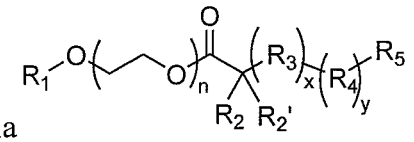
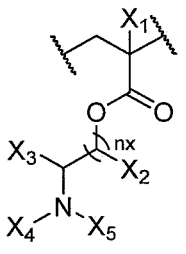
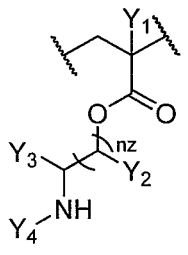
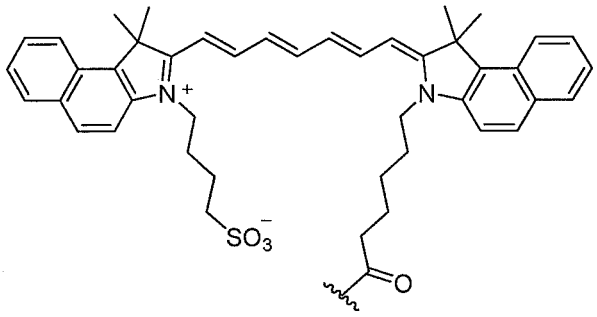
SUMMARY

In one aspect, the present invention refers to a polymer of the formula  wherein R_1 is an $alkyl_{(C\leq12)}$; n is an integer from 10-200; R_2 and R_2' are each independently a methyl;

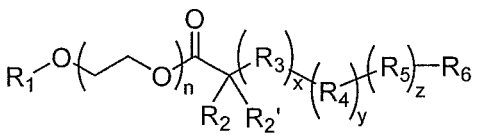
R_3 is a group of the formula  wherein n_x is 1-3; X_1 is a hydrogen or an $alkyl_{(C\leq12)}$; X_2 and X_3 are each hydrogen; X_4 is pentyl, n-propyl, or ethyl and X_5 is pentyl or n-propyl; or X_4 and X_5 are taken together and are $alkanediyl_{(C\leq9)}$ or substituted $alkanediyl_{(C\leq9)}$; x is an integer from 30 to 150;

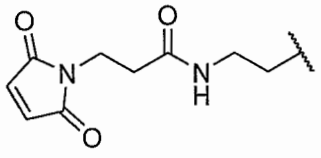
R_4 is a group of the formula:  wherein n_z is 1-10; Y_1, Y_2, and Y_3 are each independently selected from hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, or substituted $cycloalkyl_{(C\leq12)}$; and Y_4 is a dye with the following structure  ; y is an integer from 1 to 6; and

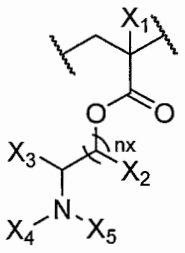
R_5 is hydrogen, halo, hydroxy, $alkyl_{(C\leq12)}$, or substituted $alkyl_{(C\leq12)}$.

In another aspect, the present invention refers to a composition comprising a micelle formed from a plurality of polymers as disclosed herein.

In some examples, there is described a polymer of the formula:

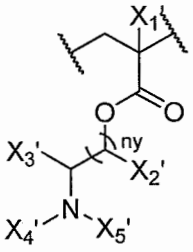
 (I)

wherein: R_1 is hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, substituted $cycloalkyl_{(C\leq12)}$, or , or a metal chelating group; n is an integer from 1 to 500; R_2 and R_2' are each independently selected from hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, or substituted $cycloalkyl_{(C\leq12)}$; R_3 is a group of the formula:



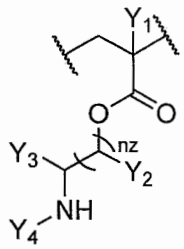
(II)

wherein: n_x is 1-10; X_1, X_2, and X_3 are each independently selected from hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, or substituted $cycloalkyl_{(C\leq12)}$; and X_4 and X_5 are each independently selected from $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$ or a substituted version of any of these groups, or X_4 and X_5 are taken together and are $alkanediyl_{(C\leq12)}$, $alkoxydiyl_{(C\leq12)}$, $alkylaminodiyl_{(C\leq12)}$, or a substituted version of any of these groups; x is an integer from 1 to 150; R_4 is a group of the formula:

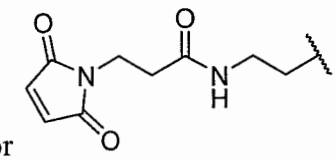


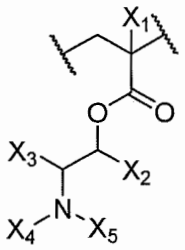
(III)

wherein: n_y is 1-10; X_1', X_2', and X_3' are each independently selected from hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, or substituted $cycloalkyl_{(C\leq12)}$; and X_4' and X_5' are each independently selected from $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$ or a substituted version of any of these groups, or X_4' and X_5' are taken together and are $alkanediyl_{(C\leq12)}$, $alkoxydiyl_{(C\leq12)}$, $alkylaminodiyl_{(C\leq12)}$, or a substituted version of any of these groups; y is an integer from 1 to 150; R_5 is a group of the formula:



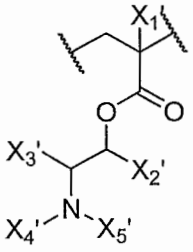
(IV)

wherein: n_z is 1-10; Y_1, Y_2, and Y_3 are each independently selected from hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, or substituted $cycloalkyl_{(C\leq12)}$; and Y_4 is hydrogen, $alkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, substituted $acyl_{(C\leq12)}$, a dye, or a fluorescence quencher; z is an integer from 0-6; and R_6 is hydrogen, halo, hydroxy, $alkyl_{(C\leq12)}$, or substituted $alkyl_{(C\leq12)}$, wherein R_3, R_4, and R_5 can occur in any order within the polymer, provided that R_3 and R_4 are not the same group. In some examples, the compound is further defined by the formula wherein: R_1 is hydrogen, $alkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, or  , or a metal chelating group; n is an integer from 10 to 500; R_2 and R_2' are each independently selected from hydrogen, $alkyl_{(C\leq12)}$, or substituted $alkyl_{(C\leq12)}$; R_3 is a group of the formula:



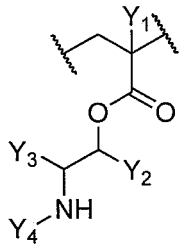
(II)

wherein: X_1, X_2, and X_3 are each independently selected from hydrogen, $alkyl_{(C\leq12)}$, or substituted $alkyl_{(C\leq12)}$; and X_4 and X_5 are each independently selected from $alkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$ or a substituted version of any of these groups, or X_4 and X_5 are taken together and are $alkanediyl_{(C\leq8)}$, $alkoxydiyl_{(C\leq8)}$, $alkylaminodiyl_{(C\leq8)}$, or a substituted version of any of these groups; x is an integer from 1 to 100; R_4 is a group of the formula:



