hSepharase, Homo sapiens extra spindle poles like 1 (S. cerevisiae) (ESPL1), mRNA (GenBank accession number: NM_012291);

CamKIId, Homo sapiens calcium/calmodulin-dependent protein kinase (CaM kinase) II delta (CAMK2D), transcript variant 3, mRNA (GenBank accession number: NM_001221);

CDK6, Homo sapiens cyclin-dependent kinase 6 (CDK6), mRNA (GenBank accession number: NM_001259); and

GRB2, Homo sapiens growth factor receptor-bound protein 2 (GRB2), transcript variant 1, mRNA (GenBank accession number: NM_002086).

16. A kit for predicting or monitoring a cancer patient's response to molecule of the taxoid family according to the method of Claim 8 wherein the kit comprises detectable-labeled antibodies, detectable-labeled antibody fragments or detectable-labeled oligonucleotides comprising nucleic acids capable of hybridizing under stringent conditions to said one or more genetic markers selected from the group consisting of:

P21(Waf1), Homo sapiens cyclin-dependent kinase inhibitor 1A (p21, Cip1) (CDKN1A), transcript variant 1, mRNA (GenBank accession number: NM_000389);

Pim-1, Homo sapiens pim-1 oncogene (PIM1), mRNA (GenBank accession number: NM_002648);

GBP-1, Homo sapiens guanylate binding protein 1, interferon-inducible, 67kDa (GBP1), mRNA (GenBank accession number: NM_002053);

RXRA, Homo sapiens retinoid X receptor, alpha (RXRA), mRNA (GenBank accession number: NM_002957);

SPF45, Homo sapiens RNA binding motif protein 17 (RBM17), mRNA (GenBank accession number: NM_032905);

Hec1, Homo sapiens kinetochore associated 2 (KNTC2), mRNA (GenBank accession number: NM_006101);

Raf1, Human mRNA for raf oncogene (GenBank accession number: X03484);

Aurora A, Homo sapiens aurora-related kinase 1 (ARK1) mRNA, complete cds (GenBank accession number: AF008551);

TACC3, Homo sapiens transforming, acidic coiled-coil containing protein 3 (TACC3), mRNA (GenBank accession number: NM_006342);

RelB, Homo sapiens v-rel reticuloendotheliosis viral oncogene homolog B, nuclear factor of kappa light polypeptide gene enhancer in B-cells 3 (avian) (RELB), mRNA (GenBank accession number: NM_006509);

PRKCD, Homo sapiens protein kinase C, delta (PRKCD), transcript variant 1, mRNA (GenBank accession number: NM_006254);

BRAF35, Homo sapiens high-mobility group 20B (HMG20B), mRNA (GenBank accession number: NM_006339);

HSPA1L, Homo sapiens heat shock 70kDa protein 1A (HSPA1A), mRNA (GenBank accession number: NM_005345);

STK11, Homo sapiens serine/threonine kinase 11 (Peutz-Jeghers syndrome) (STK11), mRNA (GenBank accession number: NM_000455); and

MKK3, Homo sapiens MAP kinase kinase 3 (MKK3) mRNA, complete cds (GenBank accession number: L36719).

17. A kit for predicting or monitoring a cancer patient's response to molecule of the taxoid family according to the method of Claim 1 wherein the kit comprises the means of:

a) obtaining total RNA from a bodily sample;

b) reverse transcribing the total RNA to obtain cDNA; and

c) subjecting the cDNA to a polymerase chain reaction using a set of primers wherein one or both primers are detectably-labeled and both primers are derived from a nucleotide sequence of one or more genetic markers selected from the group consisting of:

BubR1, Homo sapiens similar to protein kinase (BUBR1) mRNA, complete cds (GenBank accession number: AF046079);

Mad2, Homo sapiens mRNA for MAD2 protein (GenBank accession number: AJ000186);

Mps1, Homo sapiens TTK protein kinase (TTK), mRNA (GenBank accession number: NM_003318);

GEFT for Rac1/CDC42, Homo sapiens RAC/CDC42 exchange factor (GEFT), transcript variant 2, mRNA (GenBank accession number: NM_133483);

Bub1, Homo sapiens BUB1 budding uninhibited by benzimidazoles 1 homolog (yeast) (BUB1), mRNA (GenBank accession number: NM_004336);

hSepharase, Homo sapiens extra spindle poles like 1 (S. cerevisiae) (ESPL1), mRNA (GenBank accession number: NM_012291);

CamKIId, Homo sapiens calcium/calmodulin-dependent protein kinase (CaM kinase) II delta (CAMK2D), transcript variant 3, mRNA (GenBank accession number: NM_001221);

CDK6, Homo sapiens cyclin-dependent kinase 6 (CDK6), mRNA (GenBank accession number: NM_001259); and

GRB2, Homo sapiens growth factor receptor-bound protein 2 (GRB2), transcript variant 1, mRNA (GenBank accession number: NM_002086).

18. A kit for predicting or monitoring a cancer patient's response to molecule of the taxoid family according to the method of Claim 8 wherein the kit comprises the means of:

a) obtaining total RNA from a bodily sample;

b) reverse transcribing the total RNA to obtain cDNA; and

c) subjecting the cDNA to a polymerase chain reaction using a set of primers wherein one or both primers are detectably-labeled and both primers are derived from a nucleotide sequence of one or more genetic markers selected from the group consisting of:

P21(Waf1), Homo sapiens cyclin-dependent kinase inhibitor 1A (p21, Cip1) (CDKN1A), transcript variant 1, mRNA (GenBank accession number: NM_000389);

Pim-1, Homo sapiens pim-1 oncogene (PIM1), mRNA (GenBank accession number: NM_002648);

GBP-1, Homo sapiens guanylate binding protein 1, interferon-inducible, 67kDa (GBP1), mRNA (GenBank accession number: NM_002053);

RXRA, Homo sapiens retinoid X receptor, alpha (RXRA), mRNA (GenBank accession number: NM_002957);

SPF45, Homo sapiens RNA binding motif protein 17 (RBM17), mRNA (GenBank accession number: NM_032905);

Hec1, Homo sapiens kinetochore associated 2 (KNTC2), mRNA (GenBank accession number: NM_006101);

Raf1, Human mRNA for raf oncogene (GenBank accession number: X03484);

Aurora A, Homo sapiens aurora-related kinase 1 (ARK1) mRNA, complete cds (GenBank accession number: AF008551);

TACC3, Homo sapiens transforming, acidic coiled-coil containing protein 3 (TACC3), mRNA (GenBank accession number: NM_006342);

RelB, Homo sapiens v-rel reticuloendotheliosis viral oncogene homolog B, nuclear factor of kappa light polypeptide gene enhancer in B-cells 3 (avian) (RELB), mRNA (GenBank accession number: NM_006509);

PRKCD, Homo sapiens protein kinase C, delta (PRKCD), transcript variant 1, mRNA (GenBank accession number: NM_006254);

BRAF35, Homo sapiens high-mobility group 20B (HMG20B), mRNA (GenBank accession number: NM_006339);

HSPA1L, Homo sapiens heat shock 70kDa protein 1A (HSPA1A), mRNA (GenBank accession number: NM_005345);

STK11, Homo sapiens serine/threonine kinase 11 (Peutz-Jeghers syndrome) (STK11), mRNA (GenBank accession number: NM_000455); and

MKK3, Homo sapiens MAP kinase kinase 3 (MKK3) mRNA, complete cds (GenBank accession number: L36719).

19. The detectable label of any one of claims 15 – 18, wherein the detectable label is selected from the group consisting of an enzyme, a radioactive isotope, or a chemical which fluoresces, a chemiluminescent molecule, radiopaque substances, liposomes, and haptenic molecules.

20. A method for predicting or monitoring a cancer patient's response to a molecule of the taxoid family, comprising the steps of:

a) obtaining a test sample from a cancerous area of said patient;

b) measuring the level of one or more genetic markers selected from the group consisting of:

BubR1, Homo sapiens similar to protein kinase (BUBR1) mRNA, complete cds (GenBank accession number: AF046079);

Mad2, Homo sapiens mRNA for MAD2 protein (GenBank accession number: AJ000186);

Mps1, Homo sapiens TTK protein kinase (TTK), mRNA (GenBank accession number: NM_003318);

GEFT for Rac1/CDC42, Homo sapiens RAC/CDC42 exchange factor (GEFT), transcript variant 2, mRNA (GenBank accession number: NM_133483);

Bub1, Homo sapiens BUB1 budding uninhibited by benzimidazoles 1 homolog (yeast) (BUB1), mRNA (GenBank accession number: NM_004336);

hSepharase, Homo sapiens extra spindle poles like 1 (S. cerevisiae) (ESPL1), mRNA (GenBank accession number: NM_012291);

CamKIId, Homo sapiens calcium/calmodulin-dependent protein kinase (CaM kinase) II delta (CAMK2D), transcript variant 3, mRNA (GenBank accession number: NM_001221);

CDK6, Homo sapiens cyclin-dependent kinase 6 (CDK6), mRNA (GenBank accession number: NM_001259); and

GRB2, Homo sapiens growth factor receptor-bound protein 2 (GRB2), transcript variant 1, mRNA (GenBank accession number: NM_002086)

c) measuring the level of one or more reference genetic markers selected from the group consisting of:

GAPDH, Homo sapiens glyceraldehyde-3-phosphate dehydrogenase (GAPD), mRNA (GenBank accession number: NM_002046); and

RPS9, Homo sapiens cDNA clone IMAGE:6647283, partial cds (GenBank accession number: BC071941);

d) comparing the measured levels of said one or more genetic markers and said one or more reference genetic markers in the test sample;

wherein a decrease in the level of said one or more genetic markers as compared to the level of said one or more reference genetic markers indicates an increased resistance to a molecule of the taxoid family.

21. A method for predicting or monitoring a cancer patient's response to a molecule of the taxoid family, comprising the steps of:

a) obtaining a test sample from a cancerous area of said patient;

b) measuring the level of one or more genetic markers selected from the group consisting of:

P21(Waf1), Homo sapiens cyclin-dependent kinase inhibitor 1A (p21, Cip1) (CDKN1A), transcript variant 1, mRNA (GenBank accession number: NM_000389);

Pim-1, Homo sapiens pim-1 oncogene (PIM1), mRNA (GenBank accession number: NM_002648);

GBP-1, Homo sapiens guanylate binding protein 1, interferon-inducible, 67kDa (GBP1), mRNA (GenBank accession number: NM_002053);

RXRA, Homo sapiens retinoid X receptor, alpha (RXRA), mRNA (GenBank accession number: NM_002957);

SPF45, Homo sapiens RNA binding motif protein 17 (RBM17), mRNA (GenBank accession number: NM_032905);

Hec1, Homo sapiens kinetochore associated 2 (KNTC2), mRNA (GenBank accession number: NM_006101);

Raf1, Human mRNA for raf oncogene (GenBank accession number: X03484);

Aurora A, Homo sapiens aurora-related kinase 1 (ARK1) mRNA, complete cds (GenBank accession number: AF008551);

TACC3, Homo sapiens transforming, acidic coiled-coil containing protein 3 (TACC3), mRNA (GenBank accession number: NM_006342);

RelB, Homo sapiens v-rel reticuloendotheliosis viral oncogene homolog B, nuclear factor of kappa light polypeptide gene enhancer in B-cells 3 (avian) (RELB), mRNA (GenBank accession number: NM_006509);

PRKCD, Homo sapiens protein kinase C, delta (PRKCD), transcript variant 1, mRNA (GenBank accession number: NM_006254);

BRAF35, Homo sapiens high-mobility group 20B (HMG20B), mRNA (GenBank accession number: NM_006339);

HSPA1L, Homo sapiens heat shock 70kDa protein 1A (HSPA1A), mRNA (GenBank accession number: NM_005345);

STK11, Homo sapiens serine/threonine kinase 11 (Peutz-Jeghers syndrome) (STK11), mRNA (GenBank accession number: NM_000455); and

MKK3, Homo sapiens MAP kinase kinase 3 (MKK3) mRNA, complete cds (GenBank accession number: L36719);

c) measuring the level of one or more reference genetic markers selected from the group consisting of:

GAPDH, Homo sapiens glyceraldehyde-3-phosphate dehydrogenase (GAPD), mRNA (GenBank accession number: NM_002046); and

RPS9, Homo sapiens cDNA clone IMAGE:6647283, partial cds (GenBank accession number: BC071941);

d) comparing the measured levels of said one or more genetic markers and said one or more reference genetic markers in the test sample;

wherein a decrease in the level of said one or more genetic markers as compared to the level of said one or more reference genetic markers indicates an increased susceptibility to a molecule of the taxoid family.

22. The method of Claim 20 or 21 wherein said molecule of the taxoid family is selected from the group consisting of paclitaxel, docetaxel XRP9881 and XRP6258.

23. The method of Claim 20 or 21 wherein said level of one or more genetic markers is measured by mRNA, DNA or protein.

24. The method of Claim 23 wherein said mRNA is measured by using a technique selected from the group consisting of in situ hybridization, reverse-transcriptase polymerase chain reaction, nucleic acid hybridization, electrophoresis, Northern blotting and mass spectrometry.

25. The method of Claim 23 wherein said DNA is measured by using a technique selected from the group consisting of quantitative polymerase chain reaction, genomic DNA-chips, in situ hybridization, electrophoresis, Southern blotting and mass spectrometry.

26. The method of Claim 23 wherein said protein is measured by using a technique selected from the group consisting of immunoassay, Western blots, ELISA, and mass spectrometry.

27. A kit for predicting or monitoring a cancer patient's response to a molecule of the taxoid family according to the method of Claim 20 wherein the kit comprises detectable-labeled antibodies, detectable-labeled antibody fragments or detectable-labeled oligonucleotides comprising nucleic acids capable of hybridizing under stringent conditions to said one or more genetic markers and said one or more reference genetic markers selected from the group consisting of:

BubR1, Homo sapiens similar to protein kinase (BUBR1) mRNA, complete cds (GenBank accession number: AF046079);

Mad2, Homo sapiens mRNA for MAD2 protein (GenBank accession number: AJ000186);

Mps1, Homo sapiens TTK protein kinase (TTK), mRNA (GenBank accession number: NM_003318);

GEFT for Rac1/CDC42, Homo sapiens RAC/CDC42 exchange factor (GEFT), transcript variant 2, mRNA (GenBank accession number: NM_133483);

Bub1, Homo sapiens BUB1 budding uninhibited by benzimidazoles 1 homolog (yeast) (BUB1), mRNA (GenBank accession number: NM_004336);

hSepharase, Homo sapiens extra spindle poles like 1 (S. cerevisiae) (ESPL1), mRNA (GenBank accession number: NM_012291);

CamKIId, Homo sapiens calcium/calmodulin-dependent protein kinase (CaM kinase) II delta (CAMK2D), transcript variant 3, mRNA (GenBank accession number: NM_001221);

CDK6, Homo sapiens cyclin-dependent kinase 6 (CDK6), mRNA (GenBank accession number: NM_001259);

GRB2, Homo sapiens growth factor receptor-bound protein 2 (GRB2), transcript variant 1, mRNA (GenBank accession number: NM_002086);

GAPDH, Homo sapiens glyceraldehyde-3-phosphate dehydrogenase (GAPD), mRNA (GenBank accession number: NM_002046); and

RPS9, Homo sapiens cDNA clone IMAGE:6647283, partial cds (GenBank accession number: BC071941).

28. A kit for predicting or monitoring a cancer patient's response to a molecule of the taxoid family according to the method of Claim 21 wherein the kit comprises detectable-labeled antibodies, detectable-labeled antibody fragments or detectable-labeled oligonucleotides comprising nucleic acids capable of hybridizing under stringent conditions to said one or more genetic markers and said one or more genetic markers selected from the group consisting of:

P21(Waf1), Homo sapiens cyclin-dependent kinase inhibitor 1A (p21, Cip1) (CDKN1A), transcript variant 1, mRNA (GenBank accession number: NM_000389);

Pim-1, Homo sapiens pim-1 oncogene (PIM1), mRNA (GenBank accession number: NM_002648);

GBP-1, Homo sapiens guanylate binding protein 1, interferon-inducible, 67kDa (GBP1), mRNA (GenBank accession number: NM_002053);

RXRA, Homo sapiens retinoid X receptor, alpha (RXRA), mRNA (GenBank accession number: NM_002957);

SPF45, Homo sapiens RNA binding motif protein 17 (RBM17), mRNA (GenBank accession number: NM_032905);

Hec1, Homo sapiens kinetochore associated 2 (KNTC2), mRNA (GenBank accession number: NM_006101);

Raf1, Human mRNA for raf oncogene (GenBank accession number: X03484);

Aurora A, Homo sapiens aurora-related kinase 1 (ARK1) mRNA, complete cds (GenBank accession number: AF008551);

TACC3, Homo sapiens transforming, acidic coiled-coil containing protein 3 (TACC3), mRNA (GenBank accession number: NM_006342);

RelB, Homo sapiens v-rel reticuloendotheliosis viral oncogene homolog B, nuclear factor of kappa light polypeptide gene enhancer in B-cells 3 (avian) (RELB), mRNA (GenBank accession number: NM_006509);

PRKCD, Homo sapiens protein kinase C, delta (PRKCD), transcript variant 1, mRNA (GenBank accession number: NM_006254);

BRAF35, Homo sapiens high-mobility group 20B (HMG20B), mRNA (GenBank accession number: NM_006339);

HSPA1L, Homo sapiens heat shock 70kDa protein 1A (HSPA1A), mRNA (GenBank accession number: NM_005345);

STK11, Homo sapiens serine/threonine kinase 11 (Peutz-Jeghers syndrome) (STK11), mRNA (GenBank accession number: NM_000455); and

MKK3, Homo sapiens MAP kinase kinase 3 (MKK3) mRNA, complete cds (GenBank accession number: L36719);

GAPDH, Homo sapiens glyceraldehyde-3-phosphate dehydrogenase (GAPD), mRNA (GenBank accession number: NM_002046); and

RPS9, Homo sapiens cDNA clone IMAGE:6647283, partial cds (GenBank accession number: BC071941).

