 7.1 in the manufacture of a medicament for the treatment of a tumor or cancer, wherein: (a) the pharmaceutical composition is to be intravenously administered in an amount that is or is about 640 mg/m^2; and (b) after the pharmaceutical composition is administered, the lesion is to be irradiated at about 24 ± 4 hours at a wavelength of 690 ± 20 nm at a dose of at least or at least about or about 50 J cm^{-2} or 100 J/cm of fiber length.

Brief Description of the Drawings

[0049] **FIG. 1A** displays size-exclusion high performance liquid chromatography (SE-HPLC) profiles for cetuximab in the presence or absence of various concentrations of polysorbate 20. HMW corresponds to high molecular weight peaks. **FIG. 1B** displays SE-HPLC profiles for cetuximab-IR700 conjugate in the presence or absence of various concentrations of polysorbate 20. HMW corresponds to high molecular weight peaks. **FIG. 1C** displays SE-HPLC profiles for cetuximab in the presence or absence of various concentrations of polysorbate 80. HMW corresponds to high molecular weight peaks. **FIG. 1D** displays SE-HPLC profiles for cetuximab-IR700 in the presence or absence of various concentrations of polysorbate 80. HMW corresponds to high molecular weight peaks. **FIG. 1E** displays SE-HPLC profiles for cetuximab-IR700 in the presence or absence of higher concentrations of polysorbate 80 than those shown in FIG. 1D. HMW corresponds to high molecular weight peaks. The inset is an expanded view of the HMW peaks.

[0050] **FIG. 2** displays melting temperature profiles for the cetuximab-IR700 conjugate in various conditions and for the unconjugated cetuximab.

[0051] **FIG. 3** displays size exclusion high performance liquid chromatography (SE-HPLC) for the cetuximab-IR700 conjugate in formulations with various concentrations of non-ionic surfactant.

[0052] **FIG. 4** displays the effect of concentration of the cetuximab-IR700 conjugates in the formulation on the stability of the conjugates.

[0053] **FIGS. 5A-5C** displays DSC profiles cetuximab-IR680 (**FIG. 5A**), cetuximab-IR700 (**FIG. 5B**) and cetuximab-IR800 (**FIG. 5C**), formulated in PBS or in trehalose and Polysorbate 80 formulation.

[0054] **FIGS. 6A-6C** display HPLC-SEC of cetuximab-IR680 (**FIG. 6A**), cetuximab-IR700 (**FIG. 6B**) and cetuximab-IR800 (**FIG. 6C**), formulated in PBS or in trehalose and Polysorbate 80 formulation, after incubation at 40°C or 5°C for 1 month.

[0055] **FIG. 7A-7C** display HPLC-SEC results from PBS and Polysorbate 80 formulations for cetuximab-IR680 (**FIG. 7A**), cetuximab-IR700 (**FIG. 7B**), and cetuximab-IR800 (**FIG. 7C**) conjugates after agitation.

Claims

1. A pharmaceutical composition comprising: (1) a conjugate comprising a cetuximab antibody or a biosimilar, interchangeable, or biobetter thereof linked to IR700 and (2) one or more stabilizing agents in an amount effective to reduce or prevent aggregation of the conjugate, wherein the one or more stabilizing agents comprises a surfactant and/or a protectant.

2. The pharmaceutical composition of claim 1, wherein the one or more stabilizing agents comprise a non-ionic surfactant.

3. The pharmaceutical composition of claim 2, wherein the non-ionic surfactant is a polysorbate.

4. The pharmaceutical composition of claim 3, wherein the polysorbate is polysorbate 80.

5. The pharmaceutical composition of any of claims 1-4, wherein the one or more stabilizing agents comprises a protectant selected from the group consisting of trehalose, sucrose, mannitol, and sorbitol.

6. The pharmaceutical composition of any of claims 1-5, wherein the protectant is trehalose.

7. The pharmaceutical composition of any of claims 1-6, wherein the protectant is present in an amount of between 1% and 20%, by weight to volume (w/v), each inclusive.

8. A pharmaceutical composition comprising (1) a conjugate comprising a cetuximab antibody linked to IR700, (2) polysorbate 80, and (3) trehalose.

9. The pharmaceutical composition of claim 4 or 8, wherein the polysorbate 80 is present at between 0.01% and 0.1%, by weight to volume (w/v), inclusive.

10. The pharmaceutical composition of any of claims 6, 8 or 9, wherein the trehalose is present in amount of between 5% and 9% by weight to volume (w/v), inclusive.

11. The pharmaceutical composition of any of claims 1-10, wherein the composition comprises a pharmaceutically acceptable buffer, that has a pH of from or from about pH 6.8 to or to about pH 7.4, inclusive.

12. The pharmaceutical composition of claim 11, wherein the pharmaceutically acceptable buffer is sodium phosphate.

13. The pharmaceutical composition of any of claims 1-12, comprising 5 mg/mL cetuximab-IR700 conjugate in a formulation comprising 10 mM sodium phosphate, 0.02% (w/v) polysorbate 80 and 9% (w/v) trehalose at a pH of or of about pH 7.1.

14. The pharmaceutical composition of any of claims 1-13, wherein the conjugate is present in at least 85% monomeric form.

15. The pharmaceutical composition of any of claims 1-14, wherein the conjugate is present in at least 95% monomeric form.

16. A container comprising the pharmaceutical composition of any of claims 1-15, wherein the container is green, blue, amber, translucent, opaque, or is covered by a material with light transmission of less than less than 30%.

17. Use of the pharmaceutical composition of any of claims 1-15 in the manufacture of a medicament for the treatment of a tumor or cancer, wherein:

(a) the pharmaceutical composition is to be administered to the subject in a therapeutically effective amount; and

(b) after the pharmaceutical composition is administered, the cancer or tumor is to be irradiated at a wavelength to induce phototoxic activity of the conjugate.

18. Use of a pharmaceutical composition comprising a cetuximab-IR700 conjugate in a formulation comprising 10 mM sodium phosphate, 0.02% (w/v) polysorbate

80 and 9% (w/v) trehalose at pH 7.1 in the manufacture of a medicament for the treatment of a tumor or cancer, wherein:

(a) the pharmaceutical composition is to be intravenously administered in an amount that is or is about 640 mg/m^2; and

(b) after the pharmaceutical composition is administered, the lesion is to be irradiated at about 24 ± 4 hours at a wavelength of 690 ± 20 nm at a dose of at least or at least about or about 50 J cm^{-2} or 100 J/cm of fiber length.

19. The use of claim 17 or 18 wherein the cancer is a head or neck cancer.