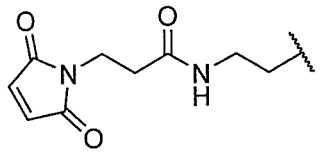
(III)

wherein: X_1', X_2', and X_3' are each independently selected from hydrogen, $alkyl_{(C\leq12)}$, or substituted $alkyl_{(C\leq12)}$; and X_4' and X_5' are each independently selected from $alkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$ or a substituted version of any of these groups, or X_4' and X_5' are taken together and are $alkanediyl_{(C\leq8)}$, $alkoxydiyl_{(C\leq8)}$, $alkylaminodiyl_{(C\leq8)}$, or a substituted version of any of these groups; y is an integer from 1 to 100; R_5 is a group of the formula:

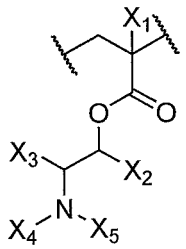


(IV)

wherein: Y_1, Y_2, and Y_3 are each independently selected from hydrogen, $alkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$; and Y_4 is hydrogen, $acyl_{(C\leq12)}$, substituted $acyl_{(C\leq12)}$, a dye, or a fluorescence quencher; z is an integer from 0-6; and R_6 is hydrogen, halo, $alkyl_{(C\leq12)}$, or substituted $alkyl_{(C\leq12)}$, wherein R_3, R_4, and R_5 can occur in any order within the polymer, provided that R_3 and R_4 are not the same group. In some examples, the compound is further defined by the formula wherein: R_1 is hydrogen, $alkyl_{(C\leq8)}$, substituted $alkyl_{(C\leq8)}$, or

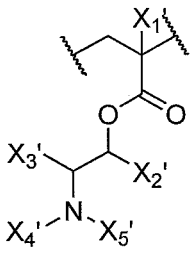


, or a metal chelating group; n is an integer from 10 to 200; R_2 and R_2' are each independently selected from hydrogen, $alkyl_{(C\leq8)}$, or substituted $alkyl_{(C\leq8)}$; R_3 is a group of the formula:



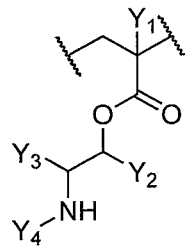
(II)

wherein: X_1, X_2, and X_3 are each independently selected from hydrogen, $alkyl_{(C\leq8)}$, or substituted $alkyl_{(C\leq8)}$; and X_4 and X_5 are each independently selected from $alkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$ or a substituted version of any of these groups, or X_4 and X_5 are taken together and are $alkanediyl_{(C\leq8)}$ or substituted $alkanediyl_{(C\leq8)}$; x is an integer from 1 to 100; R_4 is a group of the formula:

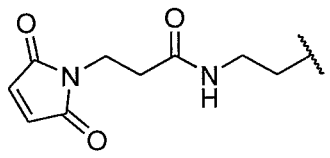


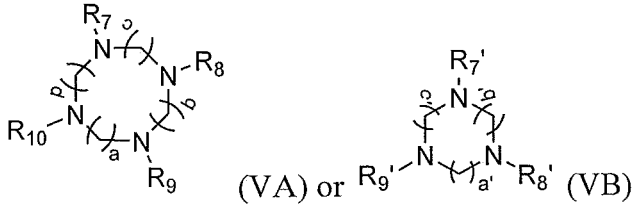
(III)

wherein: X_1', X_2', and X_3' are each independently selected from hydrogen, $alkyl_{(C\leq 8)}$, or substituted $alkyl_{(C\leq 8)}$; and X_4' and X_5' are each independently selected from $alkyl_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$ or a substituted version of any of these groups, or X_4' and X_5' are taken together and are $alkanediyl_{(C\leq 8)}$ or substituted $alkanediyl_{(C\leq 8)}$; y is an integer from 1 to 100; R_5 is a group of the formula:



(IV)

wherein: Y_1, Y_2, and Y_3 are each independently selected from hydrogen, $alkyl_{(C\leq 8)}$, substituted $alkyl_{(C\leq 8)}$; and Y_4 is hydrogen, a dye, or a fluorescence quencher; z is an integer from 0-6; and R_6 is hydrogen, halo, $alkyl_{(C\leq 6)}$, or substituted $alkyl_{(C\leq 6)}$, wherein R_3, R_4, and R_5 can occur in any order within the polymer, provided that R_3 and R_4 are not the same group. In some examples, R_1 is hydrogen. In some examples, R_1 is $alkyl_{(C\leq 6)}$. In some examples, R_1 is methyl. In some examples, R_1 is . In some examples, R_1 is a metal chelating group such as a metal chelating group selected from DOTA, TETA, Diamsar, NOTA, NETA, TACN-TM, DTPA, TRAP, NOPO, AAZTA, DATA, HBED, SHBED, BPCA, CP256, DFO, PCTA, HEHA, PEPA, or a derivative thereof. In some examples, the metal chelating group is a nitrogen containing macrocycle. In some examples, the nitrogen containing macrocycle is a compound of the formula:



(VA) or (VB)

wherein:

R_7, R_8, R_9, R_{10}, R_7', R_8', and R_9' are each independently selected from hydrogen,

$alkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $-alkanediyl_{(C\leq12)}-acyl_{(C\leq12)}$, or a substituted version of any of these groups; or a linker, wherein the linker is an $alkanediyl_{(C\leq12)}-C(O)NH-$ or a substituted $alkanediyl_{(C\leq12)}-C(O)NH-$; or

R_7 is taken together with one of R_8, R_9, or R_{10} and is $alkanediyl_{(C\leq6)}$; or

R_8 is taken together with one of R_7, R_9, or R_{10} and is $alkanediyl_{(C\leq6)}$; or

R_9 is taken together with one of R_7, R_8, or R_{10} and is $alkanediyl_{(C\leq6)}$; or

R_{10} is taken together with one of R_7, R_8, or R_9 and is $alkanediyl_{(C\leq6)}$; or

R_7' is taken together with one of R_8' or R_9' and is $alkanediyl_{(C\leq6)}$; or

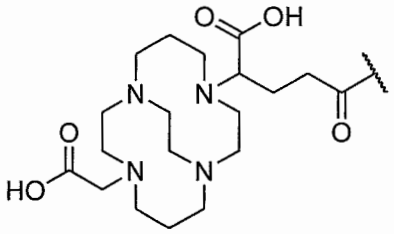
R_8' is taken together with one of R_7' or $R_9'$and is $alkanediyl_{(C\leq6)}$; or

R_9' is taken together with one of R_7' or $R_8'$and is $alkanediyl_{(C\leq6)}$; and

a, b, c, d, a′, b′, and c′ are each independently selected from 1, 2, 3, or 4.

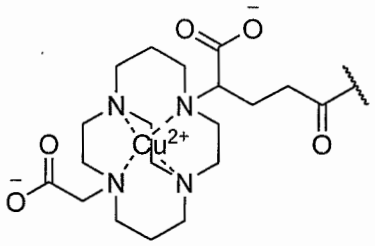
In some examples, a, b, c, d, a′, b′, and c′ are each independently selected from 2 or 3.

In some examples, the metal chelating group is:

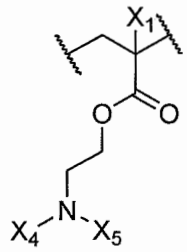


.