29. A kit for predicting or monitoring a cancer patient's response to a molecule of the taxoid family according to the method of Claim 20 wherein the kit comprises the means of:

a) obtaining total RNA from a bodily sample;

b) reverse transcribing the total RNA to obtain cDNA; and

c) subjecting the cDNA to a polymerase chain reaction using a set of primers wherein one or both primers are detectable-labeled and both primers are derived from a nucleotide sequence of one or more genetic markers selected from the group consisting of:

BubR1, Homo sapiens similar to protein kinase (BUBR1) mRNA, complete cds (GenBank accession number: AF046079);

Mad2, Homo sapiens mRNA for MAD2 protein (GenBank accession number: AJ000186);

Mps1, Homo sapiens TTK protein kinase (TTK), mRNA (GenBank accession number: NM_003318);

GEFT for Rac1/CDC42, Homo sapiens RAC/CDC42 exchange factor (GEFT), transcript variant 2, mRNA (GenBank accession number: NM_133483);

Bub1, Homo sapiens BUB1 budding uninhibited by benzimidazoles 1 homolog (yeast) (BUB1), mRNA (GenBank accession number: NM_004336);

hSepharase, Homo sapiens extra spindle poles like 1 (S. cerevisiae) (ESPL1), mRNA (GenBank accession number: NM_012291);

CamKIId, Homo sapiens calcium/calmodulin-dependent protein kinase (CaM kinase) II delta (CAMK2D), transcript variant 3, mRNA (GenBank accession number: NM_001221);

CDK6, Homo sapiens cyclin-dependent kinase 6 (CDK6), mRNA (GenBank accession number: NM_001259); and

GRB2, Homo sapiens growth factor receptor-bound protein 2 (GRB2), transcript variant 1, mRNA (GenBank accession number: NM_002086);

GAPDH, Homo sapiens glyceraldehyde-3-phosphate dehydrogenase (GAPD), mRNA (GenBank accession number: NM_002046); and

RPS9, Homo sapiens cDNA clone IMAGE:6647283, partial cds (GenBank accession number: BC071941).

30. A kit for predicting or monitoring a cancer patient's response to a molecule of the taxoid family according to the method of claim 19 wherein the kit comprises the means of:

a) obtaining total RNA from a bodily sample;

b) reverse transcribing the total RNA to obtain cDNA; and

c) subjecting the cDNA to a polymerase chain reaction using a set of primers wherein one or both primers are detectable-labeled and both primers are derived from a nucleotide sequence of one or more genetic markers selected from the group consisting of:

P21(Waf1), Homo sapiens cyclin-dependent kinase inhibitor 1A (p21, Cip1) (CDKN1A), transcript variant 1, mRNA (GenBank accession number: NM_000389);

Pim-1, Homo sapiens pim-1 oncogene (PIM1), mRNA (GenBank accession number: NM_002648);

GBP-1, Homo sapiens guanylate binding protein 1, interferon-inducible, 67kDa (GBP1), mRNA (GenBank accession number: NM_002053);

RXRA, Homo sapiens retinoid X receptor, alpha (RXRA), mRNA (GenBank accession number: NM_002957);

SPF45, Homo sapiens RNA binding motif protein 17 (RBM17), mRNA (GenBank accession number: NM_032905);

Hec1, Homo sapiens kinetochore associated 2 (KNTC2), mRNA (GenBank accession number: NM_006101);

Raf1, Human mRNA for raf oncogene (GenBank accession number: X03484);

Aurora A, Homo sapiens aurora-related kinase 1 (ARK1) mRNA, complete cds (GenBank accession number: AF008551);

TACC3, Homo sapiens transforming, acidic coiled-coil containing protein 3 (TACC3), mRNA (GenBank accession number: NM_006342);

RelB, Homo sapiens v-rel reticuloendotheliosis viral oncogene homolog B, nuclear factor of kappa light polypeptide gene enhancer in B-cells 3 (avian) (RELB), mRNA (GenBank accession number: NM_006509);

PRKCD, Homo sapiens protein kinase C, delta (PRKCD), transcript variant 1, mRNA (GenBank accession number: NM_006254);

BRAF35, Homo sapiens high-mobility group 20B (HMG20B), mRNA (GenBank accession number: NM_006339);

HSPA1L, Homo sapiens heat shock 70kDa protein 1A (HSPA1A), mRNA (GenBank accession number: NM_005345);

STK11, Homo sapiens serine/threonine kinase 11 (Peutz-Jeghers syndrome) (STK11), mRNA (GenBank accession number: NM_000455); and

MKK3, Homo sapiens MAP kinase kinase 3 (MKK3) mRNA, complete cds (GenBank accession number: L36719);

GAPDH, Homo sapiens glyceraldehyde-3-phosphate dehydrogenase (GAPD), mRNA (GenBank accession number: NM_002046); and

RPS9, Homo sapiens cDNA clone IMAGE:6647283, partial cds (GenBank accession number: BC071941).

31. The detectable label of any one of claims 24 – 27, wherein the detectable label comprises an enzyme, a radioactive isotope, or a chemical which fluoresces, a chemiluminescent molecule, radiopaque substances, liposomes, and haptenic molecules.

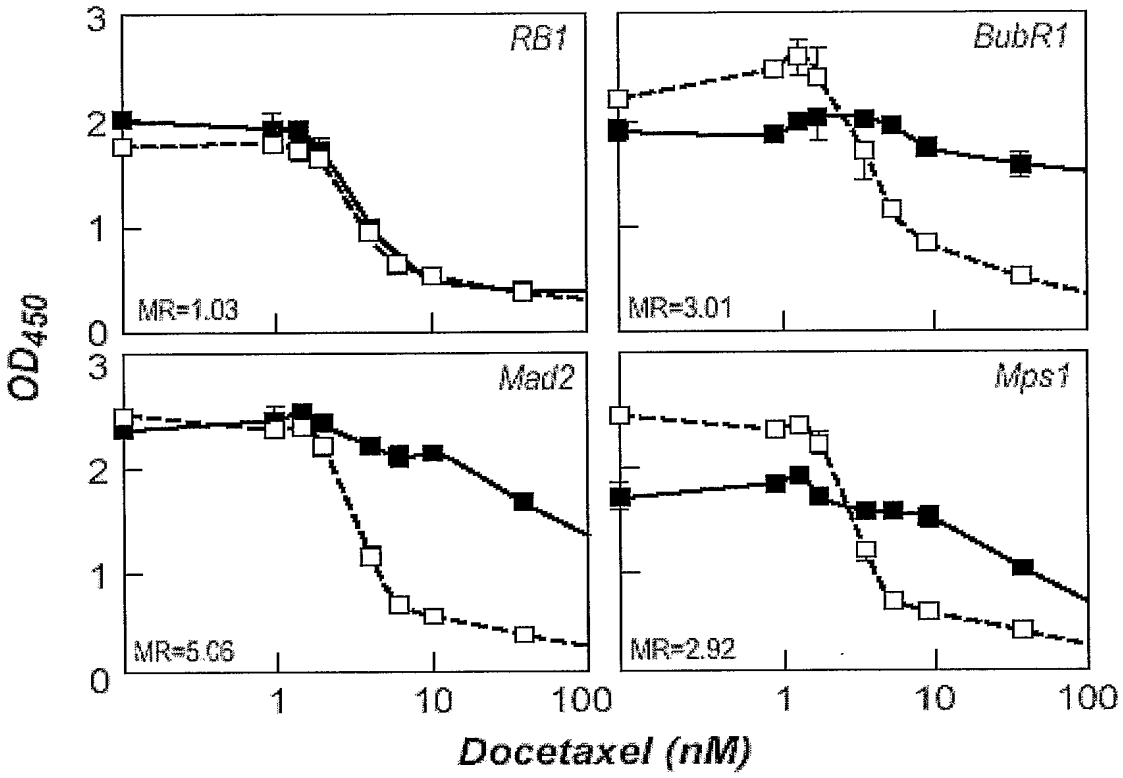

RB1
BubR1
Mad2
Mps1
MR=1.03
MR=3.01
MR=5.06
MR=2.92
OD450
Docetaxel (nM)
0
1
2
3
1
10
100

Figure 1

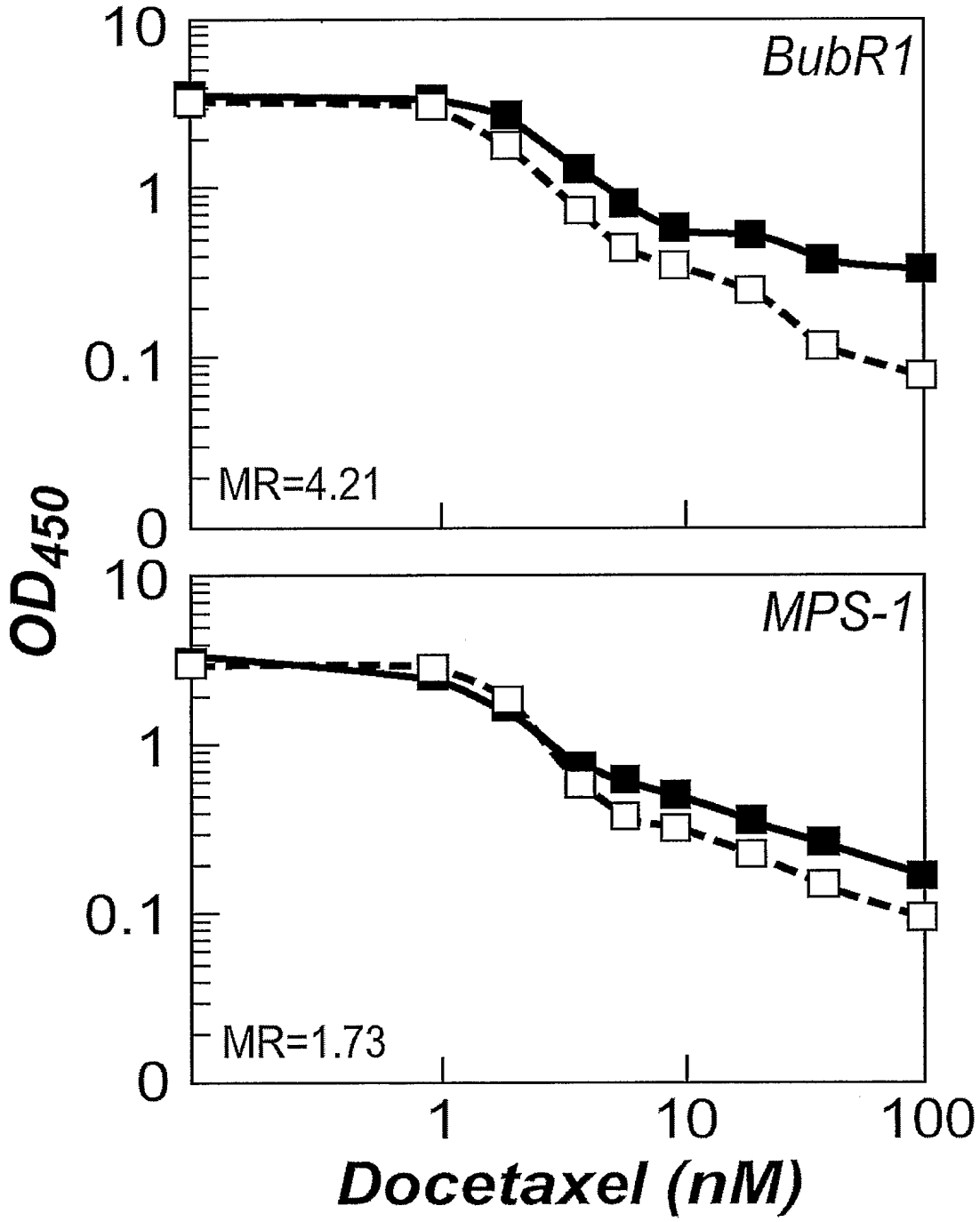


Figure 2

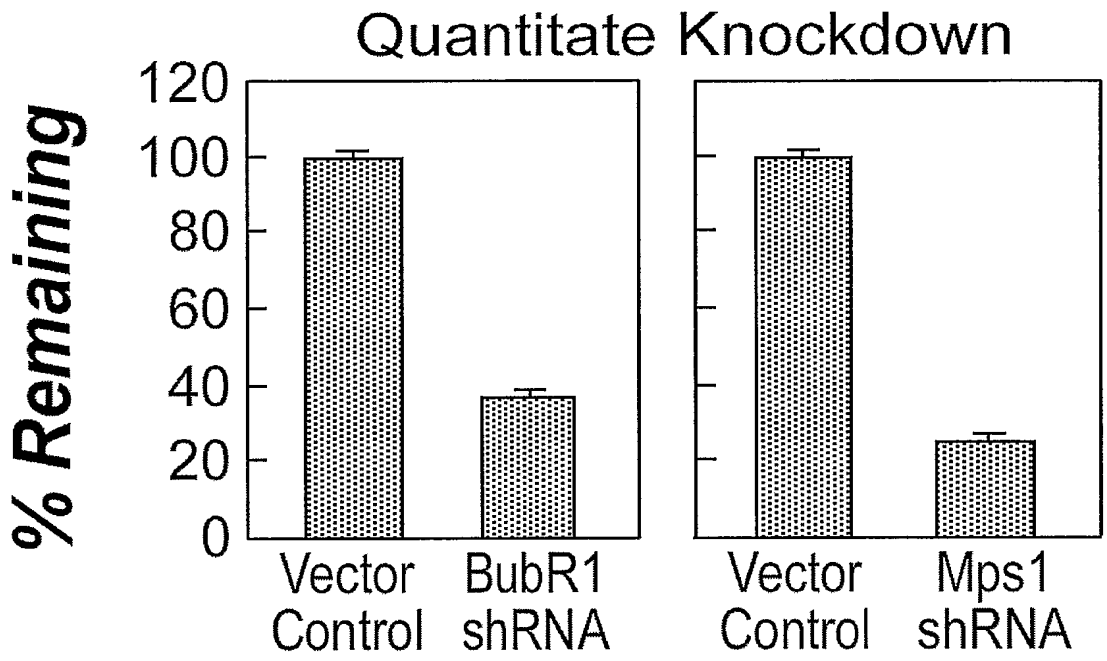

Quantitate Knockdown
% Remaining
120
100
80
60
40
20
0
Vector Control
BubR1 shRNA
Vector Control
Mps1 shRNA

Figure 3

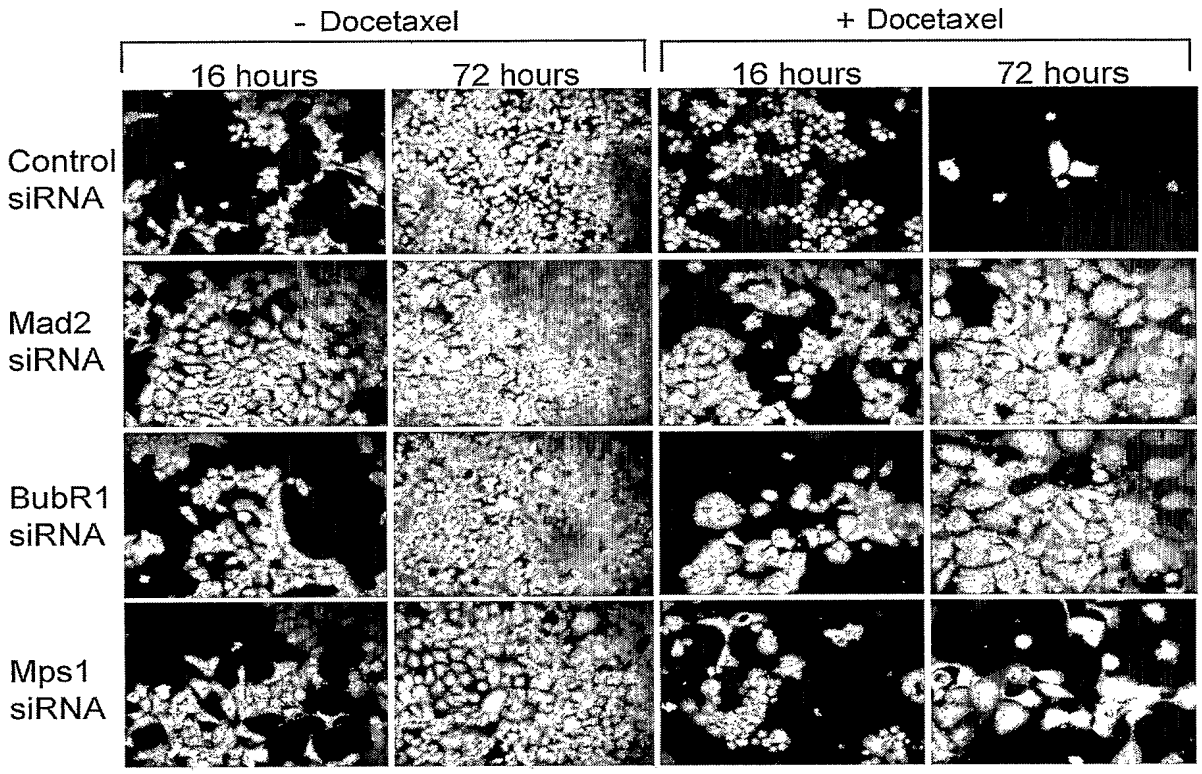

- Docetaxel
+ Docetaxel
16 hours
72 hours
16 hours
72 hours
Control siRNA
Mad2 siRNA
BubR1 siRNA
Mps1 siRNA

