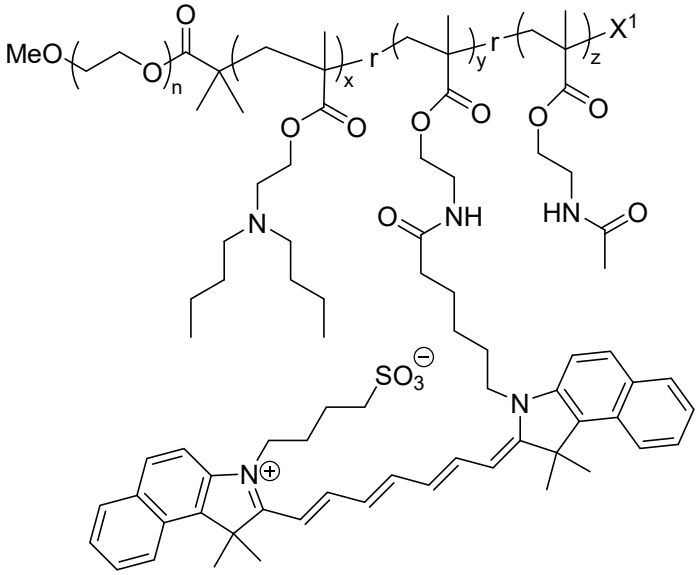
CLAIMS

~~WHAT IS CLAIMED IS:~~

1. A block copolymer having the structure of Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, or isotopic variant thereof:



Formula (II),

wherein:

X^1 is a halogen, -OH, or –C(O)OH;

n is 90-140;

x is 50-200;

y is 0-3; and

z is ~~0~~1-3.

~~2. The block copolymer of claim 1, wherein X^1 is a halogen.~~

~~3.~~2. The block copolymer of claim 1~~ or 2~~, wherein X^1 is –Br.

~~4.~~3. The block copolymer of any one of claims 1-~~3~~2, wherein n is 100-120 and x is 60–150.

~~5. The block copolymer of any one of claims 1-4, wherein n is 113.~~

~~6. The block copolymer of any one of claims 1-5, wherein x is 60-150.~~

~~7. The block copolymer of any one of claims 1-6, wherein y is 0.5-1.5.~~

~~8. The block copolymer of any one of claims 1-6, wherein y is 0.~~

~~9. The block copolymer of any one of claims 1-7, wherein z is 1.5-2.5.~~

~~10. The block copolymer of any one of claims 1-8, wherein z is 0.~~

~~11.~~4. A composition or micelle comprising of one or more block copolymers of any one of claims 1-~~10~~3.

~~12. A pH responsive composition comprising the micelle of claim 11, wherein the micelle has a pH transition point and an emission spectrum.~~

13.5. The A pH responsive composition comprising the composition or micelle of claim 124, wherein the micelle has a pH transition point and an emission spectrum, and the pH transition point is between 4.8-5.5 and the emission spectrum is between 700-900 nm.

14. The pH responsive composition of claim 12, wherein the pH transition point is about 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, or 5.5.

15. The pH responsive composition of any one of claims 12-14, wherein the emission spectrum is between 700-900 nm.

16.6. The pH responsive composition of any one of claims 12-155, wherein the composition has a pH transition range ($\Delta pH_{10\text{-}90\%}$) of less than 1 pH unit and the composition has a fluorescence activation ratio of greater than 25.