In some examples, the metal chelating complex is bound to a metal ion. In some examples, the metal ion is a radionuclide or radiometal. In some examples, the metal ion is suitable for PET or SPECT imaging. In some examples, the metal chelating complex is bound to a transition metal ion. In some examples, the metal ion is a copper ion, a gallium ion, a scandium ion, an indium ion, a lutetium ion, a ytterbium ion, a zirconium ion, a bismuth ion, a lead ion, a actinium ion, or a technetium ion. In some examples, the metal ion is an isotope selected from ^{99m}Tc, ^{60}Cu, ^{61}Cu, ^{62}Cu, ^{64}Cu, ^{86}Y, ^{90}Y, ^{89}Zr, ^{44}Sc, ^{47}Sc, ^{66}Ga, ^{67}Ga, ^{68}Ga, ^{111}In, ^{177}Lu, ^{225}Ac, ^{212}Pb, ^{212}Bi, ^{213}Bi, ^{111}In, ^{114m}In, ^{114}In, ^{186}Re, or ^{188}Re. In some examples, the transition metal is a copper(II) ion. In some examples, the copper(II) ion is a $^{64}Cu^{2+}$ ion. In some examples, the metal chelating complex is:



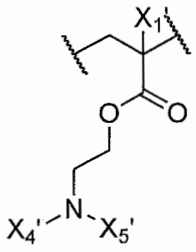
In some examples, R_2 is $alkyl_{(C\leq6)}$. In some examples, R_2 is methyl. In some examples, R_2' is $alkyl_{(C\leq6)}$. In some examples, R_2' is methyl. In some examples, R_3 is further defined by the formula:



(V)

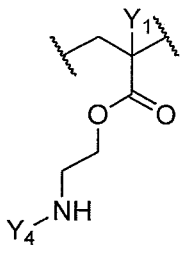
wherein: X_1 is selected from hydrogen, $alkyl_{(C\leq8)}$, or substituted $alkyl_{(C\leq8)}$; and X_4 and X_5 are each independently selected from $alkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$ or a substituted version of any of these groups, or X_4 and X_5 are taken together and are $alkanediyl_{(C\leq8)}$ or substituted $alkanediyl_{(C\leq8)}$; In some examples, X_1 is $alkyl_{(C\leq6)}$. In some examples, X_1 is methyl. In some examples, X_4 is $alkyl_{(C\leq8)}$. In some examples, X_4 is methyl, ethyl, propyl, butyl, or pentyl. In some examples, X_5 is $alkyl_{(C\leq8)}$. In some examples, X_5 is methyl, ethyl, propyl, butyl, or pentyl.

In some examples, R_4 is further defined by the formula:



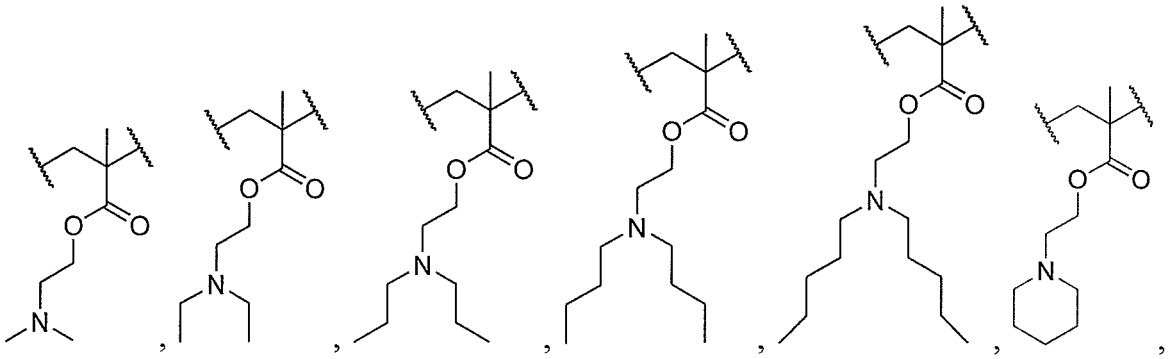
(VI)

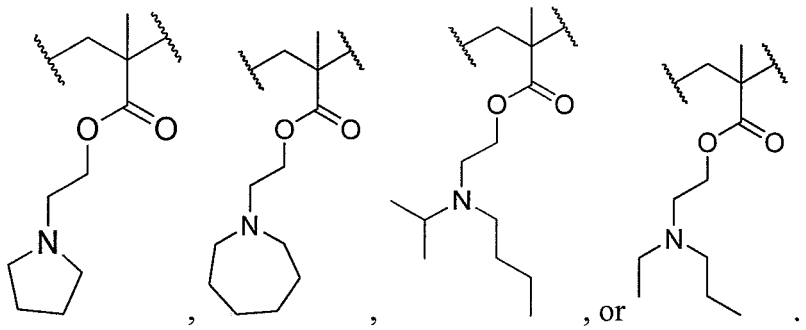
wherein: X_1' is selected from hydrogen, $alkyl_{(C\leq8)}$, or substituted $alkyl_{(C\leq8)}$; and X_4' and X_5' are each independently selected from $alkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$ or a substituted version of any of these groups, or X_4' and X_5' are taken together and are $alkanediyl_{(C\leq8)}$ or substituted $alkanediyl_{(C\leq8)}$. In some examples, X_1' is $alkyl_{(C\leq6)}$. In some examples, X_1 is methyl. In some examples, X_4' is $alkyl_{(C\leq8)}$. In some examples, X_4' is methyl, ethyl, propyl, butyl, or pentyl. In some examples, X_5' is $alkyl_{(C\leq8)}$. In some examples, X_5' is methyl, ethyl, propyl, butyl, or pentyl. In some examples, R_5 is further defined by the formula:



(VII)

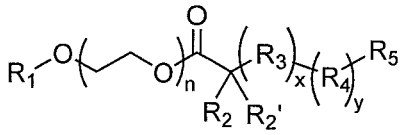
wherein: Y_1 is selected from hydrogen, $alkyl_{(C\leq 8)}$, substituted $alkyl_{(C\leq 8)}$; and Y_4 is hydrogen, a dye, or a fluorescence quencher. In some examples, Y_1 is $alkyl_{(C\leq 6)}$. In some examples, Y_1 is methyl. In some examples, Y_4 is hydrogen. In some examples, Y_4 is a dye. In some examples, Y_4 is fluorescent dye. In some examples, the fluorescent dye is a coumarin, fluorescein, rhodamine, xanthene, BODIPY®, Alexa Fluor®, or cyanine dye. In some examples, the fluorescent dye is indocyanine green, AMCA-x, Marina Blue, PyMPO, Rhodamine Green™, Tetramethylrhodamine, 5-carboxy-X-rhodamine, Bodipy493, Bodipy TMR-x, Bodipy630, Cyanine5, Cyanine5.5, and Cyanine7.5. In some examples, the fluorescent dye is indocyanine green. In some examples, Y_4 is a fluorescence quencher. In some examples, the fluorescence quencher is QSY7, QSY21, QSY35, BHQ1, BHQ2, BHQ3, TQ1, TQ2, TQ3, TQ4, TQ5, TQ6, and TQ7. In some examples, n is 75-150. In some examples, n is 100-125. In some examples, x is 1-99. In some examples, x is from 1-5, 5-10, 10-15, 15-20, 20-25, 25-30, 30-35, 35-40, 40-45, 45-50, 50-55, 55-60, 60-65, 65-70, 70-75, 75-80, 80-85, 85-90, 90-95, 95-99 or any range derivable therein. In some examples, y is 1-99. In some examples, y is from 1-5, 5-10, 10-15, 15-20, 20-25, 25-30, 30-35, 35-40, 40-45, 45-50, 50-55, 55-60, 60-65, 65-70, 70-75, 75-80, 80-85, 85-90, 90-95, 95-99 or any range derivable therein. In some examples, z is 0-6. In some examples, z is 1-6. In some examples, z is from 0-2, 2-4, 4-6, or any range derivable therein. In some examples, R_3, R_4, and R_5 can occur in any order within the polymer. In some examples, R_3, R_4, and R_5 occur in the order described in formula I. In some examples, the polymer further comprises a targeting moiety. In some examples, the targeting moiety is a small molecule, an antibody, an antibody fragment, or a signaling peptide. In some examples, R_3 and R_4 are selected from:



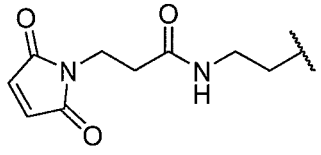


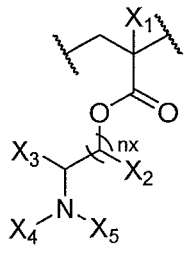
In some examples, the polymer is PEO_{114}-P(DEA_{20}-$D5A_{60}$), PEO_{114}-P(DEA_{40}-$D5A_{40}$), PEO_{114}-P(DEA_{60}-$D5A_{20}$), PEO_{114}-P(DPA_{60}-DBA_{20}), PEO_{114}-P(DPA_{40}-DBA_{40}), PEO_{114}-P(DPA_{20}-DBA_{60}), PEO_{114}-P(DEA_{76}-DPA_{24}), PEO_{114}-P(DEA_{58}-DPA_{42}), PEO_{114}-P(DEA_{39}-DPA_{61}), PEO_{114}-P(DEA_{21}-DPA_{79}), PEO_{114}-P(DPA_{30}-DBA_{50}), PEO_{114}-P(DBA_{28}-$D5A_{52}$), PEO_{114}-P(DBA_{56}-$D5A_{24}$), PEO_{114}-P(DEA_{20}-$D5A_{60}$-AMA_3), PEO_{114}-P(DEA_{40}-$D5A_{40}$-AMA_3), PEO_{114}-P(DEA_{60}-$D5A_{20}$-AMA_3), PEO_{114}-P(DPA_{60}-DBA_{20}-AMA_3), PEO_{114}-P(DPA_{40}-DBA_{40}-AMA_3), PEO_{114}-P(DPA_{20}-DBA_{60}-AMA_3), PEO_{114}-P(DEA_{76}-DPA_{24}-AMA_3), PEO_{114}-P(DEA_{58}-DPA_{42}-AMA_3), PEO_{114}-P(DEA_{39}-DPA_{61}-AMA_3), PEO_{114}-P(DEA_{21}-DPA_{79}-AMA_3), PEO_{114}-P(DPA_{30}-DBA_{50}-AMA_3), PEO_{114}-P(DBA_{28}-$D5A_{52}$-AMA_3), or PEO_{114}-P(DBA_{56}-$D5A_{24}$-AMA_3), PEO_{114}-P(DEA_{11}-EPA_{89}), PEO_{114}-P(DEA_{22}-EPA_{78}), PEO_{114}-P(EPA_{90}-DPA_{10}), PEO_{114}-P(EPA_{79}-DPA_{21}).

In another example, there is disclosed a polymer of the formula:



(V)

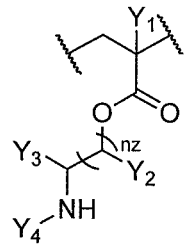
wherein: R_1 is hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, substituted $cycloalkyl_{(C\leq12)}$, or  , or a metal chelating group; n is an integer from 1 to 500; R_2 and R_2' are each independently selected from hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, or substituted $cycloalkyl_{(C\leq12)}$; R_3 is a group of the formula:



(II)

wherein: n_x is 1-10; X_1, X_2, and X_3 are each independently selected from hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, or substituted $cycloalkyl_{(C\leq12)}$; X_4 is pentyl,

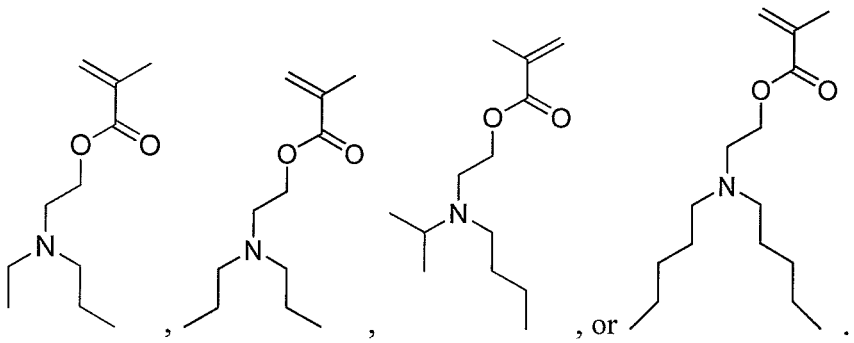
n-propyl, or ethyl; and X_5 is pentyl or n-propyl; x is an integer from 1 to 100; R_4 is a group of the formula:



(IV)

wherein: Y_1, Y_2, and Y_3 are each independently selected from hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, or substituted $cycloalkyl_{(C\leq12)}$; and Y_4 is hydrogen, $alkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, substituted $acyl_{(C\leq12)}$, a dye, or a fluorescence quencher; y is an integer from 1 to 6; and R_5 is hydrogen, halo, hydroxy, $alkyl_{(C\leq12)}$, or substituted $alkyl_{(C\leq12)}$. In some examples, Y_4 is a fluorescent dye. In some examples, the fluorescent dye is indocyanine green. In some examples, the polymer is PEO_{114}-$P(D5A_{80})$, PEO_{114}-$P(D5A_{100})$, PEO_{114}-$P(DPA_{80})$, PEO_{114}-$P(DPA_{100})$, PEO_{114}-$P(EPA_{80})$, and PEO_{114}-$P(EPA_{100})$.

In yet another example, there is disclosed a compound of the formula:



, , , or .

In another example, there is disclosed a micelle of a polymer of the present disclosure.

In yet another example, there is disclosed a pH responsive system comprising a micelle of a first polymer of the present disclosure, wherein z is not 0 and Y_4 is a dye, and wherein the micelle has a pH transition point and an emission spectra. In some examples, the micelle further comprises a second polymer of the present disclosure, wherein z is not 0 and Y_4 is a fluorescence quencher. In some examples, the second polymer has the same formula as the first polymer except that Y_4 is a fluorescence quencher. In some examples, the pH transition point is between 3-9. In some examples, the pH transition point is between 4-8. In some examples, the pH transition point is between 4-6. In some examples, the pH transition point is between 6-7.5. In some examples, the pH transition point is 4.38, 4.67, 4.96, 5.27, 5.63, 5.91, 6.21, 6.45, 6.76, 7.08, or 7.44. In some examples, the emission spectra is between 400-850 nm. In some examples, the system has a pH response ($\Delta pH_{10\text{-}90\%}$) of less than 1 pH unit. In some examples, the pH response is less than 0.25 pH units. In some examples, the pH response is less than 0.15 pH units. In some

examples, the fluorescence signal has a fluorescence activation ratio of greater than 25. In some examples, the fluorescence activation ratio is greater than 50.