Figure 4

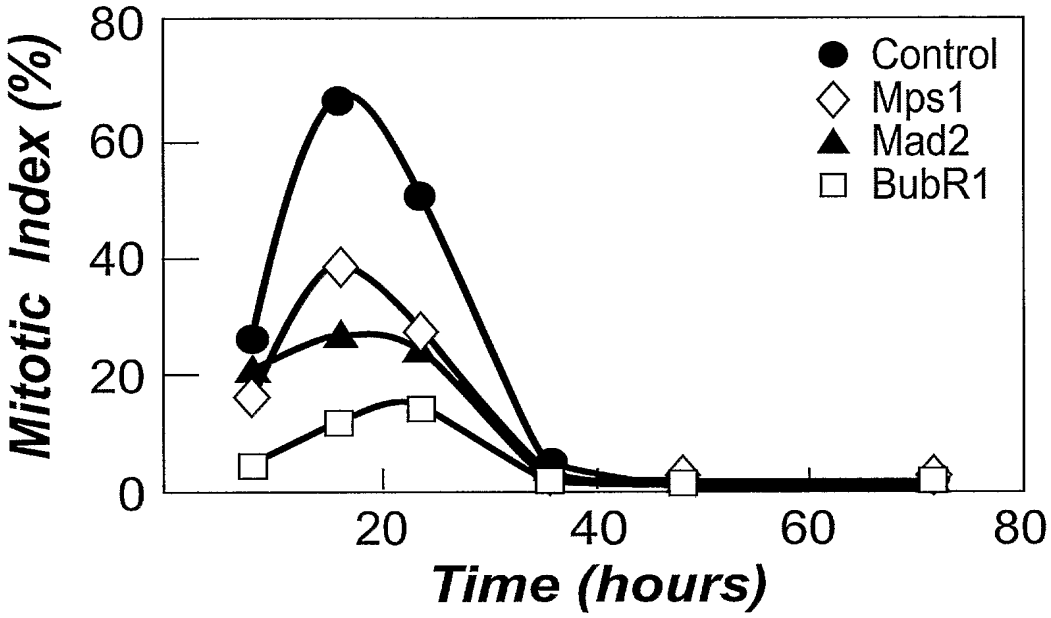

Mitotic Index (%)
80
60
40
20
0
20
40
60
80
Time (hours)
Control
Mps1
Mad2
BubR1

Figure 5

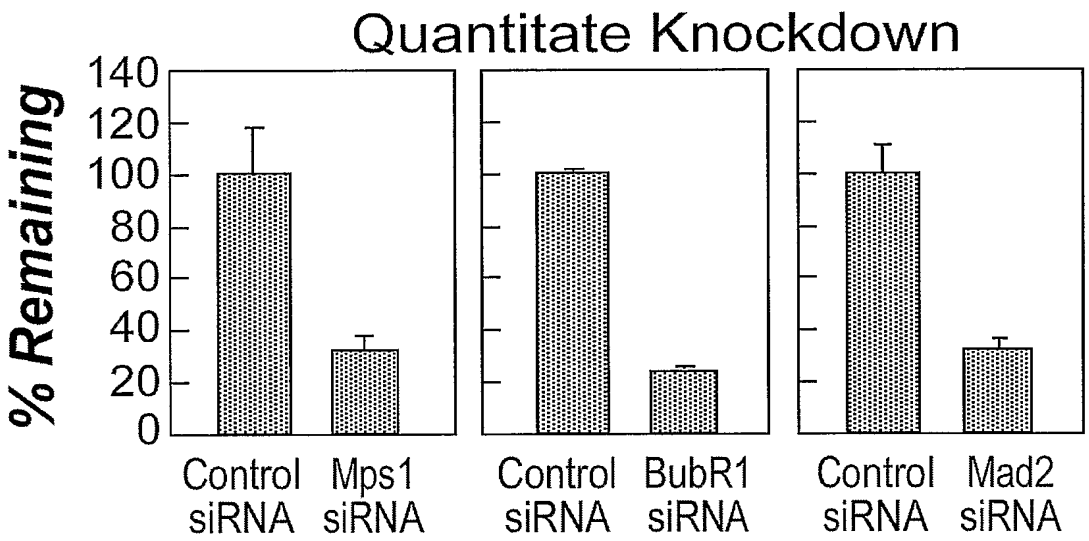

Quantitate Knockdown
% Remaining
140
120
100
80
60
40
20
0
Control siRNA
Mps1 siRNA
Control siRNA
BubR1 siRNA
Control siRNA
Mad2 siRNA

Figure 6

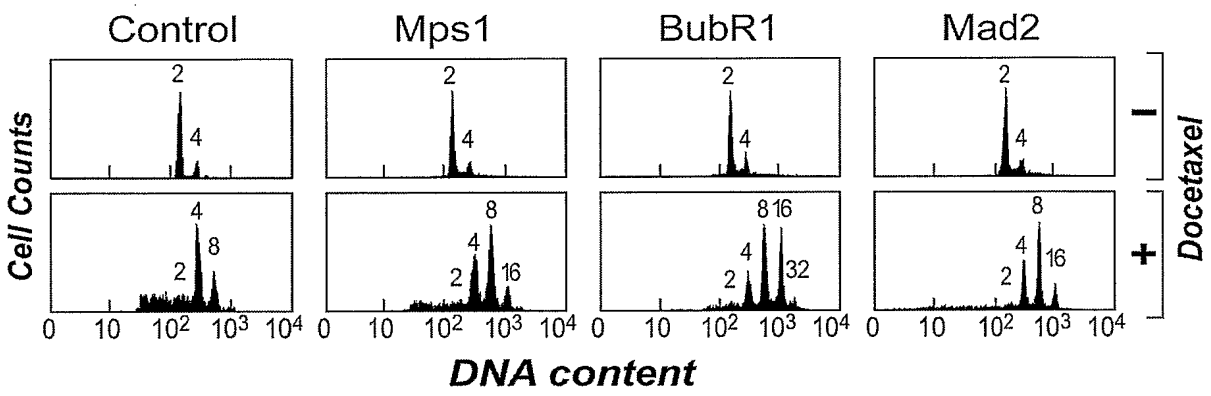

Control
Mps1
BubR1
Mad2
Cell Counts
DNA content
Docetaxel
-
+
0
10
10^2
10^3
10^4
2
4
8
16
32

Figure 7

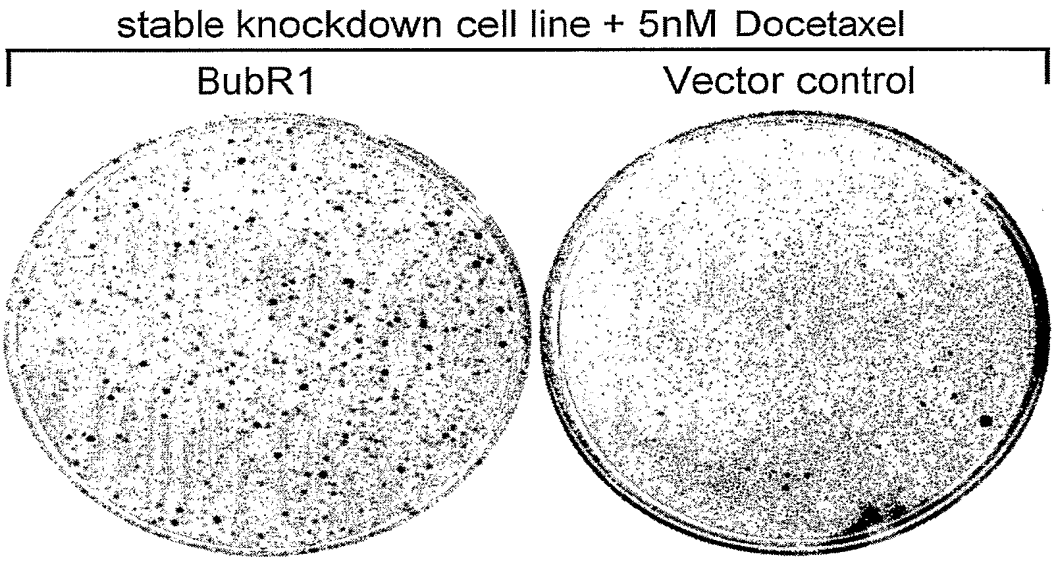

stable knockdown cell line + 5nM Docetaxel
BubR1
Vector control

Figure 8

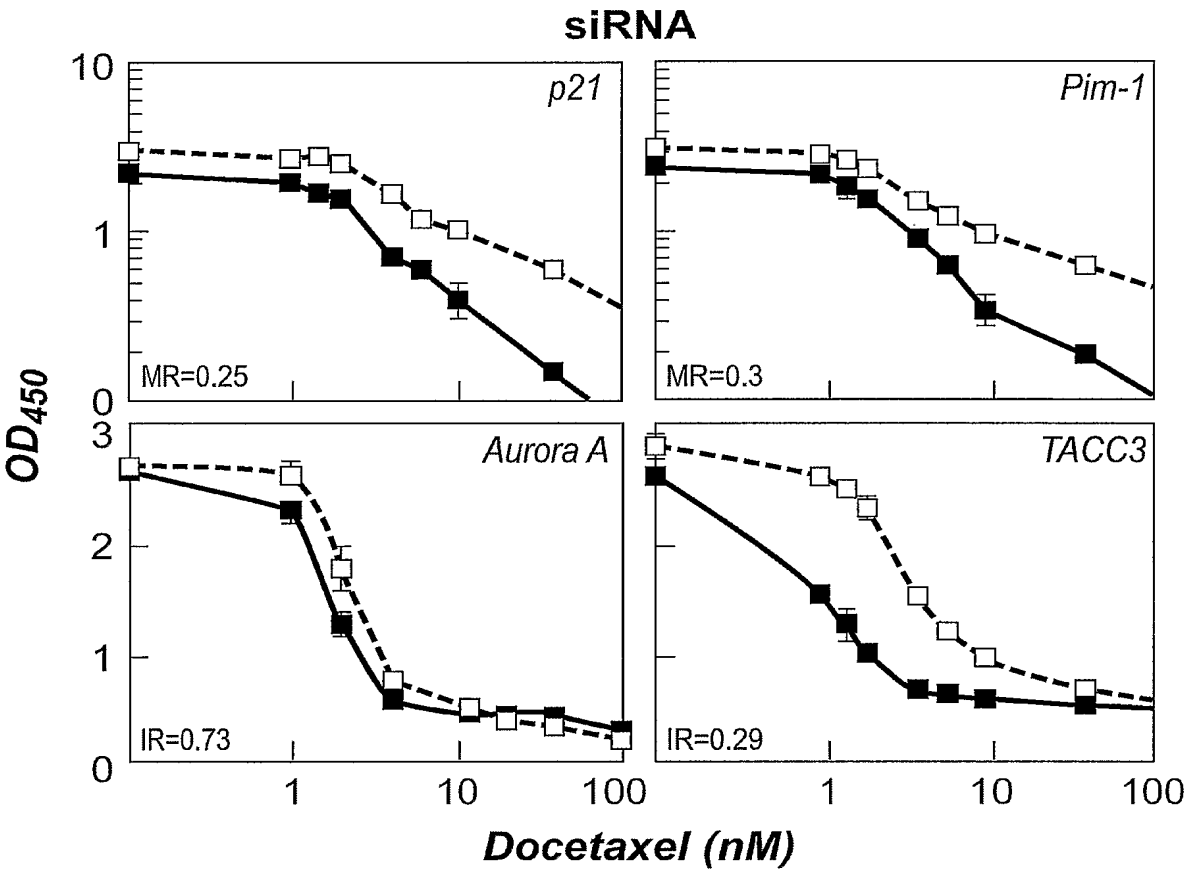

siRNA
p21
Pim-1
MR=0.25
MR=0.3
Aurora A
TACC3
IR=0.73
IR=0.29
OD450
Docetaxel (nM)
10
1
0
3
2
1
0
1
10
100

Figure 9

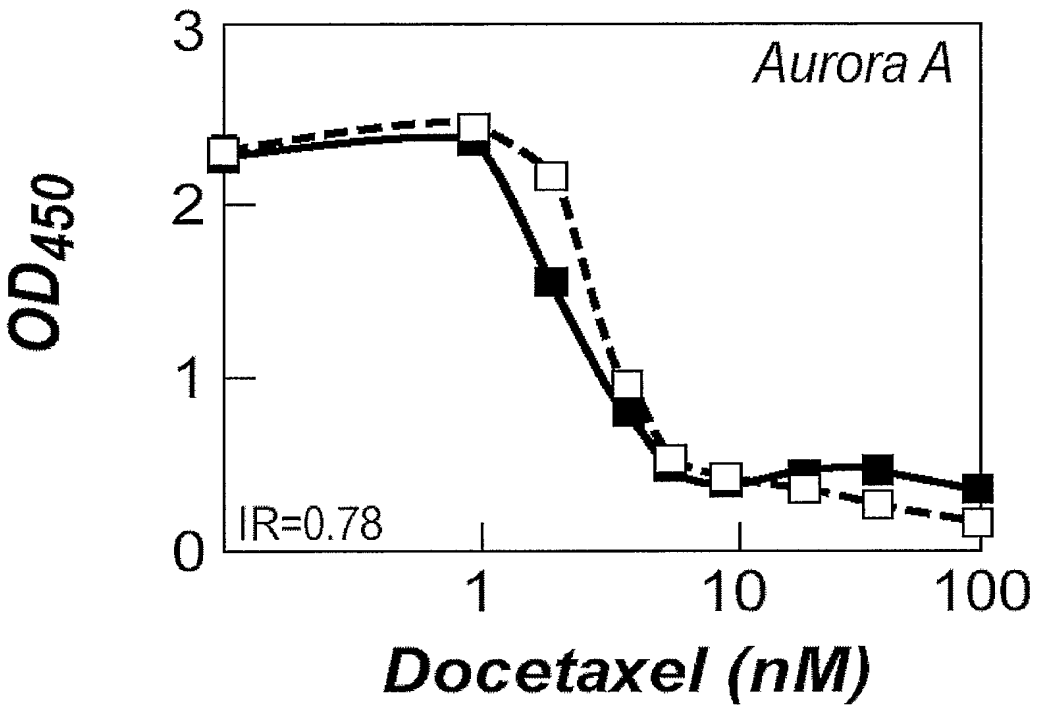


Figure 10

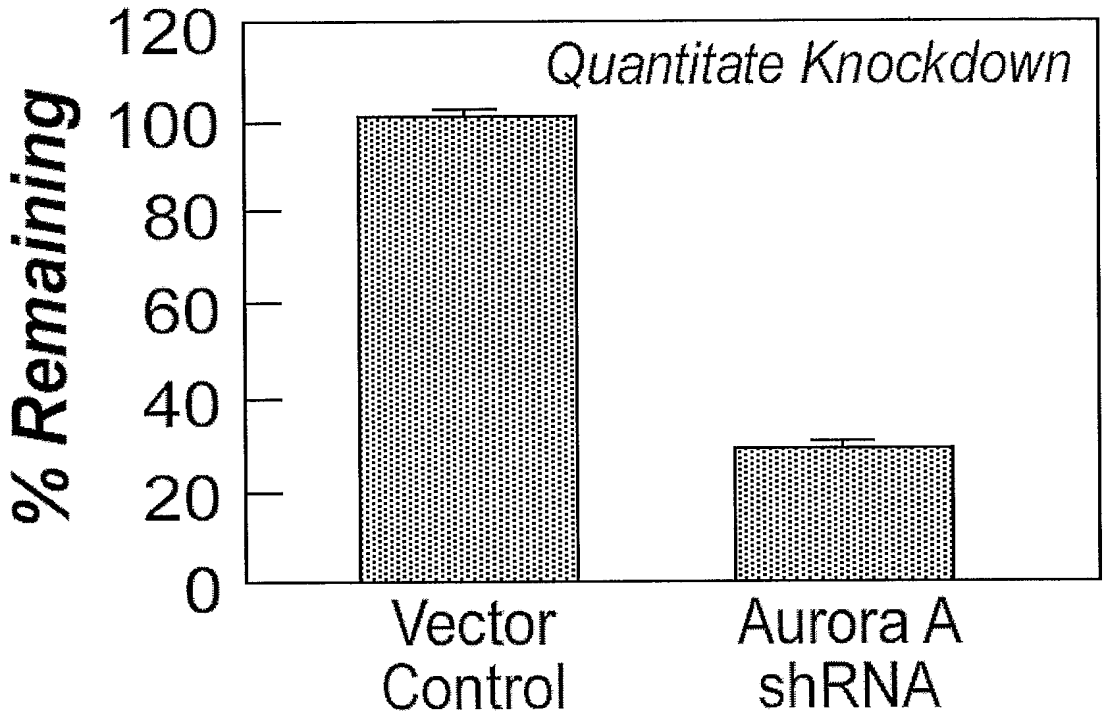

Quantitate Knockdown
% Remaining
120
100
80
60
40
20
0
Vector Control
Aurora A shRNA