17. The pH responsive composition of claim 16, wherein the pH transition range is less than 0.25 pH units.

18. The pH responsive composition of claim 16, wherein the pH transition range is less than 0.15 pH units.

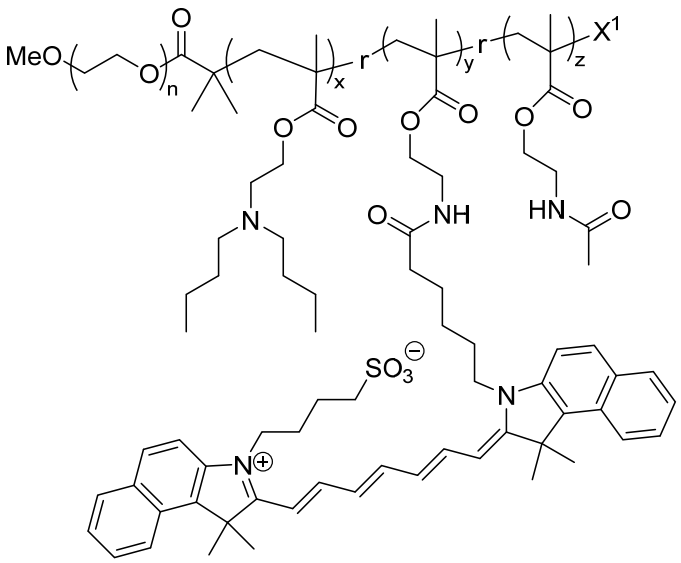
19. The pH responsive composition of any one of claims 12-18, wherein the composition has a fluorescence activation ratio of greater than 25.

20. The pH responsive composition of any one of claims 12-18, wherein the composition has a fluorescence activation ratio of greater than 50.

21.7. An imaging agent comprising one or more block copolymers of any one of claims 1-103, wherein the imaging agent comprises poly(ethyleneoxide)-b-poly(dibutylaminoethyl methacrylate-r-aminoethylmethylacrylate hydrochloride) copolymer indocyanine green and acetic acid conjugate.

22. The imaging agent of claim 21, comprising poly(ethyleneoxide)-*b*-poly(dibutylaminoethyl methacrylate-r-aminoethylmethylacrylate hydrochloride) copolymer indocyanine green and acetic acid conjugate.

23.8. A pharmaceutical composition comprising a micelle, wherein the micelle comprises 1) one or more block copolymers having the structure of Formula (II), or a pharmaceutically acceptable salt, solvate, or hydrate:



Formula (II),

wherein:

X^1 is a halogen, -OH, or –C(O)OH;

n is 90-140;

x is 50-200;

y is 0-3;

z is ~~0~~1-3; and

2) a stabilizing agent.

~~24.~~9. The pharmaceutical composition of claim ~~23~~8, wherein the stabilizing agent is a cryoprotectant, a sugar , a sugar derivative, a detergent, or a salt.

~~25. The pharmaceutical composition of claim 23, wherein the stabilizing agent is a sugar , a sugar derivative, a detergent, or a salt.~~

~~26. The pharmaceutical composition of claim 25, wherein the stabilizing agent is a sugar derivative.~~

~~27. The pharmaceutical composition of claim 25 or claim 26, wherein the stabilizing agent is a monosaccharide, disaccharide, trisaccharide, water soluble polysaccharide, or sugar alcohol, a polyol, or combination thereof.~~

~~28. The pharmaceutical composition of any one of claims 23-27, wherein the stabilizing agent is fructose, galactose, glucose, lactose, sucrose, trehalose, maltose, mannitol, sorbitol, ribose, dextrin, cyclodextrin, maltodextrin, raffinose, or xylose, or a combination thereof.~~

~~29.~~10. The pharmaceutical composition of ~~any one of~~ claim~~s~~ ~~23-28~~9, wherein the stabilizing agent is trehalose.

30.11. The pharmaceutical composition of any one of claims 23-298-10, comprising from about 0.5% to about 25% w/v, from about 1% to about 20% w/v, from about 5% to about 15% w/v, from about 6% to about 13% w/v, from about 7% to about 12% w/v, or from about 8% to about 11% w/v of the stabilizing agent.

31. The pharmaceutical composition of any one of claims 23-29, comprising about 5% w/v, about 6% w/v, about 7% w/v, about 8% w/v, about 9% w/v, about 10% w/v, about 11% w/v, about 12% w/v, about 13% w/v, about 14% w/v, or about 15% w/v of the stabilizing agent.

32.12. The pharmaceutical composition of any one of claims 23-318-11, further comprising a liquid carrier, wherein the liquid carrier is sterile water, normal saline, half normal saline, 5% dextrose in water (D5W), ringers lactate solution, or a combination thereof.

33. The pharmaceutical composition of claim 31, wherein the liquid carrier is sterile water, normal saline, half normal saline, 5% dextrose in water (D5W), ringers lactate solution, or a combination thereof.