In yet another example, there is disclosed a method of imaging the pH of a intracellular or extracellular environment comprising:

(a) contacting a micelle of the present disclosure with the environment; and

(b) detecting one or more optical signals from the environment, wherein the detection of the optical signal indicates that the micelle has reached its pH transition point and disassociated.

In some examples, the optical signal is a fluorescent signal. In some examples, when the intracellular environment is imaged, the cell is contacted with the micelle under conditions suitable to cause uptake of the micelle. In some examples, the intracellular environment is part of a cell. In some examples, the part of the cell is lysosome or an endosome. In some examples, the extracellular environment is of a tumor or vascular cell. In some examples, the extracellular environment is intravascular or extravascular. In some examples, the imaging the pH of the tumor environment comprises imaging the sentinel lymph node or nodes. In some examples, imaging sentinel lymph node or nodes allows for the surgical resection of the tumor and staging of the tumor metastasis. In some examples, imaging the pH of the tumor environment allows determination of the tumor size and margins. In some examples, imaging the pH of the tumor environment allows for more precise removal of the tumor during surgery. In some examples, imaging the pH of the sentential lymph node or nodes allows for more precise removal of the sentential lymph node or nodes during surgery. In some examples, the method further comprises:

(a) contacting the cell with a compound of interest;

(b) detecting one or more optical signals in the environment; and

(c) determining whether a change in the optical signal occurred following contacting the cell with the compound of interest.

In some examples, the compound of interest is a drug, antibody, peptide, protein, nucleic acid, or small molecule.

In yet another example, there is disclosed a method of delivering a compound of interest to a target cell comprising:

(a) encapsulating the compound of interest with a micelle of a polymer of claims 1-55; and

(b) contacting the target cell with the micelle under such conditions that the pH of the target cell triggers the disassociation of the micelle and release of the compound, thereby delivering the compound of interest.

In some examples, the compound of interest is delivered into the cell. In some examples, the compound of interest is delivered to the cell. In some examples, the compound of interest is a drug, antibody, peptide, protein, nucleic acid, or small molecule. In some examples, the method comprises administering the micelle to a patient.

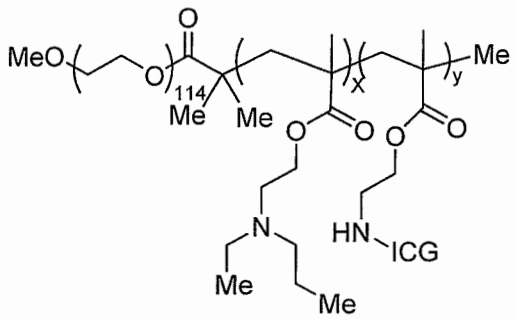
In still yet another example, there is disclosed a method of resecting a tumor in a patient comprising:

(a) administering to the patient an effective dose of a pH responsive system of the present disclosure;

(b) detecting one or more optical signals for the patient; wherein the optical signals indicate the presence of a tumor; and

(c) resecting the tumor via surgery.

In some examples, the optical signals indicate the margins of the tumor. In some examples, the tumor is 90% resected, or the tumor is 95% resected., or the tumor is 99% resected. In some examples, the tumor is a solid tumor such as a solid tumor is from a cancer. In some examples, the cancer is a breast cancer or a head and neck cancer such as a head and neck squamous cell carcinoma. In some examples, the pH responsive system is comprised of a polymer of the formula:



wherein: x is an integer from 30 to 150, y is an integer from 1 or 2; x and y are randomly distributed throughout the polymer; and ICG is the fluorescent dye indocyanine green.

In yet another example, there are disclosed methods of treating a cancer susceptible to endosomal/lysosomal pH arrest in a patient comprising administering to the patient in need thereof a pH responsive system of the present disclosure. In some examples, the cancer is a lung cancer such as a non-small cell lung cancer. In some examples, the cancer comprises a mutation in the *KRAS* gene or a mutation in the *LKB1* gene. In other examples, the cancer comprises a mutation in both the *KRAS* and *LKB1* gene. In some examples, methods are sufficient to induce apoptosis.

In still yet another example, there are disclosed methods of identifying the presence of a genetic mutation in a cell:

(a) contacting a pH responsive systems comprising two or more micelles with the cell or cellular environment; and

(b) detecting two or more optical signals from the environment, wherein the detection of the optical signal indicates that one of the micelles has reached its pH transition point and disassociated; and

(c) correlate the two or more optical signals to determine the presence of the genetic mutation in the cell.

In some examples, the genetic mutation is a mutation in the *KRAS* gene. In some examples, the two or more micelles comprises three micelles with a pH transition point at 6.9, 6.2, and 5.3. In some examples, each of the three micelles is prepared from a polymer selected from PDPA-TMR, PEPA-BDY493, and PDBA-Cy5. In some examples, the method is performed *in vivo* and contact a cell comprising administering the one or more micelles to a patient.

In still yet another example, there are disclosed methods of identifying the tumor acidosis pathway comprising:

(a) contacting a pH responsive system of the present disclosure comprising one or more micelles with a cell or a cellular environment;

(b) contacting the cell with an inhibitor of the pH regulatory pathway;

(c) detecting two or more optical signals from the cell or cellular environment, wherein the detection of the optical signal indicates that one of the micelles has reached its pH transition point and disassociated; and

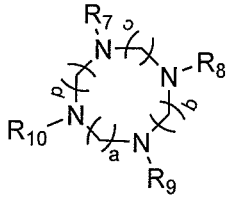
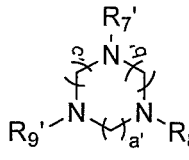
(d) correlating the two or more optical signals with a modification in the tumor acidosis pathway.

In some examples, the inhibitor of the pH regulatory pathway is an inhibitor of a monocarboxylate transporter, a carbonic anhydrase, an anion exchanger, a Na^+-bicarbonate exchanger, a Na^+/H^+ exchanger, or a V-ATPase. In some examples, the one or more micelles comprise a polymer with two or more fluorophores attached to the polymer backbone. In some examples, the method comprises one micelle and the micelle comprises two or more polymers with different fluorophores or different R_3 groups. In some examples, the micelle comprises two or more polymers with different fluorophores and different R_3 groups.

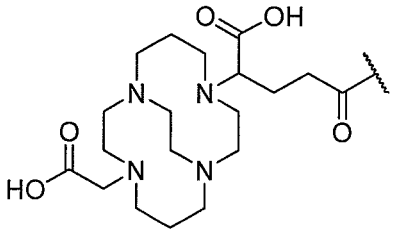
In another example, there is disclosed method of imaging a patient to determine the presence of a tumor comprising (a) contacting a pH responsive system comprising one or more micelles of the present disclosure with the tumor, wherein the micelle further comprises a metal chelating group at R_1; (b) collecting one or more PET or SPECT imaging scans; and (c) collecting one or more optical imaging scans, wherein the detection of the optical signal indicates that one of the micelles has reached its pH transition point and disassociated; wherein the one or more PET or

SPECT imaging scans and the one or more optical imaging scans result in the identification of a tumor.