Figure 11

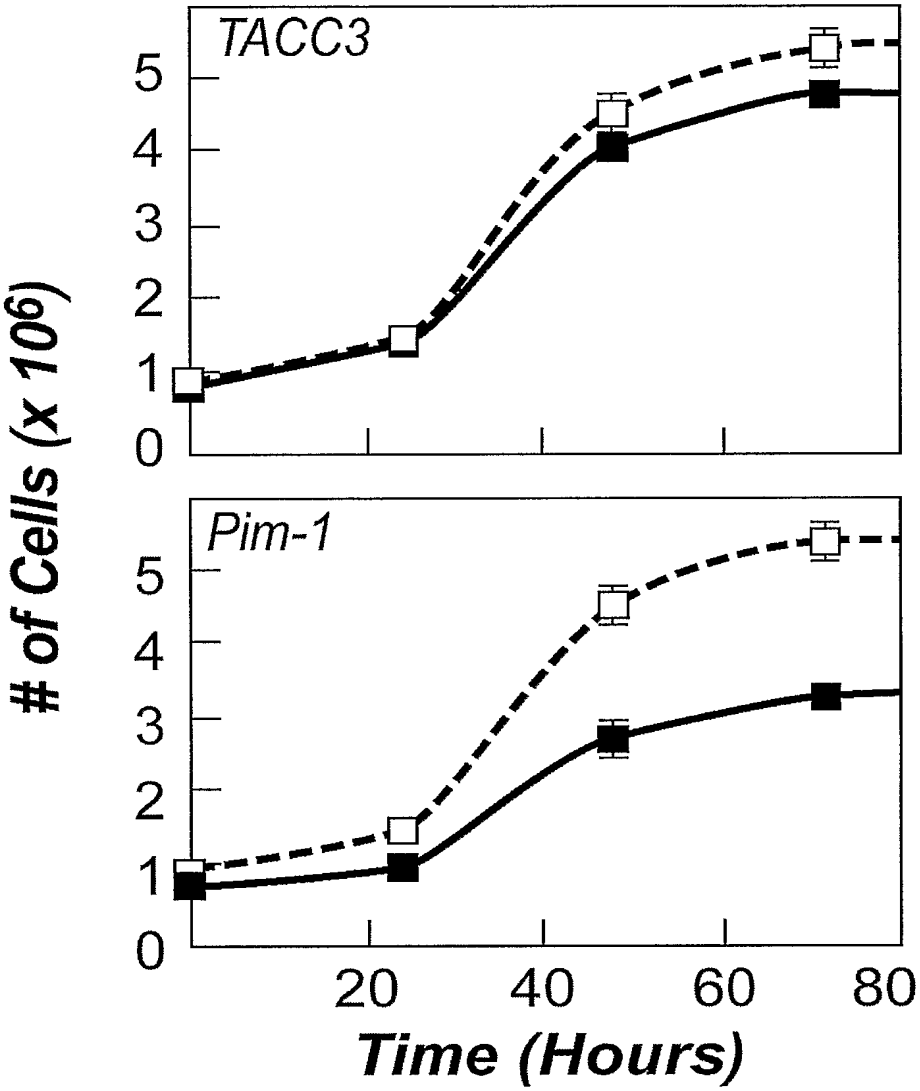


Figure 12

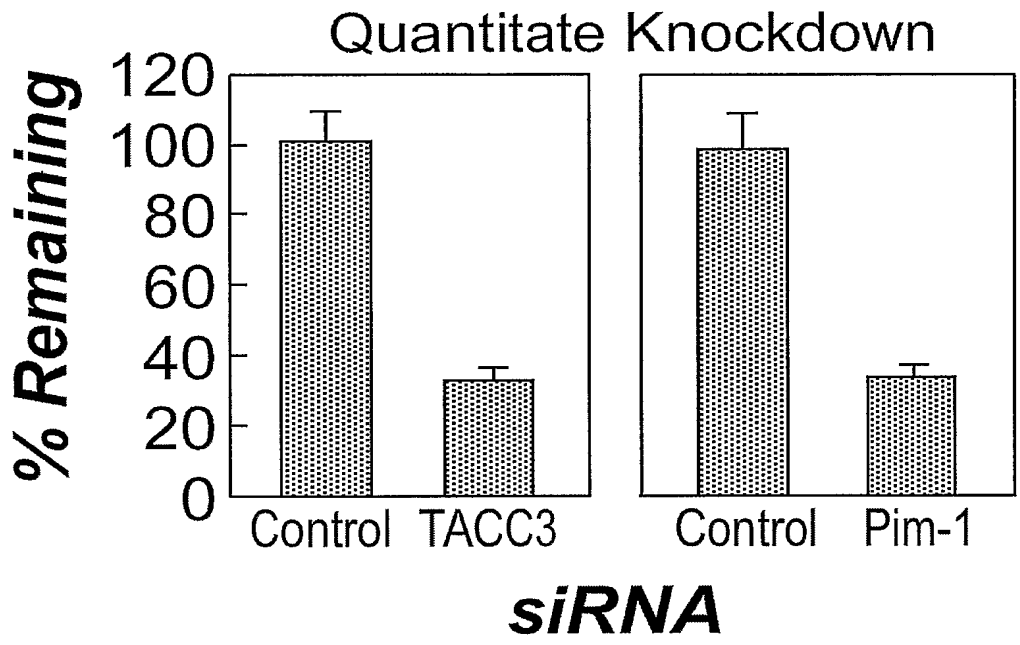

Quantitate Knockdown
% Remaining
120
100
80
60
40
20
0
Control
TACC3
Control
Pim-1
siRNA

Figure 13

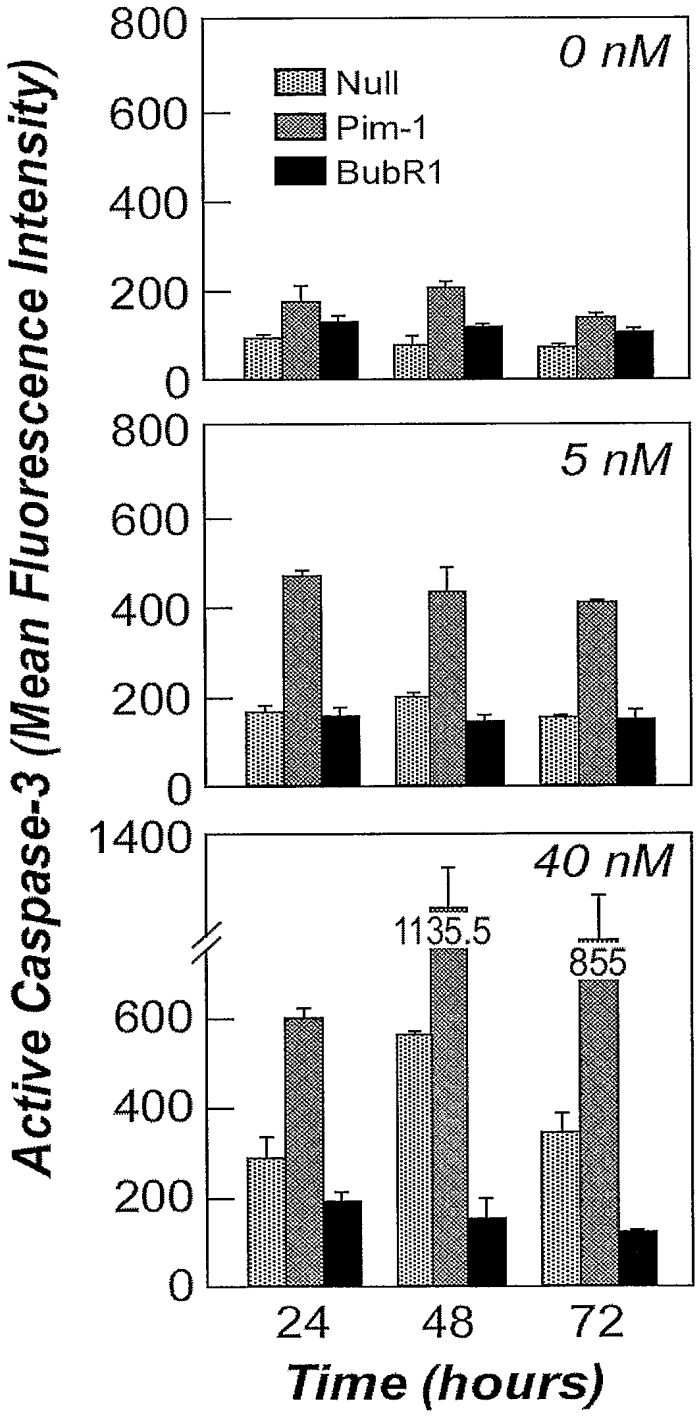

Active Caspase-3 (Mean Fluorescence Intensity)
0 nM
Null
Pim-1
BubR1
800
600
400
200
0
5 nM
800
600
400
200
0
40 nM
1400
1135.5
855
600
400
200
0
24
48
72
Time (hours)

Figure 14

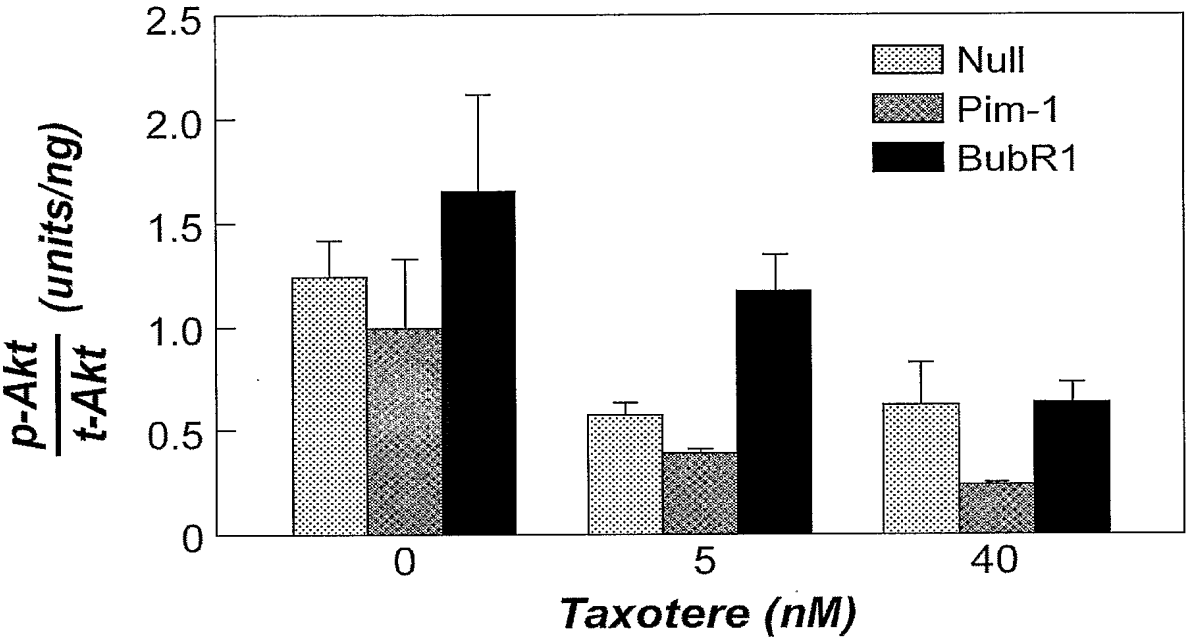

2.5
2.0
1.5
1.0
0.5
0
p-Akt / t-Akt (units/ng)
Null
Pim-1
BubR1
0
5
40
Taxotere (nM)

Figure 15

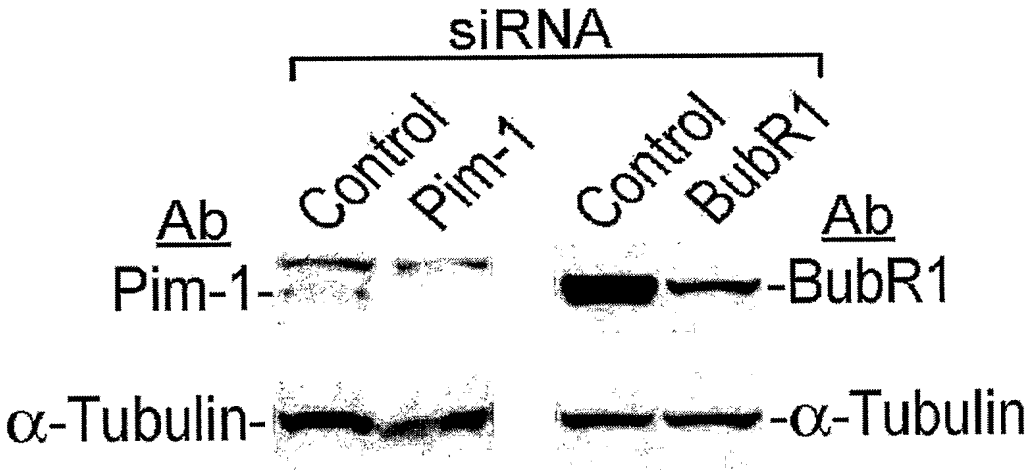

siRNA
Control
Pim-1
Control
BubR1
Ab
Ab
Pim-1-
-BubR1
α-Tubulin-
-α-Tubulin

Figure 16

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 October 2010 (14.10.2010)

PCT

(10) International Publication Number
WO 2010/117668 A1

(51) International Patent Classification:
A61K 9/00 (2006.01)

(21) International Application Number:
PCT/US2010/028770

(22) International Filing Date:
26 March 2010 (26.03.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/164,734	30 March 2009 (30.03.2009)	US
61/164,722	30 March 2009 (30.03.2009)	US
61/164,720	30 March 2009 (30.03.2009)	US
61/164,725	30 March 2009 (30.03.2009)	US
61/164,728	30 March 2009 (30.03.2009)	US
61/164,731	30 March 2009 (30.03.2009)	US
61/262,993	20 November 2009 (20.11.2009)	US
61/262,994	20 November 2009 (20.11.2009)	US

(71) Applicant *(for all designated States except US)*: **CERULEAN PHARMA INC.** [US/US]; 840 Memorial Drive, 5th Floor, Cambridge, MA 02139 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ELIASOF, Scott** [US/US]; 35 Brandon St., Lexington, MA 02420 (US). **CRAWFORD, Thomas, C.** [US/US]; 13 Clark Ln., Essex, CT 06426 (US). **GANGEL, Geeti** [IN/US]; 118 Sherman St., Cambridge, MA 02140 (US). **REITER, Lawrence, Alan** [US/US]; 32 W. Mystic Ave., Mystic, CT 06355 (US). **NG, Pei-Sze** [SG/US]; 21 Wendell St. #17, Cambridge, MA 02138 (US).

(74) Agent: **LAWRENCE, Laurie, Butler**; Lando & Anastasi, LLP, One Main Street, Eleventh Floor, Cambridge, MA 02142 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2010/117668 A1

(54) Title: POLYMER-AGENT CONJUGATES, PARTICLES, COMPOSITIONS, AND RELATED METHODS OF USE

(57) Abstract: Described herein are polymer-agent conjugates and particles, which can be used, for example, in the treatment of cancer. Also described herein are mixtures, compositions and dosage forms containing the particles, methods of using the particles (e.g., to treat a disorder), kits including the polymer-agent conjugates and particles, methods of making the polymer- agent conjugates and particles, methods of storing the particles and methods of analyzing the particles.

T2021-7000WO

POLYMER-AGENT CONJUGATES, PARTICLES, COMPOSITIONS, AND RELATED METHODS OF USE

RELATED APPLICATIONS

This application claims priority to U.S.S.N. 61/164,720, filed March 30, 2009; U.S.S.N. 61/164,722, filed March 30, 2009; U.S.S.N. 61/164,725, filed March 30, 2009; U.S.S.N. 61/164,728, filed March 30, 2009; U.S.S.N. 61/164,731, filed March 30, 2009; U.S.S.N. 61/164,734, filed March 30, 2009; U.S.S.N. 61/262,993, filed November 20, 2009; and U.S.S.N. 61/262,994, filed November 20, 2009. The disclosures of the prior applications are considered part of (and are incorporated by reference in) the disclosure of this application.