34. The pharmaceutical composition of claim 32 or claim 33, wherein the liquid carrier is sterile water.

35. The pharmaceutical composition of any one of claims 23-34, comprising from about 1.0 mg/mL to about 5.0 mg/mL of the block copolymer of Formula (II).

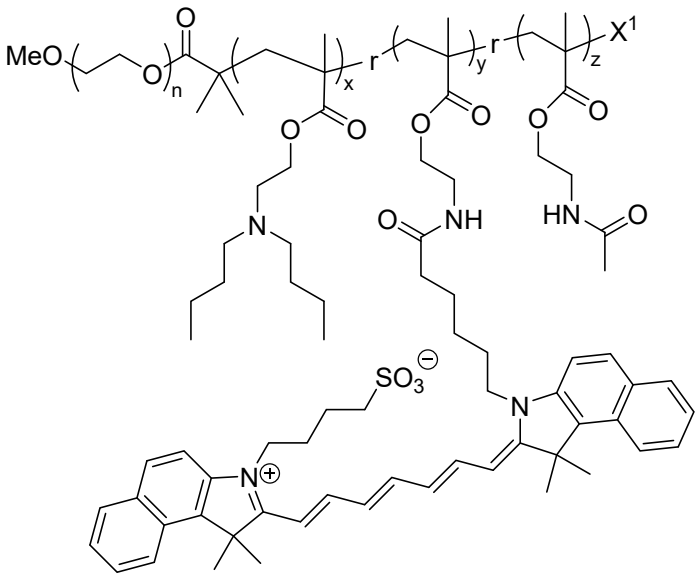
36. The pharmaceutical composition of any one of claims 23-34, comprising about 1 mg/mL, about 1.5 mg/mL, about 2 mg/mL, about 2.5 mg/mL, about 3 mg/mL, about 3.5 mg/mL, about 4 mg/mL, about 4.5 mg/mL, or about 5 mg/mL of the block copolymer of Formula (II).

37. The pharmaceutical composition of any one of claims 23-34, comprising from about 0.1 mg/kg to about 3 mg/kg, from about 0.1 to about 1.2 mg/kg, or from about 0.5 to about 7 mg/kg of the block copolymer of Formula (II).

38. The pharmaceutical composition of any of claims 23-34, comprising about 1 mg/kg, 2 mg/kg, 3mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, or about 7 mg/kg of the block copolymer of Formula (II).

39. The pharmaceutical composition of any one of claims 23-34, comprising about: 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.8 mg/kg, 1 mg/kg, 1.2 mg/kg, 1.4 mg/kg, 1.6 mg/kg, 1.8 mg/kg, 2 mg/kg, 2.5 mg/kg, or 3 mg/kg of the block copolymer of Formula (II).

40.13. A pharmaceutical composition, comprising 1) at least about 3 mg/mL of a block copolymer having the structure of Formula (II), or a pharmaceutically acceptable salt, solvate, or hydrate thereof:



Formula (II),

wherein:

X^1 is –Br;

n is 90-140;

x is 60-150;

y is 0-3;

z is ~~0~~1-3; and

2) about 10% trehalose w/v in water.

~~41. The composition of any one of claims 1-10 and 23-40, wherein the composition is formulated for oral, intramuscular, subcutaneous, intratumoral, or intravenous administration.~~

~~42. The composition of any one of claims 1-10 and 23-40, wherein the composition is formulated for intravenous administration.~~

~~43.~~14. A method of imaging the pH of an intracellular or extracellular environment, the method comprising:

a) contacting the intracellular or extracellular environment with a block copolymer of any one of claims 1-~~10~~ 3 or a pharmaceutical composition of any one of claims ~~23-41~~8-13; and

b) detecting one or more optical signals from the intracellular or extracellular environment, wherein a detected optical signal indicates that the micelle comprising one or more block copolymers of Formula (II) has reached its pH transition point and disassociated.