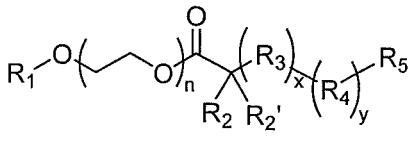
In some examples, the optical imaging scans are collected before the PET or SPECT imaging scans. In other examples, the optical imaging scans are collected after the PET or SPECT imaging scans. In other examples, the optical imaging scans are collected simultaneously with the PET or SPECT imaging scans. In some examples, the imaging scans are PET imaging scans. In other examples, the imaging scans are SPECT imaging scans. In some examples, the metal chelating group is bound to a ^{64}Cu ion. In some examples, the metal chelating group is a nitrogen containing macrocycle. In some examples, the nitrogen containing macrocycle is:


(VA) or

(VB)

wherein: R_7, R_8, R_9, R_{10}, R_7', R_8', R_9' a, b, c, d, a′, b′, and c′ are as defined above. In some examples, the nitrogen containing macrocycle is:



In still yet another example, there are disclosed polymers of the formula:


(IX)

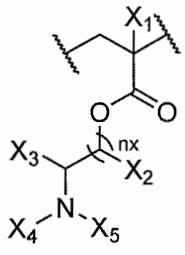
wherein:

R_1 is a metal chelating group;

n is an integer from 1 to 500;

R_2 and R_2' are each independently selected from hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, or substituted $cycloalkyl_{(C\leq12)}$;

R_3 is a group of the formula:



(II)

wherein:

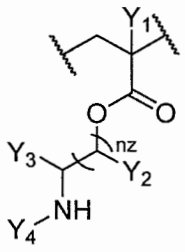
n_x is 1-10;

X_1, X_2, and X_3 are each independently selected from hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, or substituted $cycloalkyl_{(C\leq12)}$; and

X_4 and X_5 are each independently selected from $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$ or a substituted version of any of these groups, or X_4 and X_5 are taken together and are $alkanediyl_{(C\leq12)}$, $alkoxydiyl_{(C\leq12)}$, $alkylaminodiyl_{(C\leq12)}$, or a substituted version of any of these groups;

x is an integer from 1 to 150;

R_4 is a group of the formula:



(IV)

wherein:

n_z is 1-10;

Y_1, Y_2, and Y_3 are each independently selected from hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, or substituted $cycloalkyl_{(C\leq12)}$; and

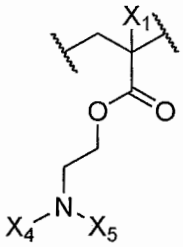
Y_4 is hydrogen, $alkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, substituted $acyl_{(C\leq12)}$, a dye, or a fluorescence quencher;

y is an integer from 0-6; and

R_4 is hydrogen, halo, hydroxy, $alkyl_{(C\leq12)}$, or substituted $alkyl_{(C\leq12)}$,

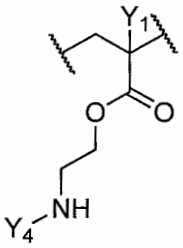
wherein R_3 and R_4 can occur in any order within the polymer, provided that R_3 and R_4 are not the same group.

In some examples, R_3 is:



wherein: X_1, X_4, and X_5 are as defined above.

In some examples, X_1 is $alkyl_{(C\leq12)}$ such as X_1 is methyl. In some examples, X_4 and X_5 are taken together and are $alkanediyl_{(C\leq12)}$ or substituted $alkanediyl_{(C\leq12)}$. In some examples, wherein X_4 and X_5 are taken together and are $-CH_2CH_2CH_2CH_2CH_2CH_2-$. In some examples, R_4 is:



wherein: Y_1 and Y_4 are as defined above. In some examples, Y_4 is a dye. In some examples, Y_4 is a fluorescent dye. In some examples, Y_1 is $alkyl_{(C\leq12)}$ such as Y_1 is methyl. In some examples, x is 40, 60, 80, 100, or 120. In some examples, y is 1, 2, or 3, such as when y is 3. In some examples, the polymer is PEO_{114}-P(C7A_{40}-r-ICG_3), PEO_{114}-P(C7A_{60}-r-ICG_3), PEO_{114}-P(C7A_{80}-r-ICG_3), PEO_{114}-P(C7A_{100}-r-ICG_3), or PEO_{114}-P(C7A_{120}-r-ICG_3), wherein the PEO group is capped with a metal chelating group.

As used herein, "pH responsive system," "micelle," "pH-responsive micelle," "pH-sensitive micelle," "pH-activatable micelle" and "pH-activatable micellar (pHAM) nanoparticle" are used interchangeably herein to indicate a micelle comprising one or more block copolymers, which disassociates depending on the pH (*e.g.,* above or below a certain pH). As a non-limiting example, at a certain pH, the block copolymer is substantially in micellar form. As the pH changes (*e.g.,* decreases), the micelles begin to disassociate, and as the pH further changes (*e.g.,* further decreases), the block copolymer is present substantially in disassociated (non-micellar) form.

As used herein, "pH transition range" indicates the pH range over which the micelles disassociate.

As used herein, "pH transition value" (pH_t) indicates the pH at which half of the micelles are disassociated.

It is contemplated that any method or composition described herein can be implemented with respect to any other method or composition described herein.

The terms "comprise" (and any form of comprise, such as "comprises" and "comprising"), "have" (and any form of have, such as "has" and "having"), "contain" (and any form of contain, such as "contains" and "containing"), and "include" (and any form of include, such as "includes" and "including") are open-ended linking verbs. As a result, a method, composition, kit, or system that "comprises," "has," "contains," or "includes" one or more recited steps or elements possesses those recited steps or elements, but is not limited to possessing only those steps or elements; it may possess (*i.e.*, cover) elements or steps that are not recited. Likewise, an element of a method, composition, kit, or system that "comprises," "has," "contains," or "includes" one or more recited features possesses those features, but is not limited to possessing only those features; it may possess features that are not recited.

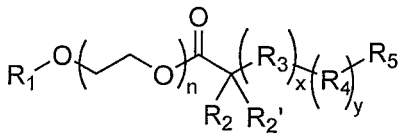
Any embodiment of any of the present methods, composition, kit, and systems may consist of or consist essentially of—rather than comprise/include/contain/have—the described steps and/or features. Thus, in any of the claims, the term "consisting of" or "consisting essentially of" may be substituted for any of the open-ended linking verbs recited above, in order to change the scope of a given claim from what it would otherwise be using the open-ended linking verb.

The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or." Throughout this application, the term "about" is used to indicate that a value includes the standard deviation of error for the device or method being employed to determine the value. Following long-standing patent law, the words "a" and "an," when used in conjunction with the word "comprising" in the claims or specification, denotes one or more, unless specifically noted.