BACKGROUND OF INVENTION

The delivery of a drug with controlled release of the active agent is desirable to provide optimal use and effectiveness. Controlled release polymer systems may increase the efficacy of the drug and minimize problems with patient compliance.

SUMMARY OF INVENTION

Described herein are polymer-agent conjugates and particles, which can be used, for example, in the treatment of cancer, cardiovascular diseases, inflammatory disorders (e.g., an inflammatory disorder that includes an inflammatory disorder caused by, e.g., an infectious disease) or autoimmune disorders. Also described herein are mixtures, compositions and dosage forms containing the particles, methods of using the particles (e.g., to treat a disorder), kits including the polymer-agent conjugates and particles, methods of making the polymer-agent conjugates and particles, methods of storing the particles and methods of analyzing the particles.

Accordingly, in one aspect, the invention features a polymer-agent conjugate comprising:

a polymer; and

an agent (e.g., a therapeutic or diagnostic agent) attached to the polymer.

In some embodiments, the polymer is a biodegradable polymer (e.g., polylactic acid (PLA), polyglycolic acid (PGA), poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), polydioxanone (PDO), polyanhydrides, polyorthoesters, or chitosan). In some embodiments, the polymer is a hydrophobic polymer. In some embodiments, the polymer is PLA. In some embodiments, the polymer is PGA.

In some embodiments, the polymer is a copolymer of lactic and glycolic acid (e.g., PLGA). In some embodiments, the polymer is a PLGA-ester. In some embodiments, the polymer is a PLGA-lauryl ester. In some embodiments, the polymer comprises a terminal free acid prior to conjugation to an agent. In some embodiments, the polymer comprises a terminal acyl group (e.g., an acetyl group). In some embodiments, the polymer comprises a terminal hydroxyl group. In some embodiments, the ratio of lactic acid monomers to glycolic acid monomers in PLGA is from about 0.1:99.9 to about 99.9:0.1. In some embodiments, the ratio of lactic acid monomers to glycolic acid monomers in PLGA is from about 75:25 to about 25:75, e.g., about 60:40 to about 40:60 (e.g., about 50:50), about 60:40, or about 75:25.

In some embodiments, the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 1 kDa to about 15 kDa, from about 2 kDa to about 12 kDa, from about 6 kDa to about 20 kDa, from about 5 kDa to about 15 kDa, from about 7 kDa to about 11 kDa, from about 5 kDa to about 10 kDa, from about 7 kDa to about 10 kDa, from about 5 kDa to about 7 kDa, from about 6 kDa to about 8 kDa, about 6 kDa, about 7 kDa, about 8 kDa, about 9 kDa, about 10 kDa, about 11 kDa, about 12 kDa, about 13 kDa, about 14 kDa, about 15 kDa, about 16 kDa or about 17 kDa). In some embodiments, the polymer has a glass transition temperature of about 20 °C to about 60 °C. In some embodiments, the polymer has a polymer polydispersity index of less than or equal to about 2.5 (e.g., less than or equal to about 2.2, or less than or equal to about 2.0). In some embodiments, the polymer has a polymer polydispersity index of about 1.0 to about 2.5, e.g., from about 1.0 to about 2.0, from about 1.0 to about 1.8, from about 1.0 to about 1.7, or from about 1.0 to about 1.6.

In some embodiments, the polymer has a hydrophilic portion and a hydrophobic portion. In some embodiments, the polymer is a block copolymer. In some embodiments, the polymer comprises two regions, the two regions together being at least about 70% by weight of the polymer (e.g., at least about 80%, at least about 90%, at least about 95%). In some embodiments, the polymer is a block copolymer comprising a hydrophobic polymer and a hydrophilic polymer. In some embodiments, the polymer, e.g., a diblock copolymer, comprises a hydrophobic polymer and a hydrophilic polymer. In some embodiments, the polymer, e.g., a triblock copolymer, comprises a hydrophobic polymer, a hydrophilic polymer and a hydrophobic polymer, e.g., PLA-PEG-PLA, PGA-PEG-PGA, PLGA-PEG-PLGA, PCL-PEG-PCL, PDO-PEG-PDO, PEG-PLGA-PEG, PLA-PEG-PGA, PGA-PEG-PLA, PLGA-PEG-PLA or PGA-PEG-PLGA.

In some embodiments, the hydrophobic portion of the polymer is a biodegradable polymer (e.g., PLA, PGA, PLGA, PCL, PDO, polyanhydrides, polyorthoesters, or chitosan). In some embodiments, the hydrophobic portion of the polymer is PLA. In some embodiments, the hydrophobic portion of the polymer is PGA. In some embodiments, the hydrophobic portion of the polymer is a copolymer of lactic and glycolic acid (e.g., PLGA). In some embodiments, the hydrophobic portion of the polymer has a weight average molecular weight of from about 1 kDa to about 20 kDa (e.g., from about 1 kDa to about 18 kDa, 17 kDa, 16 kDa, 15 kDa, 14 kDa or 13 kDa, from about 2 kDa to about 12 kDa, from about 6 kDa to about 20 kDa, from about 5 kDa to about 18 kDa, from about 7 kDa to about 17 kDa, from about 8 kDa to about 13 kDa, from about 9 kDa to about 11 kDa, from about 10 kDa to about 14 kDa, from about 6 kDa to about 8 kDa, about 6 kDa, about 7 kDa, about 8 kDa, about 9 kDa, about 10 kDa, about 11 kDa, about 12 kDa, about 13 kDa, about 14 kDa, about 15 kDa, about 16 kDa or about 17 kDa).

In some embodiments, the hydrophilic portion of the polymer is polyethylene glycol (PEG). In some embodiments, the hydrophilic portion of the polymer has a weight average molecular weight of from about 1 kDa to about 21 kDa (e.g., from about 1 kDa to about 3 kDa, e.g., about 2 kDa, or from about 2 kDa to about 5 kDa, e.g., about 3.5 kDa, or from about 4 kDa to about 6 kDa, e.g., about 5 kDa). In some

embodiments, the ratio of the weight average molecular weights of the hydrophilic to hydrophobic portions of the polymer is from about 1:1 to about 1:20 (e.g., about 1:4 to about 1:10, about 1:4 to about 1:7, about 1:3 to about 1:7, about 1:3 to about 1:6, about 1:4 to about 1:6.5 (e.g., 1:4, 1:4.5, 1:5, 1:5.5, 1:6, 1:6.5) or about 1:1 to about 1:4 (e.g., about 1:1.4, 1:1.8, 1:2, 1:2.4, 1:2.8, 1:3, 1:3.2, 1:3.5 or 1:4). In one embodiment, the hydrophilic portion of the polymer has a weight average molecular weight of from about 2 kDa to 3.5 kDa and the ratio of the weight average molecular weight of the hydrophilic to hydrophobic portions of the polymer is from about 1:4 to about 1:6.5 (e.g., 1:4, 1:4.5, 1:5, 1:5.5, 1:6, 1:6.5). In one embodiment, the hydrophilic portion of the polymer has a weight average molecular weight of from about 4 kDa to 6 kDa (e.g., 5 kDa) and the ratio of the weight average molecular weight of the hydrophilic to hydrophobic portions of the polymer is from about 1:1 to about 1:3.5 (e.g., about 1:1.4, 1:1.8, 1:2, 1:2.4, 1:2.8, 1:3, 1:3.2, or 1:3.5).

In some embodiments, the hydrophilic portion of the polymer has a terminal hydroxyl moiety prior to conjugation to an agent. In some embodiments, the hydrophilic portion of has a terminal alkoxy moiety. In some embodiments, the hydrophilic portion of the polymer is a methoxy PEG (e.g., a terminal methoxy PEG). In some embodiments, the hydrophilic polymer portion of the polymer does not have a terminal alkoxy moiety. In some embodiments, the terminus of the hydrophilic polymer portion of the polymer is conjugated to a hydrophobic polymer, e.g., to make a triblock copolymer.

In some embodiments, the hydrophilic portion of the polymer is attached to the hydrophobic portion through a covalent bond. In some embodiments, the hydrophilic polymer is attached to the hydrophobic polymer through an amide, ester, ether, amino, carbamate, or carbonate bond (e.g., an ester or an amide).

In some embodiments, a single agent is attached to a single polymer, e.g., to a terminal end of the polymer. In some embodiments, a plurality of agents are attached to a single polymer (e.g., 2, 3, 4, 5, 6, or more). In some embodiments, the agents are the same agent. In some embodiments, the agents are different agents. In some embodiments, the agent is a diagnostic agent.

In some embodiments, the agent is a therapeutic agent. In some embodiments, the therapeutic agent is an anti-inflammatory agent. In some embodiments, the therapeutic agent is an anti-cancer agent. In some embodiments, the anti-cancer agent is an alkylating agent, a vascular disrupting agent, a microtubule targeting agent, a mitotic inhibitor, a topoisomerase inhibitor, an anti-angiogenic agent or an anti-metabolite. In some embodiments, the anti-cancer agent is a taxane (e.g., paclitaxel, docetaxel, larotaxel or cabazitaxel). In some embodiments, the anti-cancer agent is an anthracycline (e.g., doxorubicin). In some embodiments, the anti-cancer agent is a platinum-based agent (e.g., cisplatin). In some embodiments, the anti-cancer agent is a pyrimidine analog (e.g., gemcitabine).

In some embodiments, the anti-cancer agent is paclitaxel, attached to the polymer via the hydroxyl group at the 2' position, the hydroxyl group at the 1 position and/or the hydroxyl group at the 7 position. In some embodiments, the anti-cancer agent is paclitaxel, attached to the polymer via the 2' position and/or the 7 position.

In some embodiments, the anti-cancer agent is docetaxel, attached to the polymer via the hydroxyl group at the 2' position, the hydroxyl group at the 7 position, the hydroxyl group at the 10 position and/or the hydroxyl group at the 1 position. In some embodiments, the anti-cancer agent is docetaxel, attached to the polymer via the hydroxyl group at the 2' position, the hydroxyl group at the 7 position and/or the hydroxyl group at the 10 position.

In some embodiments, the anti-cancer agent is docetaxel-succinate.

In some embodiments, the anti-cancer agent is a taxane that is attached to the polymer via the hydroxyl group at the 7 position and has an acyl group or a hydroxy protecting group on the hydroxyl group at the 2' position (e.g., wherein the anti-cancer agent is a taxane such as paclitaxel, docetaxel, larotaxel or cabazitaxel). In some embodiments, the anti-cancer agent is larotaxel. In some embodiments, the anti-cancer agent is cabazitaxel.

In some embodiments, the anti-cancer agent is doxorubicin.

In some embodiments, the therapeutic agent is an agent for the treatment or prevention of cardiovascular disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the treatment of cardiovascular

disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the prevention of cardiovascular disease, for example as described herein.

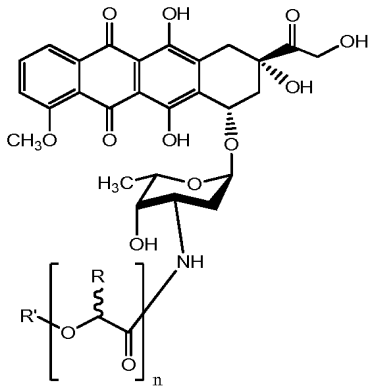
In some embodiments, the therapeutic agent is an agent for the treatment or prevention of an inflammatory or autoimmune disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the treatment of an inflammatory or autoimmune disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the prevention of an inflammatory or autoimmune disease, for example as described herein.

In some embodiments, the agent is attached directly to the polymer, e.g., through a covalent bond. In some embodiments, the agent is attached to a terminal end of the polymer via an amide, ester, ether, amino, carbamate or carbonate bond. In some embodiments, the agent is attached to a terminal end of the polymer. In some embodiments, the polymer comprises one or more side chains and the agent is directly attached to the polymer through one or more of the side chains.

In some embodiments, a single agent is attached to a polymer. In some embodiments, multiple agents are attached to a polymer (e.g., 2, 3, 4, 5, 6 or more agents). In some embodiments, the agents are the same agent. In some embodiments, the agents are different agents.

In some embodiments, the agent is doxorubicin, and is covalently attached to the polymer through an amide bond.

In some embodiments, the polymer-agent conjugate is:

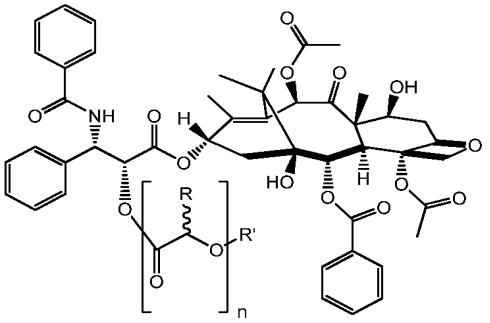


,

wherein about 30% to about 70%, 35% to about 65%, 40% to about 60%, 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, 35% to about 65%, 40% to about 60%, 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is paclitaxel, and is covalently attached to the polymer through an ester bond. In some embodiments, the agent is paclitaxel, and is attached to the polymer via the hydroxyl group at the 2' position.

In some embodiments, the polymer-agent conjugate is:

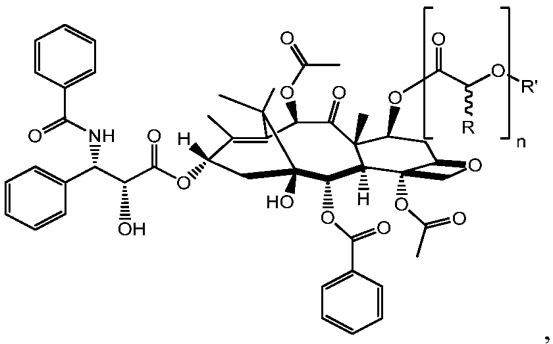


,

wherein about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, 40% to about 60%, 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is paclitaxel, and is attached to the polymer via the hydroxyl group at the 7 position.

In some embodiments, the polymer-agent conjugate is:

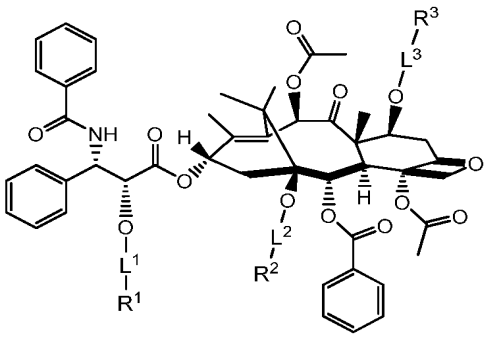


,

wherein about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the particle includes a combination of polymer-paclitaxel conjugates described herein, e.g., polymer-paclitaxel conjugates illustrated above.

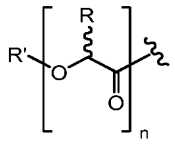
In some embodiments, the polymer-agent conjugate has the following formula (I):



(I),

wherein L^1, L^2 and L^3 are each independently a bond or a linker, e.g., a linker described herein;

wherein R^1, R^2 and R^3 are each independently hydrogen, C_1-C_6 alkyl, acyl, or a polymer of formula (II):



(II),

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)); and

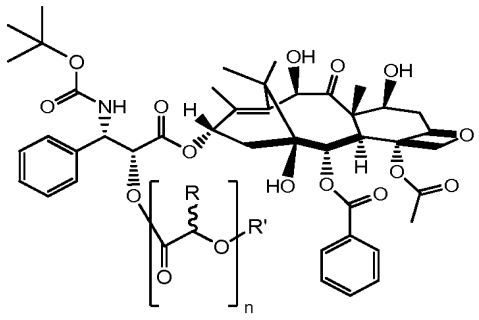
wherein at least one of R^1, R^2 and R^3 is a polymer of formula (II).

In some embodiments, L^2 is a bond and R^2 is hydrogen.

In some embodiments, the agent is paclitaxel, and is covalently attached to the polymer via a carbonate bond.

In some embodiments, the agent is docetaxel, and is covalently attached to the polymer through an ester bond. In some embodiments, the agent is docetaxel, and is attached to the polymer via the hydroxyl group at the 2' position.

In some embodiments, the polymer-agent conjugate is:



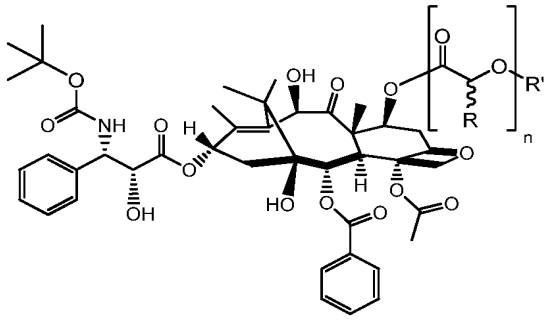
,

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and

about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is docetaxel, and is attached to the polymer via the hydroxyl group at the 7 position.