~~44. The method of claim 43, wherein the extracellular environment is intravascular or extravascular~~

~~45. The method of claim 43, wherein imaging the pH of an intracellular or extracellular environment comprises imaging a metastatic disease.~~

~~46. The method of claim 43, wherein imaging the pH of an intracellular or extracellular environment comprises imaging the pH of a tumor environment.~~

~~47. The method of claim 46, wherein imaging the pH of the tumor environment comprises imaging a lymph node or nodes.~~

~~48. The method of claim 46, wherein imaging the lymph node or nodes informs the surgical resection of the tumor or staging of the tumor metastasis.~~

~~49. The method of claim 46, wherein imaging the pH of the tumor environment enables determination of the tumor size.~~

~~50. The method of claim 46, wherein imaging the pH of the tumor environment enables determination of the tumor margins.~~

~~51. The method of claim 46, wherein imaging the pH of the tumor environment enables more precise removal of the tumor during surgery.~~

~~52. The method of claim 46, wherein imaging the pH of the tumor environment enables determination of a satellite, multi-focal, or occult tumor.~~

~~53. The method of claim 46, wherein imaging the pH of the tumor environment enables the detection of a residual metastatic disease.~~

~~54. The method of claim 46, wherein imaging the lymph node or nodes enables more precise removal of the lymph node or nodes during surgery.~~

~~55.~~15. The method of ~~any one of~~ claim~~s 43-54~~14, wherein~~comprising administering to the patient in need~~ the pharmaceutical composition is to be administered to the patient in need prior to a surgery.

~~56. The method of claim 55, wherein the surgery is a tumor resection.~~

~~57. The method of claim 46, wherein imaging the pH of the tumor environment informs patient management.~~

~~58.~~16. Use of a block copolymer of any one of claims 1-3 or a pharmaceutical composition of any one of claims 8-13 in the preparation of a medicament for treatment in a~~A~~ method of resecting a tumor in a patient in need thereof, ~~the method~~ comprising:

a) detecting one or more optical signals from the tumor or a sample thereof from the patient administered with an effective dose of a block copolymer of any one of claims 1-~~10~~ 3 or a pharmaceutical composition of any one of claims ~~23-41~~8-13, wherein a detected optical signal(s) indicates the presence of the tumor; and

b) wherein ~~resecting~~ the tumor is to be resected via a surgery.

~~59. The method of claim 58, wherein the one or more optical signals is a fluorescent signal.~~

~~60. The method of claim 58, wherein the tumor is at least 90% resected.~~

~~61. The method of claim 58, wherein the tumor is at least 95% resected.~~

~~62. The method of claim 58, wherein the tumor is at least 99% resected.~~

~~63. The method of any one of claims 58-62, wherein the tumor is a solid tumor.~~

~~64. The method of any one of claims 58-62, wherein the tumor is a non-solid tumor.~~

~~65. The method of claim 63 or claim 64, wherein the solid or non-solid tumor is from a cancer.~~

~~66.~~17. The ~~method~~ use of claim ~~65~~16, wherein the ~~cancer~~ tumor is breast cancer, head and neck squamous cell carcinoma (NHSCC), lung cancer, ovarian cancer, prostate cancer, bladder cancer, urethral cancer, esophageal cancer, brain cancer, pancreatic cancer, skin cancer, melanoma, sarcoma, pleural metastasis, kidney cancer, lymph node cancer, cervical cancer, or colorectal cancer.

~~67. The method of claim 65, wherein the cancer is breast cancer, head and neck squamous cell carcinoma (NHSCC), esophageal cancer, ovarian cancer, prostate cancer, or colorectal cancer.~~

~~68.~~18. The ~~method~~ use of any one of claims ~~58-67~~16-17, wherein the copolymer or the pharmaceutical composition is to be administered as an injection or an infusion.

~~69. The method of any one of claims 58-68, wherein the pharmaceutical composition is administered as a single dose or as multiple doses.~~

~~70.~~19. The ~~method~~ use of any one of claims ~~58-69~~16-18, wherein the pharmaceutical composition is to be administered at least 1 hour~~, at least 2 hours, at least 4 hours, at least 6 hours, at least 8 hours, at least 10 hours, at least 12 hours, at least 14 hours, at least 16 hours, at least 18 hours, at least 20 hours, at least 24 hours, at least 28 hours, at least 32 hours, at least 80 hours, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 7 days, at least 1 week, or at least 2 weeks~~ prior to a surgery.