Other objects, features and advantages of the present disclosure will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the disclosure, are given by way of illustration only, since various changes and modifications within the spirit and scope of the disclosure will become apparent to those skilled in the art from this detailed description.

WHAT IS CLAIMED IS:

1. A polymer of the formula:



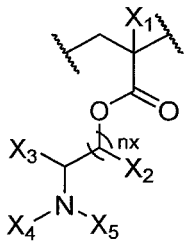
wherein:

R_1 is an $alkyl_{(C\leq12)}$;

n is an integer from 10-200;

R_2 and R_2' are each independently a methyl;

R_3 is a group of the formula:



wherein:

n_x is 1-3;

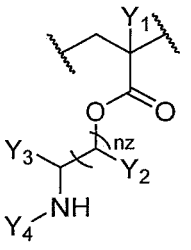
X_1 is a hydrogen or an $alkyl_{(C\leq12)}$;

X_2 and X_3 are each hydrogen;

X_4 is pentyl, n-propyl, or ethyl and X_5 is pentyl or n-propyl; or X_4 and X_5 are taken together and are $alkanediyl_{(C\leq9)}$ or substituted $alkanediyl_{(C\leq9)}$;

x is an integer from 30 to 150;

R_4 is a group of the formula:

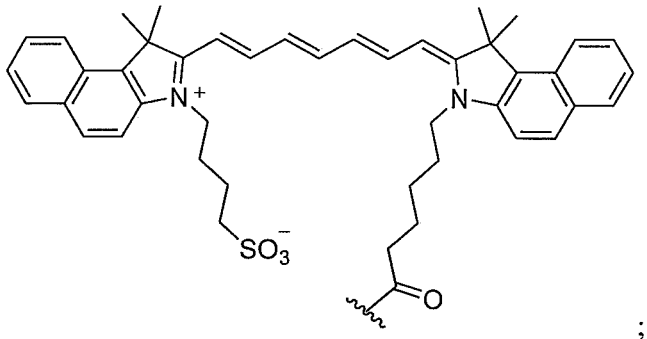


wherein:

n_z is 1-10;

Y_1, Y_2, and Y_3 are each independently selected from hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, or substituted $cycloalkyl_{(C\leq12)}$; and

Y_4 is a dye with the following structure:

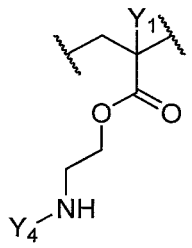


;

y is an integer from 1 to 6; and

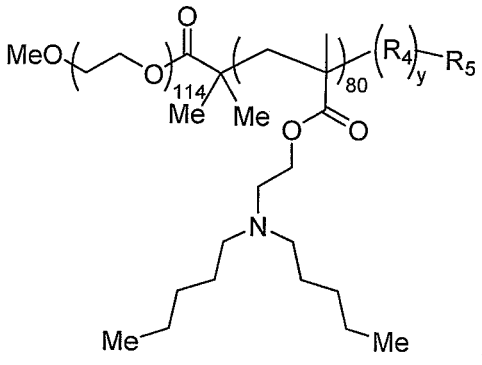
R_5 is hydrogen, halo, hydroxy, $alkyl_{(C\leq12)}$, or substituted $alkyl_{(C\leq12)}$.

2. The polymer of claim 1, wherein R_1 is methyl.
3. The polymer of claim 1, wherein R_4 is:

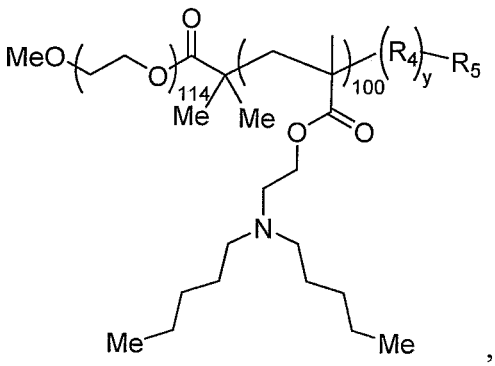


.

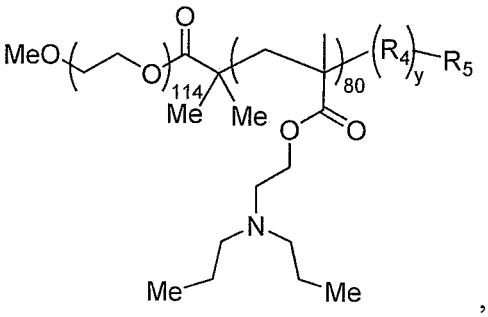
4. The polymer of claim 1, wherein X_1 or Y_1 is $alkyl_{(C\leq12)}$.
5. The polymer of claim 4, wherein X_1 is methyl.
6. The polymer of claim 4, wherein Y_1 is methyl.
7. The polymer of claim 1, wherein the polymer is



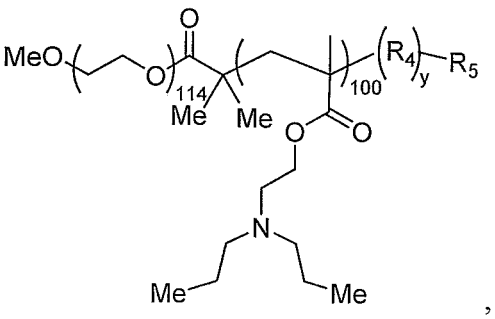
,



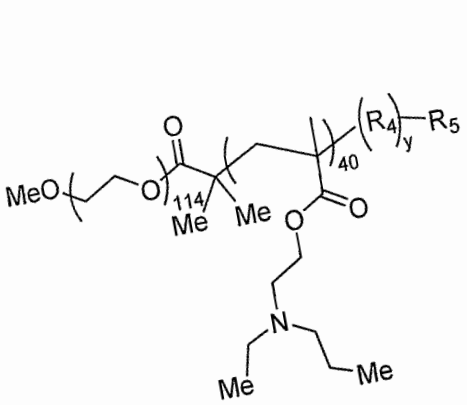
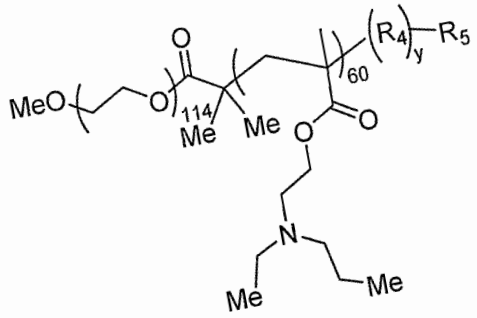
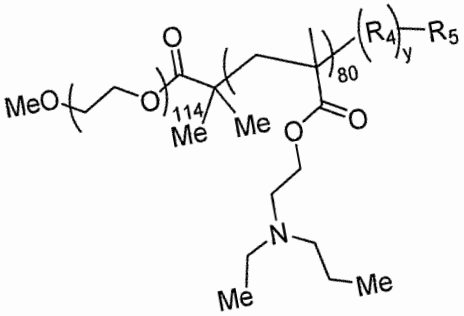
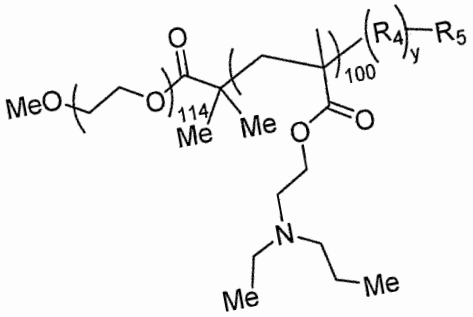
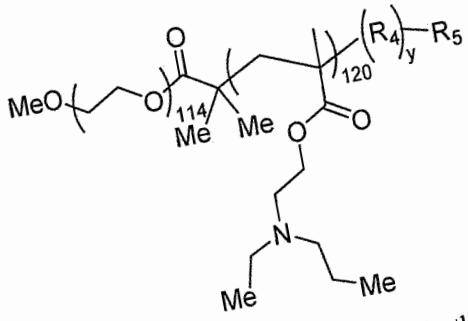
,