In some embodiments, the polymer-agent conjugate is:

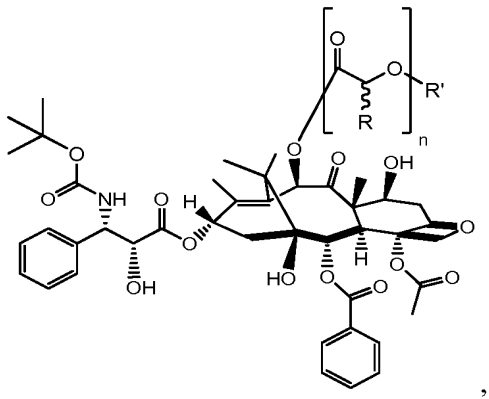


,

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is docetaxel, and is attached to the polymer via the hydroxyl group at the 10 position.

In some embodiments, the polymer-agent conjugate is:



,

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

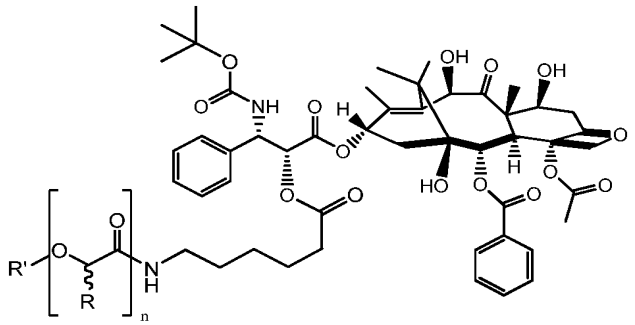
In some embodiments, the agent is docetaxel, and is covalently attached to the polymer through a carbonate bond.

In some embodiments, the particle includes a combination of polymer-docetaxel conjugates described herein, e.g., polymer-docetaxel conjugates illustrated above.

In some embodiments, the agent is attached to the polymer through a linker. In some embodiments, the linker is an alkanoate linker. In some embodiments, the linker is a PEG-based linker. In some embodiments, the linker comprises a disulfide bond. In some embodiments, the linker is a self-immolative linker. In some embodiments, the linker is an amino acid or a peptide (e.g., glutamic acid such as L-glutamic acid, D-glutamic acid, DL-glutamic acid or β-glutamic acid, branched glutamic acid or polyglutamic acid). In some embodiments, the linker is β-alanine glycolate.

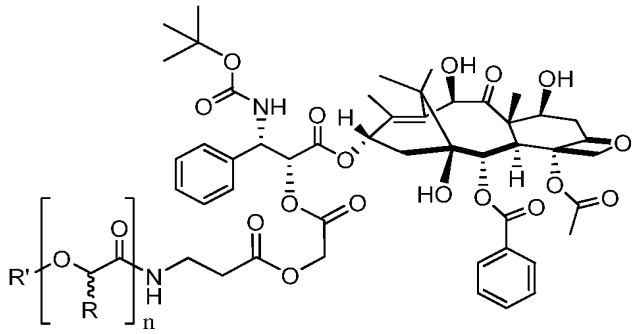
In some embodiments the linker is a multifunctional linker. In some embodiments, the multifunctional linker has 2, 3, 4, 5, 6 or more reactive moieties that may be functionalized with an agent. In some embodiments, all reactive moieties are functionalized with an agent. In some embodiments, not all of the reactive moieties are functionalized with an agent (e.g., the multifunctional linker has two reactive moieties, and only one reacts with an agent; or the multifunctional linker has four reactive moieties, and only one, two or three react with an agent.)

In some embodiments, the polymer-agent conjugate is:



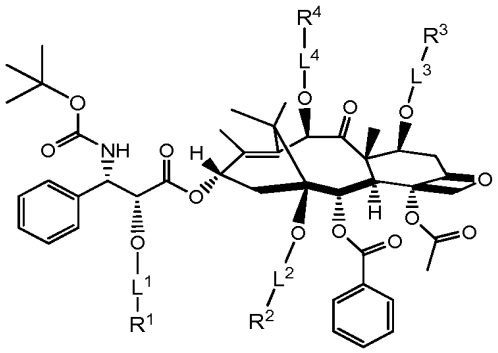
wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the polymer-agent conjugate is:



wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

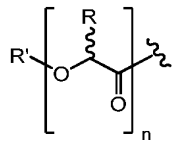
In some embodiments, the polymer-agent conjugate has the following formula (III):



(III)

wherein L^1, L^2, L^3 and L^4 are each independently a bond or a linker, e.g., a linker described herein;

R^1, R^2, R^3 and R^4 are each independently hydrogen, C_1-C_6 alkyl, acyl, a hydroxy protecting group, or a polymer of formula (IV):



(IV)

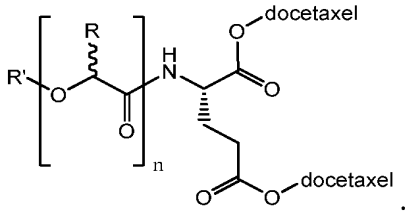
wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)); and

wherein at least one of R^1, R^2, R^3 and R^4 is a polymer of formula (IV).

In some embodiments, L^2 is a bond and R^2 is hydrogen.

In some embodiments, two agents are attached to a polymer via a multifunctional linker. In some embodiments, the two agents are the same agent. In some embodiments, the two agents are different agents. In some embodiments, the agent is docetaxel, and is covalently attached to the polymer via a glutamate linker.

In some embodiments, the polymer-agent conjugate is:



.

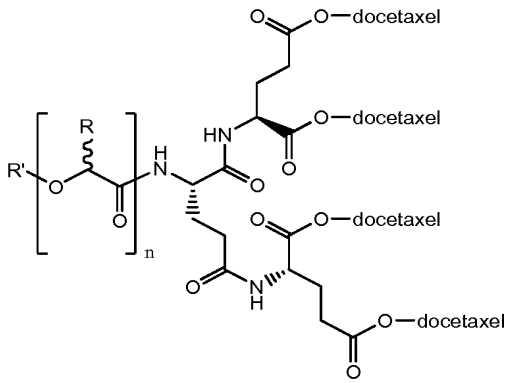
wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g.,

from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 2' position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 7 position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 10 position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 1 position. In some embodiments, each docetaxel is attached via the same hydroxyl group, e.g., the hydroxy group at the 2' position, the hydroxyl group at the 7 position or the hydroxyl group at the 10 position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 2' position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 7 position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 10 position. In some embodiments, each docetaxel is attached via a different hydroxyl group, e.g., one docetaxel is attached via the hydroxyl group at the 2' position and the other is attached via the hydroxyl group at the 7 position.

In some embodiments, four agents are attached to a polymer via a multifunctional linker. In some embodiments, the four agents are the same agent. In some embodiments, the four agents are different agents. In some embodiments, the agent is docetaxel, and is covalently attached to the polymer via a tri(glutamate) linker.

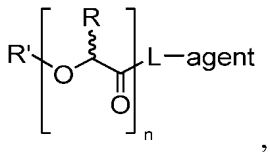
In some embodiments, the polymer-agent conjugate is:



wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 2' position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 7 position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 10 position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 1 position. In some embodiments, each docetaxel is attached via the same hydroxyl group, e.g., the hydroxyl group at the 2' position, the hydroxyl group at the 7 position or the hydroxyl group at the 10 position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 2' position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 7 position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 10 position. In some embodiments, docetaxel molecules may be attached via different hydroxyl groups, e.g., three docetaxel molecules are attached via the hydroxyl group at the 2' position and the other is attached via the hydroxyl group at the 7 position.

In another aspect, the invention features a composition comprising a plurality of polymer-agent conjugates, wherein the polymer-agent conjugate has the following formula:



,

wherein L is a bond or linker, e.g., a linker described herein; and

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is a taxane, e.g., docetaxel, paclitaxel, larotaxel or cabazitaxel.

In some embodiments, L is a bond.

In some embodiments, L is a linker, e.g., a linker described herein.

In some embodiments, the composition comprises a plurality of polymer-agent conjugates wherein the polymer-agent conjugates have the same polymer and the same agent, and differ in the nature of the linkage between the agent and the polymer. For example, in some embodiments, the polymer is PLGA, the agent is paclitaxel, and the plurality of polymer-agent conjugates includes PLGA attached to paclitaxel via the hydroxyl group at the 2' position and PLGA attached to paclitaxel via the hydroxyl group at the 7 position. In some embodiments, the polymer is PLGA, the agent is paclitaxel, and the plurality of polymer-agent conjugates includes PLGA attached to paclitaxel via the hydroxyl group at the 2' position, PLGA attached to paclitaxel via the hydroxyl group at the 7 position, and/or PLGA attached to paclitaxel via the hydroxyl group at the 1 position.

In some embodiments, the polymer is PLGA, the agent is docetaxel, and the plurality of polymer-agent conjugates includes PLGA attached to docetaxel via the

hydroxyl group at the 2' position and PLGA attached to docetaxel via the hydroxyl group at the 7 position. In some embodiments, the polymer is PLGA, the agent is docetaxel, and the plurality of polymer-agent conjugates includes PLGA attached to docetaxel via the hydroxyl group at the 2' position, PLGA attached to docetaxel via the hydroxyl group at the 7 position, and/or PLGA attached to docetaxel via the hydroxyl group at the 10 position. In some embodiments, the polymer is PLGA, the agent is docetaxel, and the plurality of polymer-agent conjugates includes PLGA attached to docetaxel via the hydroxyl group at the 2' position, PLGA attached to docetaxel via the hydroxyl group at the 7 position, PLGA attached to docetaxel via the 10 position and/or PLGA attached to docetaxel via the hydroxyl group at the 1 position.

In another aspect, the invention features a particle. The particle comprises:

a first polymer,

a second polymer having a hydrophilic portion and a hydrophobic portion,

an agent (e.g., a therapeutic or diagnostic agent) attached to the first polymer or second polymer, and

optionally, the particle comprises one or more of the following properties:

it further comprises a compound comprising at least one acidic moiety, wherein the compound is a polymer or a small molecule;

it further comprises a surfactant;

the first polymer is a PLGA polymer, wherein the ratio of lactic acid to glycolic acid is from about 25:75 to about 75:25 and, optionally, the agent is attached to the first polymer;

the first polymer is PLGA polymer, and the weight average molecular weight of the first polymer is from about 1 to about 20 kDa, e.g., is about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 kDa; or

the ratio of the first polymer to the second polymer is such that the particle comprises at least 5%, 8%, 10%, 12%, 15%, 18%, 20%, 23%, 25% or 30% by weight of a polymer having a hydrophobic portion and a hydrophilic portion.

In some embodiments, the particle is a nanoparticle. In some embodiments, the nanoparticle has a diameter of less than or equal to about 220 nm (e.g., less than or equal to about 215 nm, 210 nm, 205 nm, 200 nm, 195 nm, 190 nm, 185 nm, 180 nm, 175 nm, 170 nm, 165 nm, 160 nm, 155 nm, 150 nm, 145 nm, 140 nm, 135 nm, 130 nm, 125 nm, 120 nm, 115 nm, 110 nm, 105 nm, 100 nm, 95 nm, 90 nm, 85 nm, 80 nm, 75 nm, 70 nm, 65 nm, 60 nm, 55 nm or 50 nm).

In some embodiments, the particle further comprises a compound comprising at least one acidic moiety, wherein the compound is a polymer or a small molecule.

In some embodiments, the compound comprising at least one acidic moiety is a polymer comprising an acidic group. In some embodiments, the compound comprising at least one acidic moiety is a hydrophobic polymer. In some embodiments, the first polymer and the compound comprising at least one acidic moiety are the same polymer. In some embodiments, the compound comprising at least one acidic moiety is PLGA. In some embodiments, the ratio of lactic acid monomers to glycolic acid monomers in PLGA is from about 0.1:99.9 to about 99.9:0.1. In some embodiments, the ratio of lactic acid monomers to glycolic acid monomers in PLGA is from about 75:25 to about 25:75, e.g., about 60:40 to about 40:60 (e.g., about 50:50), about 60:40, or about 75:25. In some embodiments, the PLGA comprises a terminal hydroxyl group. In some embodiments, the PLGA comprises a terminal acyl group (e.g., an acetyl group).

In some embodiments, the weight average molecular weight of the compound comprising at least one acidic moiety is from about 1 kDa to about 20 kDa (e.g., from about 1 kDa to about 15 kDa, from about 2 kDa to about 12 kDa, from about 6 kDa to about 20 kDa, from about 5 kDa to about 15 kDa, from about 7 kDa to about 11 kDa, from about 5 kDa to about 10 kDa, from about 7 kDa to about 10 kDa, from about 5 kDa to about 7 kDa, from about 6 kDa to about 8 kDa, about 6 kDa, about 7 kDa, about 8 kDa, about 9 kDa, about 10 kDa, about 11 kDa, about 12 kDa, about 13 kDa, about 14 kDa, about 15 kDa, about 16 kDa or about 17 kDa). In some embodiments, the compound comprising at least one acidic moiety has a glass transition temperature of from about 20 °C to about 60 °C.

In some embodiments, the compound comprising at least one acidic moiety has a polymer polydispersity index of less than or equal to about 2.5 (e.g., less than or equal to about 2.2, or less than or equal to about 2.0). In some embodiments, the compound comprising at least one acidic moiety has a polymer polydispersity index of about 1.0 to about 2.5, e.g., from about 1.0 to about 2.0, from about 1.0 to about 1.8, from about 1.0 to about 1.7, or from about 1.0 to about 1.6.

In some embodiments, the particle comprises a plurality of compounds comprising at least one acidic moiety. For example, in some embodiments, one compound of the plurality of compounds comprising at least one acidic moiety is a PLGA polymer wherein the hydroxy terminus is functionalized with an acetyl group, and another compound in the plurality is a PLGA polymer wherein the hydroxy terminus is unfunctionalized.

In some embodiments, the percent by weight of the compound comprising at least one acidic moiety within the particle is up to about 50% (e.g., up to about 45% by weight, up to about 40% by weight, up to about 35% by weight, up to about 30% by weight, from about 0 to about 30% by weight, e.g., about 4.5%, about 9%, about 12%, about 15%, about 18%, about 20%, about 22%, about 24%, about 26%, about 28% or about 30%).

In some embodiments, the compound comprising at least one acidic moiety is a small molecule comprising an acidic group.

In some embodiments, the particle further comprises a surfactant. In some embodiments, the surfactant is PEG, poly(vinyl alcohol) (PVA), poly(vinylpyrrolidone) (PVP), poloxamer, a polysorbate, a polyoxyethylene ester, a PEG-lipid (e.g., PEG-ceramide, d-alpha-tocopheryl polyethylene glycol 1000 succinate), 1,2-Distearoyl-*sn*-Glycero-3-[Phospho-*rac*-(1-glycerol)] or lecithin. In some embodiments, the surfactant is PVA and the PVA is from about 3 kDa to about 50 kDa (e.g., from about 5 kDa to about 45 kDa, about 7 kDa to about 42 kDa, from about 9 kDa to about 30 kDa, or from about 11 to about 28 kDa) and up to about 98% hydrolyzed (e.g., about 75-95%, about 80-90% hydrolyzed, or about 85% hydrolyzed). In some embodiments, the surfactant is polysorbate 80. In some embodiments, the surfactant is Solutol® HS 15. In some embodiments, the surfactant

is present in an amount of up to about 35% by weight of the particle (e.g., up to about 20% by weight or up to about 25% by weight, from about 15 % to about 35% by weight, from about 20% to about 30% by weight, or from about 23% to about 26% by weight).

In some embodiments, the particle further comprises a stabilizer or lyoprotectant, e.g., a stabilizer or lyoprotectant described herein. In some embodiments, the stabilizer or lyoprotectant is a carbohydrate (e.g., a carbohydrate described herein, such as, e.g., sucrose, cyclodextrin or a derivative of cyclodextrin (e.g. 2-hydroxypropyl-β-cyclodextrin)), salt, PEG, PVP or crown ether.

In some embodiments, the agent is attached to the first polymer to form a polymer-agent conjugate. In some embodiments, the agent is attached to the second polymer to form a polymer-agent conjugate.

In some embodiments the amount of agent in the particle that is not attached to the first or second polymer is less than about 5% (e.g., less than about 2% or less than about 1%, e.g., in terms of w/w or number/number) of the amount of agent attached to the first polymer or second polymer.

In some embodiments, the first polymer is a biodegradable polymer (e.g., PLA, PGA, PLGA, PCL, PDO, polyanhydrides, polyorthoesters, or chitosan). In some embodiments, the first polymer is a hydrophobic polymer. In some embodiments, the percent by weight of the first polymer within the particle is from about 20% to about 90% (e.g., from about 20% to about 80%, from about 25% to about 75%, or from about 30% to about 70%). In some embodiments, the first polymer is PLA. In some embodiments, the first polymer is PGA.

In some embodiments, the first polymer is a copolymer of lactic and glycolic acid (e.g., PLGA). In some embodiments, the first polymer is a PLGA-ester. In some embodiments, the first polymer is a PLGA-lauryl ester. In some embodiments, the first polymer comprises a terminal free acid. In some embodiments, the first polymer comprises a terminal acyl group (e.g., an acetyl group). In some embodiments, the polymer comprises a terminal hydroxyl group. In some embodiments, the ratio of lactic acid monomers to glycolic acid monomers in PLGA is from about 0.1:99.9 to about 99.9:0.1. In some embodiments, the ratio of lactic acid monomers to glycolic

acid monomers in PLGA is from about 75:25 to about 25:75, e.g., about 60:40 to about 40:60 (e.g., about 50:50), about 60:40, or about 75:25.