~~71. The method of any one of claims 58-69, wherein the pharmaceutical composition is administered from about 1 hour to about 32 hours, about 2 hours to about 32 hours, 16 hours to about 32 hours, about 20 hours to about 28 hours, about 1 hour to about 5 hours, or about 3 hours to about 9 hours prior to a surgery.~~

~~72.~~20. Use of the block copolymer of any one of claims 1-3 or the pharmaceutical composition of any one of claims 8-13 in the preparation of a medicament for ~~A method of~~ treating cancer, ~~the method~~ comprising:

a) detecting one or more optical signals in a cancer patient in need thereof to be administered with an effective dose of a block copolymer of any one of clams 1-

~~10~~ 3 or a pharmaceutical composition of any one of claims ~~23-41~~8-13, wherein a detected optical signal indicates the presence of a cancerous tumor; and

b) wherein ~~removing~~ the cancerous tumor is to be removed, thereby treating the cancer.

~~73. The method of claim 72, the method further comprising imaging the body cavity of the cancer patient, or imaing the cancerous tumor or a slice or specimen thereof (e.g. fresh or formalin fixed), optionally by back-table fluorescence-guided imaging after the removal from the patient.~~

~~74. A method of detecting a cancerous tumor, the method comprising:~~

~~a) detecting one or more optical signals in a cancer patient in need thereof administered with an effective dose of a block copolymer of any one of claims 1-10 or a pharmaceutical composition of any one of claims 23-41, wherein a detected optical signal indicates the presence of the cancerous tumor.~~

~~75. A method of minimizing recurrence of cancer for at least five years, the method comprising:~~

~~a) detecting one or more optical signals in a cancer patient in need thereof administered with an effective dose of a block copolymer of any one of claims 1-10 or a pharmaceutical composition of any one of claims 23-41, wherein a detected optical signal indicates the presence of a cancerous tumor, and wherein the presence of the tumor indicates the recurrence of the cancer; and~~

~~b) treating the cancer to minimize the recurrence if the one or more optical signals is detected.~~

~~76. The method of claim 75, the method further comprising resecting the tumor.~~

~~77. The method of any one of claims 72-76, wherein the cancer is breast cancer, head and neck squamous cell carcinoma (NHSCC), lung cancer, ovarian cancer, prostate cancer, bladder cancer, urethral cancer, esophageal cancer, brain cancer, pancreatic cancer, skin cancer, melanoma, sarcoma, pleural metastasis, kidney cancer, lymph node cancer, cervical cancer, or colorectal cancer.~~

~~78. The method of any one of claims 72-76, wherein the cancer is breast cancer, head and neck squamous cell carcinoma (NHSCC), esophageal cancer, ovarian cancer, prostate cancer, or colorectal cancer.~~

~~79. The method of any one of claims 72-78, wherein the pharmaceutical composition is administered at least 1 hour, at least 2 hours, at least 4 hours, at least 6 hours, at least 8 hours, at least 10 hours, at least 12 hours, at least 14 hours, at least 16 hours, at least 18 hours, at least 20 hours, at least 24 hours, at least 28 hours, at least 32 hours, at least 80~~

hours, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 7 days, at least 1 week, or at least 2 weeks prior to imaging the patient.

80. The method of any one of claims 72-78, wherein the pharmaceutical composition is administered from about 1 hour to about 32 hours, about 2 hours to about 32 hours, 16 hours to about 32 hours, about 20 hours to about 28 hours, about 1 hour to about 5 hours, or about 3 hours to about 9 hours prior to imaging the patient.

81. The method of any one of claims 72-80, wherein the pharmaceutical composition is administered as an injection or an infusion.

82. The method of any one of claims 72-81, wherein the pharmaceutical composition is administered as a single dose or multiple doses.

83. The method of any one of claims 72-82, the method further comprising imaging the cancer patient comprises an intra-operative camera, a near-infrared camera, or an endoscopic camera.

84. The method of any one of claims 58-83, wherein the patient in need is a human patient.

85. The method of any one of claims 58-84, wherein the patient in need is a canine, feline, horse, cattle, rabbit, or pig patient.