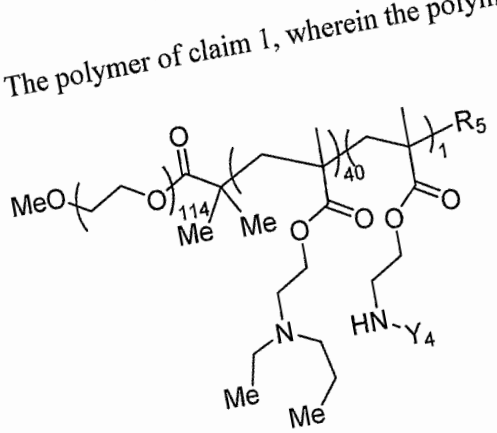
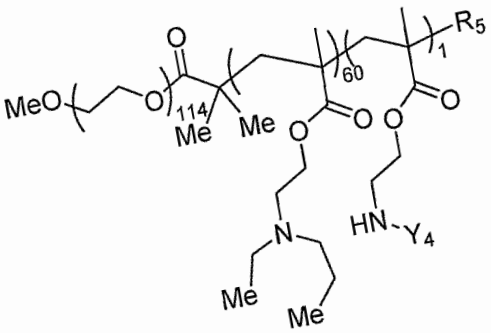
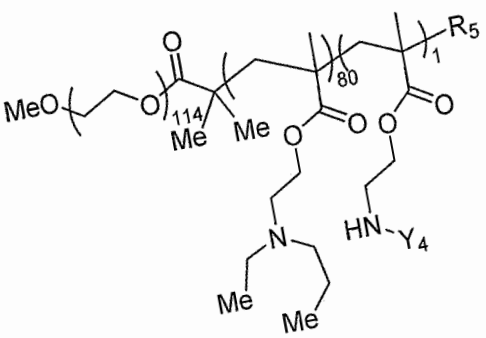
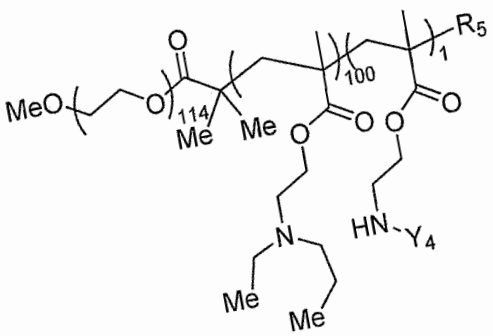
,

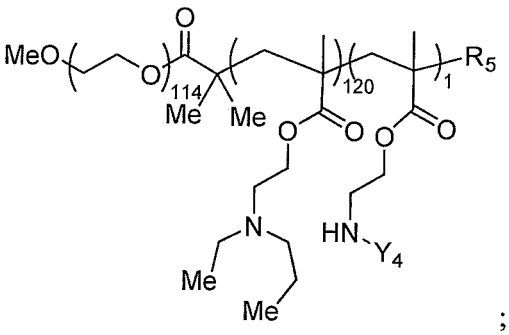


,

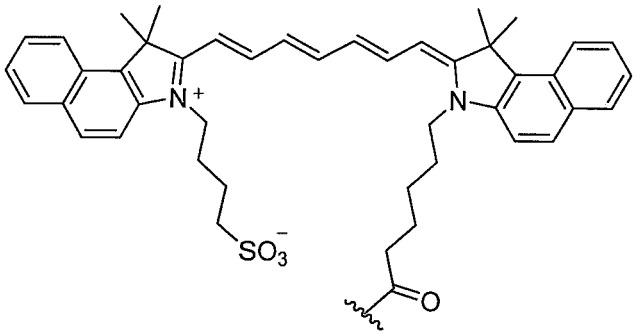
8. The polymer of claim 1, wherein the polymer is



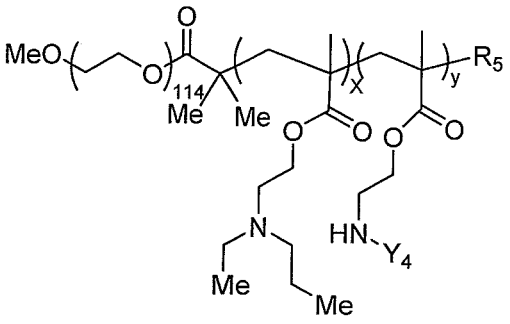
;

wherein Y_4 is the dye with the following structure:

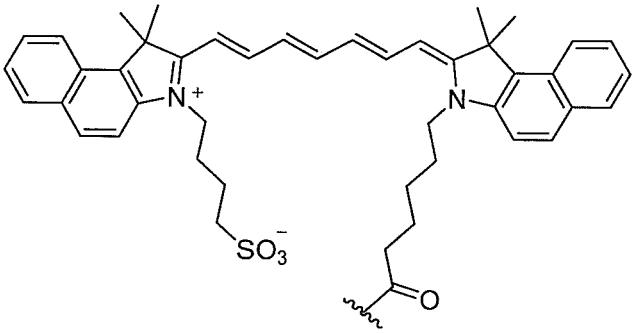


.

9. The polymer of claim 1, wherein the polymer is:



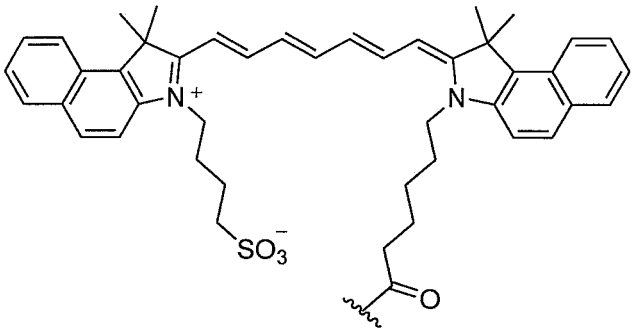
wherein: x is an integer from 30 to 150, y is an integer from 1 to 2; and Y_4 is the dye with the following structure:



.

10. A composition comprising a micelle formed from a plurality of polymers according to claim 1.

11. The composition of claim 10, wherein the micelle has a pH transition point and an emission spectra, wherein the micelle dissociates at a pH below the pH transition point; and wherein Y_4 is a dye with the following structure:



12. The polymer of claim 1, where n_x is and integer from 1-2.

13. The polymer of claim 1, where n_x is 1.