In some embodiments, the weight average molecular weight of the first polymer is from about 1 kDa to about 20 kDa (e.g., from about 1 kDa to about 15 kDa, from about 2 kDa to about 12 kDa, from about 6 kDa to about 20 kDa, from about 5 kDa to about 15 kDa, from about 7 kDa to about 11 kDa, from about 5 kDa to about 10 kDa, from about 7 kDa to about 10 kDa, from about 5 kDa to about 7 kDa, from about 6 kDa to about 8 kDa, about 6 kDa, about 7 kDa, about 8 kDa, about 9 kDa, about 10 kDa, about 11 kDa, about 12 kDa, about 13 kDa, about 14 kDa, about 15 kDa, about 16 kDa or about 17 kDa). In some embodiments, the first polymer has a glass transition temperature of from about 20 °C to about 60 °C. In some embodiments, the first polymer has a polymer polydispersity index of less than or equal to about 2.5 (e.g., less than or equal to about 2.2, or less than or equal to about 2.0). In some embodiments, the first polymer has a polymer polydispersity index of about 1.0 to about 2.5, e.g., from about 1.0 to about 2.0, from about 1.0 to about 1.8, from about 1.0 to about 1.7, or from about 1.0 to about 1.6.

In some embodiments, the percent by weight of the second polymer within the particle is up to about 50% by weight (e.g., from about 4 to any of about 50%, about 5%, about 8%, about 10%, about 15%, about 20%, about 23%, about 25%, about 30%, about 35%, about 40%, about 45% or about 50% by weight). For example, the percent by weight of the second polymer within the particle is from about 3% to 30%, from about 5% to 25% or from about 8% to 23%. In some embodiments, the second polymer has a hydrophilic portion and a hydrophobic portion. In some embodiments, the second polymer is a copolymer, e.g., a block copolymer. In some embodiments, the second polymer comprises two regions, the two regions together being at least about 70% by weight of the polymer (e.g., at least about 80%, at least about 90%, at least about 95%). In some embodiments, the second polymer is a block copolymer comprising a hydrophobic polymer and a hydrophilic polymer. In some embodiments, the second polymer, e.g., a diblock copolymer, comprises a hydrophobic polymer and a hydrophilic polymer. In some embodiments, the second polymer, e.g., a triblock copolymer, comprises a hydrophobic polymer, a hydrophilic

polymer and a hydrophobic polymer, e.g., PLA-PEG-PLA, PGA-PEG-PGA, PLGA-PEG-PLGA, PCL-PEG-PCL, PDO-PEG-PDO, PEG-PLGA-PEG, PLA-PEG-PGA, PGA-PEG-PLA, PLGA-PEG-PLA or PGA-PEG-PLGA.

In some embodiments, the hydrophobic portion of the second polymer is a biodegradable polymer (e.g., PLA, PGA, PLGA, PCL, PDO, polyanhydrides, polyorthoesters, or chitosan). In some embodiments, the hydrophobic portion of the second polymer is PLA. In some embodiments, the hydrophobic portion of the second polymer is PGA. In some embodiments, the hydrophobic portion of the second polymer is a copolymer of lactic and glycolic acid (e.g., PLGA). In some embodiments, the hydrophobic portion of the second polymer has a weight average molecular weight of from about 1 kDa to about 20 kDa (e.g., from about 1 kDa to about 18 kDa, 17 kDa, 16 kDa, 15 kDa, 14 kDa or 13 kDa, from about 2 kDa to about 12 kDa, from about 6 kDa to about 20 kDa, from about 5 kDa to about 18 kDa, from about 7 kDa to about 17 kDa, from about 8 kDa to about 13 kDa, from about 9 kDa to about 11 kDa, from about 10 kDa to about 14 kDa, from about 6 kDa to about 8 kDa, about 6 kDa, about 7 kDa, about 8 kDa, about 9 kDa, about 10 kDa, about 11 kDa, about 12 kDa, about 13 kDa, about 14 kDa, about 15 kDa, about 16 kDa or about 17 kDa).

In some embodiments, the hydrophilic polymer portion of the second polymer is PEG. In some embodiments, the hydrophilic portion of the second polymer has a weight average molecular weight of from about 1 kDa to about 21 kDa (e.g., from about 1 kDa to about 3 kDa, e.g., about 2 kDa, or from about 2 kDa to about 5 kDa, e.g., about 3.5 kDa, or from about 4 kDa to about 6 kDa, e.g., about 5 kDa). In some embodiments, the ratio of weight average molecular weight of the hydrophilic to hydrophobic polymer portions of the second polymer from about 1:1 to about 1:20 (e.g., about 1:4 to about 1:10, about 1:4 to about 1:7, about 1:3 to about 1:7, about 1:3 to about 1:6, about 1:4 to about 1:6.5 (e.g., 1:4, 1:4.5, 1:5, 1:5.5, 1:6, 1:6.5) or about 1:1 to about 1:4 (e.g., about 1:1.4, 1:1.8, 1:2, 1:2.4, 1:2.8, 1:3, 1:3.2, 1:3.5 or 1:4). In one embodiment, the hydrophilic portion of the second polymer has a weight average molecular weight of from about 2 kDa to 3.5 kDa and the ratio of the weight average molecular weight of the hydrophilic to hydrophobic portions of the second polymer is

from about 1:4 to about 1:6.5 (e.g., 1:4, 1:4.5, 1:5, 1:5.5, 1:6, 1:6.5). In one embodiment, the hydrophilic portion of the second polymer has a weight average molecular weight of from about 4 kDa to 6 kDa (e.g., 5 kDa) and the ratio of the weight average molecular weight of the hydrophilic to hydrophobic portions of the second polymer is from about 1:1 to about 1:3.5 (e.g., about 1:1.4, 1:1.8, 1:2, 1:2.4, 1:2.8, 1:3, 1:3.2, or 1:3.5).

In some embodiments, the hydrophilic polymer portion of the second polymer has a terminal hydroxyl moiety. In some embodiments, the hydrophilic polymer portion of the second polymer has a terminal alkoxy moiety. In some embodiments, the hydrophilic polymer portion of the second polymer is a methoxy PEG (e.g., a terminal methoxy PEG). In some embodiments, the hydrophilic polymer portion of the second polymer does not have a terminal alkoxy moiety. In some embodiments, the terminus of the hydrophilic polymer portion of the second polymer is conjugated to a hydrophobic polymer, e.g., to make a triblock copolymer.

In some embodiments, the hydrophilic polymer portion of the second polymer comprises a terminal conjugate. In some embodiments, the terminal conjugate is a targeting agent or a dye. In some embodiments, the terminal conjugate is a folate or a rhodamine. In some embodiments, the terminal conjugate is a targeting peptide (e.g., an RGD peptide).

In some embodiments, the hydrophilic polymer portion of the second polymer is attached to the hydrophobic polymer portion through a covalent bond. In some embodiments, the hydrophilic polymer is attached to the hydrophobic polymer through an amide, ester, ether, amino, carbamate, or carbonate bond (e.g., an ester or an amide).

In some embodiments, the ratio by weight of the first to the second polymer is from about 1:1 to about 20:1, e.g., about 1:1 to about 10:1, e.g., about 1:1 to 9:1, or about 1.2: to 8:1. In some embodiments, the ratio of the first and second polymer is from about 85:15 to about 55:45 percent by weight or about 84:16 to about 60:40 percent by weight. In some embodiments, the ratio by weight of the first polymer to the compound comprising at least one acidic moiety is from about 1:3 to about 1000:1, e.g., about 1:1 to about 10:1, or about 1.5:1. In some embodiments, the ratio

by weight of the second polymer to the compound comprising at least one acidic moiety is from about 1:10 to about 250:1, e.g., from about 1:5 to about 5:1, or from about 1:3.5 to about 1:1.

In some embodiments the particle is substantially free of a targeting agent (e.g., of a targeting agent covalently linked to a component of the particle, e.g., to the first or second polymer or agent), e.g., a targeting agent able to bind to or otherwise associate with a target biological entity, e.g., a membrane component, a cell surface receptor, prostate specific membrane antigen, or the like. In some embodiments the particle is substantially free of a targeting agent that causes the particle to become localized to a tumor, a disease site, a tissue, an organ, a type of cell, e.g., a cancer cell, within the body of a subject to whom a therapeutically effective amount of the particle is administered. In some embodiments, the particle is substantially free of a targeting agent selected from nucleic acid aptamers, growth factors, hormones, cytokines, interleukins, antibodies, integrins, fibronectin receptors, p-glycoprotein receptors, peptides and cell binding sequences. In some embodiments, no polymer is conjugated to a targeting moiety. In an embodiment substantially free of a targeting agent means substantially free of any moiety other than the first polymer, the second polymer, a third polymer (if present), a surfactant (if present), and the agent, e.g., an anti-cancer agent or other therapeutic or diagnostic agent, that targets the particle. Thus, in such embodiments, any contribution to localization by the first polymer, the second polymer, a third polymer (if present), a surfactant (if present), and the agent is not considered to be "targeting." In an embodiment the particle is free of moieties added for the purpose of selectively targeting the particle to a site in a subject, e.g., by the use of a moiety on the particle having a high and specific affinity for a target in the subject.

In some embodiments the second polymer is other than a lipid, e.g., other than a phospholipid. In some embodiments the particle is substantially free of an amphiphilic layer that reduces water penetration into the nanoparticle. In some embodiment the particle comprises less than 5 or 10% (e.g., as determined as w/w, v/v) of a lipid, e.g., a phospholipid. In some embodiments the particle is substantially free of a lipid layer, e.g., a phospholipid layer, e.g., that reduces water penetration into

the nanoparticle. In some embodiments the particle is substantially free of lipid, e.g., is substantially free of phospholipid.

In some embodiments the agent is covalently bound to a PLGA polymer.

In some embodiments the particle is substantially free of a radiopharmaceutical agent, e.g., a radiotherapeutic agent, radiodiagnostic agent, prophylactic agent, or other radioisotope. In some embodiments the particle is substantially free of an immunomodulatory agent, e.g., an immunostimulatory agent or immunosuppressive agent. In some embodiments the particle is substantially free of a vaccine or immunogen, e.g., a peptide, sugar, lipid-based immunogen, B cell antigen or T cell antigen. In some embodiments, the particle is substantially free of water soluble PLGA (e.g., PLGA having a weight average molecular weight of less than about 1 kDa).

In some embodiments, the ratio of the first polymer to the second polymer is such that the particle comprises at least 5%, 8%, 10%, 12%, 15%, 18%, 20%, 23%, 25%, or 30% by weight of a polymer having a hydrophobic portion and a hydrophilic portion.

In some embodiments, the zeta potential of the particle surface, when measured in water, is from about -80 mV to about 50 mV, e.g., about -50 mV to about 30 mV, about -20 mV to about 20 mV, or about -10 mV to about 10 mV. In some embodiments, the zeta potential of the particle surface, when measured in water, is neutral or slightly negative. In some embodiments, the zeta potential of the particle surface, when measured in water, is less than 0, e.g., about 0 mV to about -20 mV.

In some embodiments, the particle comprises less than 5000 ppm of a solvent (e.g., acetone, *tert*-butylmethyl ether, heptane, dichloromethane, dimethylformamide, ethyl acetate, acetonitrile, tetrahydrofuran, ethanol, methanol, isopropyl alcohol, methyl ethyl ketone, butyl acetate, or propyl acetate), (e.g., less than 4500 ppm, less than 4000 ppm, less than 3500 ppm, less than 3000 ppm, less than 2500 ppm, less than 2000 ppm, less than 1500 ppm, less than 1000 ppm, less than 500 ppm, less than 250 ppm, less than 100 ppm, less than 50 ppm, less than 25 ppm, less than 10 ppm, less than 5 ppm, less than 2 ppm, or less than 1 ppm). In some embodiments, the particle is substantially free of a solvent (e.g., acetone, *tert*-butylmethyl ether,

heptane, dichloromethane, dimethylformamide, ethyl acetate, acetonitrile, tetrahydrofuran, ethanol, methanol, isopropyl alcohol, methyl ethyl ketone, butyl acetate, or propyl acetate).

In some embodiments, the particle is substantially free of a class II or class III solvent as defined by the United States Department of Health and Human Services Food and Drug Administration "Q3c -Tables and List." In some embodiments, the particle comprises less than 5000 ppm of acetone. In some embodiments, the particle comprises less than 5000 ppm of *tert*-butylmethyl ether. In some embodiments, the particle comprises less than 5000 ppm of heptane. In some embodiments, the particle comprises less than 600 ppm of dichloromethane. In some embodiments, the particle comprises less than 880 ppm of dimethylformamide. In some embodiments, the particle comprises less than 5000 ppm of ethyl acetate. In some embodiments, the particle comprises less than 410 ppm of acetonitrile. In some embodiments, the particle comprises less than 720 ppm of tetrahydrofuran. In some embodiments, the particle comprises less than 5000 ppm of ethanol. In some embodiments, the particle comprises less than 3000 ppm of methanol. In some embodiments, the particle comprises less than 5000 ppm of isopropyl alcohol. In some embodiments, the particle comprises less than 5000 ppm of methyl ethyl ketone. In some embodiments, the particle comprises less than 5000 ppm of butyl acetate. In some embodiments, the particle comprises less than 5000 ppm of propyl acetate.

In some embodiments, a composition comprising a plurality of particles is substantially free of solvent.

In some embodiments, in a composition of a plurality of particles, the particles have an average diameter of from about 50 nm to about 500 nm (e.g., from about 50 to about 200 nm). In some embodiments, in a composition of a plurality of particles, the particles have a Dv50 (median particle size) from about 50 nm to about 220 nm (e.g., from about 75 nm to about 200 nm). In some embodiments, in a composition of a plurality of particles, the particles have a Dv90 (particle size below which 90% of the volume of particles exists) of about 50 nm to about 500 nm (e.g., about 75 nm to about 220 nm).

In some embodiments, a single agent is attached to a single polymer (e.g., a single first polymer or a single second polymer), e.g., to a terminal end of the polymer. In some embodiments, a plurality of agents are attached to a single polymer (e.g., a single first polymer or a single second polymer) (e.g., 2, 3, 4, 5, 6, or more). In some embodiments, the agents are the same agent. In some embodiments, the agents are different agents. In some embodiments, the agent is a diagnostic agent.

In some embodiments, the agent is a therapeutic agent. In some embodiments, the therapeutic agent is an anti-inflammatory agent. In some embodiments, the therapeutic agent is an anti-cancer agent. In some embodiments, the anti-cancer agent is an alkylating agent, a vascular disrupting agent, a microtubule targeting agent, a mitotic inhibitor, a topoisomerase inhibitor, an anti-angiogenic agent or an anti-metabolite. In some embodiments, the anti-cancer agent is a taxane (e.g., paclitaxel, docetaxel, larotaxel or cabazitaxel). In some embodiments, the anti-cancer agent is an anthracycline (e.g., doxorubicin). In some embodiments, the anti-cancer agent is a platinum-based agent (e.g., cisplatin). In some embodiments, the anti-cancer agent is a pyrimidine analog (e.g., gemcitabine).

In some embodiments, the anti-cancer agent is paclitaxel, attached to the polymer via the hydroxyl group at the 2' position, the hydroxyl group at the 1 position and/or the hydroxyl group at the 7 position. In some embodiments, the anti-cancer agent is paclitaxel, attached to the polymer via the 2' position and/or the 7 position.

In some embodiments, the anti-cancer agent is docetaxel, attached to the polymer via the hydroxyl group at the 2' position, the hydroxyl group at the 7 position, the hydroxyl group at the 10 position and/or the hydroxyl group at the 1 position. In some embodiments, the anti-cancer agent is docetaxel, attached to the polymer via the hydroxyl group at the 2' position, the hydroxyl group at the 7 position and/or the hydroxyl group at the 10 position.

In some embodiments, the anti-cancer agent is docetaxel-succinate.

In some embodiments, the anti-cancer agent is a taxane that is attached to the polymer via the hydroxyl group at the 7 position and has an acyl group or a hydroxy protecting group on the hydroxyl group at the 2' position (e.g., wherein the anti-cancer agent is a taxane such as paclitaxel, docetaxel, larotaxel or cabazitaxel). In

some embodiments, the anti-cancer agent is larotaxel. In some embodiments, the anti-cancer agent is cabazitaxel.

In some embodiments, the anti-cancer agent is doxorubicin.

In some embodiments, the therapeutic agent is an agent for the treatment or prevention of cardiovascular disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the treatment of cardiovascular disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the prevention of cardiovascular disease, for example as described herein.

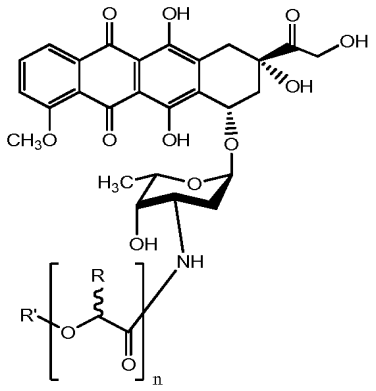
In some embodiments, the therapeutic agent is an agent for the treatment or prevention of an inflammatory or autoimmune disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the treatment of inflammatory or autoimmune disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the prevention of an inflammatory or autoimmune disease, for example as described herein.

In some embodiments, the agent is attached directly to the polymer, e.g., through a covalent bond. In some embodiments, the agent is attached to a terminal end of the polymer via an amide, ester, ether, amino, carbamate or carbonate bond. In some embodiments, the agent is attached to a terminal end of the polymer. In some embodiments, the polymer comprises one or more side chains and the agent is directly attached to the polymer through one or more of the side chains.

In some embodiments, a single agent is attached to a polymer. In some embodiments, multiple agents are attached to a polymer (e.g., 2, 3, 4, 5, 6 or more agents). In some embodiments, the agents are the same agent. In some embodiments, the agents are different agents.

In some embodiments, the agent is doxorubicin, and is covalently attached to the first polymer through an amide bond.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:

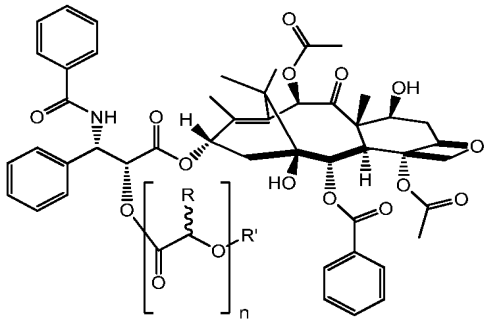


,

wherein about 30% to about 70%, 35% to about 65%, 40% to about 60%, 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, 35% to about 65%, 40% to about 60%, 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is paclitaxel, and is covalently attached to the polymer through an ester bond. In some embodiments, the agent is paclitaxel, and is attached to the polymer via the hydroxyl group at the 2' position.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:



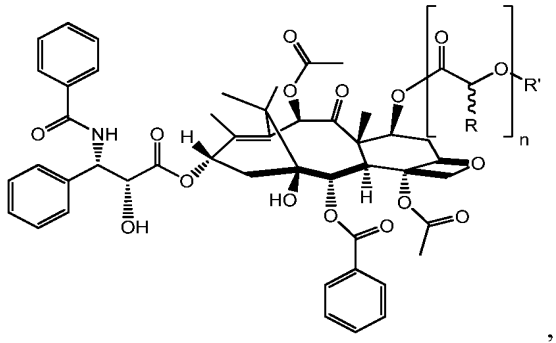
,

wherein about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, 40% to about 60%, 45% to

about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is paclitaxel, and is attached to the polymer via the hydroxyl group at the 7 position.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:

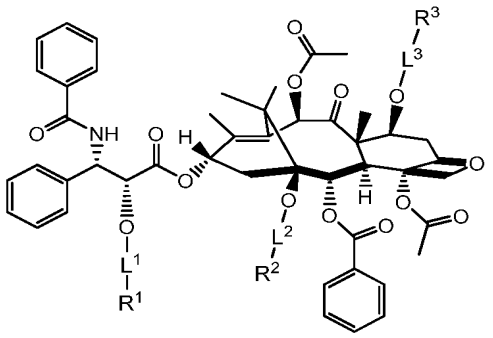


,

wherein about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the particle includes a combination of polymer-paclitaxel conjugates described herein, e.g., polymer-paclitaxel conjugates illustrated above.

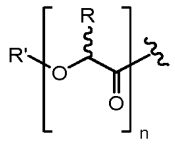
In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, has the following formula (I):



(I),

wherein L^1, L^2 and L^3 are each independently a bond or a linker, e.g., a linker described herein;

wherein R^1, R^2 and R^3 are each independently hydrogen, C_1-C_6 alkyl, acyl, or a polymer of formula (II):



(II),

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)); and

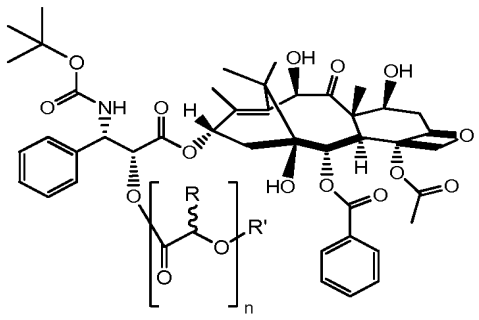
wherein at least one of R^1, R^2 and R^3 is a polymer of formula (II).

In some embodiments, L^2 is a bond and R^2 is hydrogen.

In some embodiments, the agent is paclitaxel, and is covalently attached to the polymer via a carbonate bond.

In some embodiments, the agent is docetaxel, and is covalently attached to the polymer through an ester bond. In some embodiments, the agent is docetaxel, and is attached to the polymer via the hydroxyl group at the 2' position.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:

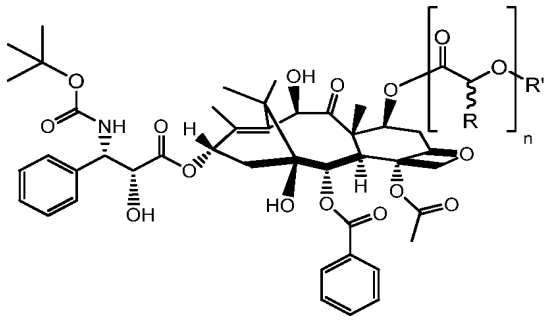


,

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is docetaxel, and is attached to the polymer via the hydroxyl group at the 7 position.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:



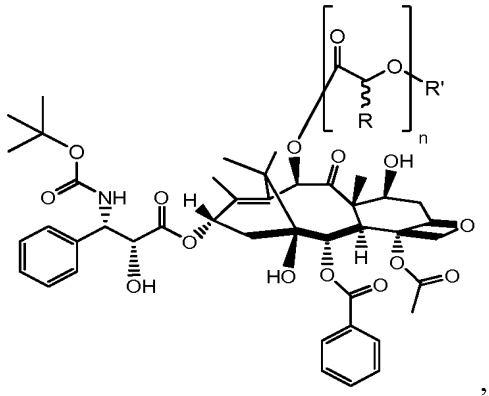
,

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about

45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is docetaxel, and is attached to the polymer via the hydroxyl group at the 10 position.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:



,

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

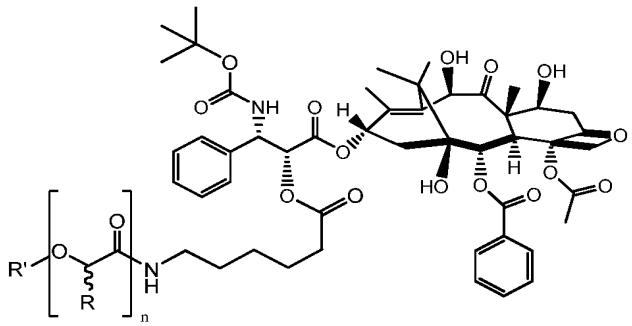
In some embodiments, the agent is docetaxel, and is covalently attached to the polymer through a carbonate bond.

In some embodiments, the particle includes a combination of polymer-docetaxel conjugates described herein, e.g., polymer-docetaxel conjugates illustrated above.

In some embodiments, the agent is attached to the polymer through a linker. In some embodiments, the linker is an alkanoate linker. In some embodiments, the linker is a PEG-based linker. In some embodiments, the linker comprises a disulfide bond. In some embodiments, the linker is a self-immolative linker. In some embodiments, the linker is an amino acid or a peptide (e.g., glutamic acid such as L-glutamic acid, D-glutamic acid, DL-glutamic acid or β-glutamic acid, branched glutamic acid or polyglutamic acid). In some embodiments, the linker is β-alanine glycolate.

In some embodiments the linker is a multifunctional linker. In some embodiments, the multifunctional linker has 2, 3, 4, 5, 6 or more reactive moieties that may be functionalized with an agent. In some embodiments, all reactive moieties are functionalized with an agent. In some embodiments, not all of the reactive moieties are functionalized with an agent (e.g., the multifunctional linker has two reactive moieties, and only one reacts with an agent; or the multifunctional linker has four reactive moieties, and only one, two or three react with an agent.)

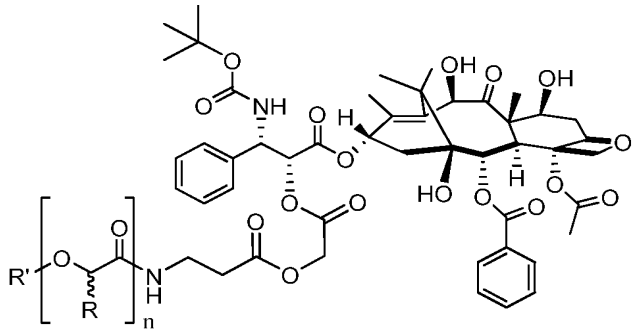
In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:



wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and

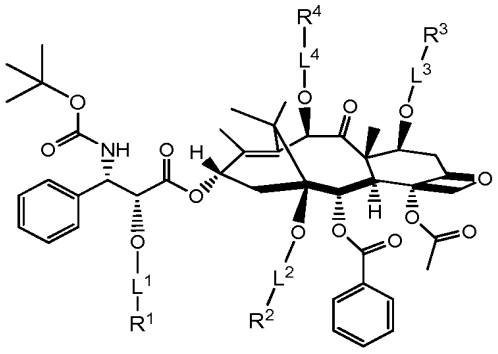
acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the polymer-agent conjugate is:



wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

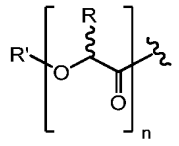
In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, has the following formula (III):



(III)

wherein L^1, L^2, L^3 and L^4 are each independently a bond or a linker, e.g., a linker described herein;

R^1, R^2, R^3 and R^4 are each independently hydrogen, C_1-C_6 alkyl, acyl, a hydroxy protecting group, or a polymer of formula (IV):



(IV)

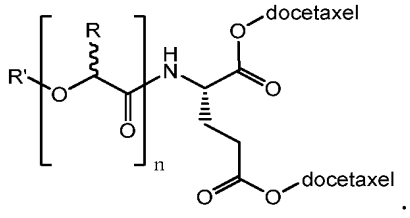
wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)); and

wherein at least one of R^1, R^2, R^3 and R^4 is a polymer of formula (IV).

In some embodiments, L^2 is a bond and R^2 is hydrogen.

In some embodiments, two agents are attached to a polymer via a multifunctional linker. In some embodiments, the two agents are the same agent. In some embodiments, the two agents are different agents. In some embodiments, the agent is docetaxel, and is covalently attached to the polymer via a glutamate linker.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:



.

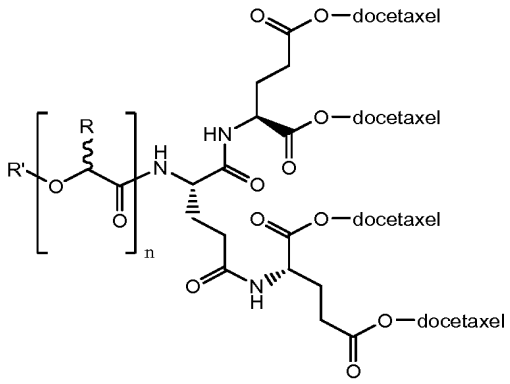
wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and

about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 2' position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 7 position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 10 position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 1 position. In some embodiments, each docetaxel is attached via the same hydroxyl group, e.g., the hydroxyl group at the 2' position, the hydroxyl group at the 7 position or the hydroxyl group at the 10 position. In some embodiments, each docetaxel is attached via the 2' hydroxyl group at the position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 7 position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 10 position. In some embodiments, each docetaxel is attached via a different hydroxyl group, e.g., one docetaxel is attached via the hydroxyl group at the 2' position and the other is attached via the hydroxyl group at the 7 position.

In some embodiments, four agents are attached to a polymer via a multifunctional linker. In some embodiments, the four agents are the same agent. In some embodiments, the four agents are different agents. In some embodiments, the agent is docetaxel, and is covalently attached to the polymer via a tri(glutamate) linker.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:

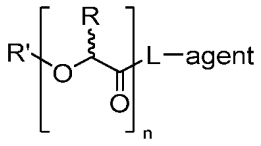


wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 2' position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 7 position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 10 position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 1 position. In some embodiments, each docetaxel is attached via the same hydroxyl group, e.g., the hydroxyl group at the 2' position, the hydroxyl group at the 7 position or the hydroxyl group at the 10 position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 2' position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 7 position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 10 position. In some embodiments, docetaxel molecules may be attached via different hydroxyl groups, e.g., three docetaxel molecules are attached via the

hydroxyl group at the 2' position and the other is attached via the hydroxyl group at the 7 position.

In some embodiments, the polymer-agent conjugate has the following formula:



,

wherein L is a bond or linker, e.g., a linker described herein; and

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is a taxane, e.g., docetaxel, paclitaxel, larotaxel or cabazitaxel.

In some embodiments, L is a bond.

In some embodiments, L is a linker, e.g., a linker described herein.

In some embodiments, the particle comprises a plurality of polymer-agent conjugates. In some embodiments, the plurality of polymer-agent conjugates have the same polymer and the same agent, and differ in the nature of the linkage between the agent and the polymer. For example, in some embodiments, the polymer is PLGA, the agent is paclitaxel, and the plurality of polymer-agent conjugates includes PLGA polymers attached to paclitaxel via the hydroxyl group at the 2' position, and PLGA polymers attached to paclitaxel via the hydroxyl group at the 7 position. In some embodiments, the polymer is PLGA, the agent is paclitaxel, and the plurality of polymer-agent conjugates includes PLGA polymers attached to paclitaxel via the

hydroxyl group at the 2' position, PLGA polymers attached to paclitaxel via the hydroxyl group at the 7 position, and/or PLGA polymers attached to paclitaxel via the hydroxyl group at the 1 position. In some embodiments, the polymer is PLGA, the agent is paclitaxel, and the plurality of polymer-agent conjugates includes paclitaxel molecules attached to more than one polymer chain, e.g., paclitaxel molecules with PLGA polymers attached to the hydroxyl group at the 2' position, the hydroxyl group at the 7 position and/or the hydroxyl group at the 1 position.

In some embodiments, the polymer is PLGA, the agent is docetaxel, and the plurality of polymer-agent conjugates includes PLGA attached to docetaxel via the hydroxyl group at the 2' position and PLGA attached to docetaxel via the hydroxyl group at the 7 position. In some embodiments, the polymer is PLGA, the agent is docetaxel, and the plurality of polymer-agent conjugates includes PLGA polymers attached to docetaxel via the hydroxyl group at the 2' position, PLGA polymers attached to docetaxel via the hydroxyl group at the 7 position, and/or PLGA polymers attached to docetaxel via the hydroxyl group at the 10 position. In some embodiments, the polymer is PLGA, the agent is docetaxel, and the plurality of polymer-agent conjugates includes PLGA polymers attached to docetaxel via the hydroxyl group at the 2' position, PLGA polymers attached to docetaxel via the hydroxyl group at the 7 position, PLGA polymers attached to docetaxel via the hydroxyl group at the 10 position and/or PLGA polymers attached to docetaxel via the hydroxyl group at the 1 position. In some embodiments, the polymer is PLGA, the agent is docetaxel, and the plurality of polymer-agent conjugates includes docetaxel molecules attached to more than one polymer chain, e.g., docetaxel molecules with PLGA polymers attached to the hydroxyl group at the 2' position, the hydroxyl group at the 7 position, the hydroxyl group at the 10 position and/or the hydroxyl group at the 1 position.

In some embodiments, the plurality of polymer-agent conjugates have the same polymer and the same agent, but the agent may be attached to the polymer via different linkers. In some embodiments, the plurality of polymer-agent conjugates includes a polymer directly attached to an agent and a polymer attached to an agent via a linker. In an embodiment, one agent is released from one polymer-agent

conjugate in the plurality with a first release profile and a second agent is released from a second polymer-agent conjugate in the plurality with a second release profile. E.g., a bond between the first agent and the first polymer is more rapidly broken than a bond between the second agent and the second polymer. E.g., the first polymer-agent conjugate can comprise a first linker linking the first agent to the first polymer and the second polymer-agent conjugate can comprise a second linker linking the second agent to the second polymer, wherein the linkers provide for different profiles for release of the first and second agents from their respective agent-polymer conjugates.

In some embodiments, the plurality of polymer-agent conjugates includes different polymers. In some embodiments, the plurality of polymer-agent conjugates includes different agents.

In some embodiments, the agent is present in the particle in an amount of from about 1 to about 30% by weight (e.g., from about 3 to about 30% by weight, from about 4 to about 25 % by weight, or from about 5 to about 13%, 14%, 15%, 16%, 17%, 18%, 19% or 20% by weight).

In an embodiment the particle comprises the enumerated elements.

In an embodiment the particle consists of the enumerated elements.

In an embodiment the particle consists essentially of the enumerated elements.

In another aspect, the invention features a particle. The particle comprises:

a first polymer,

a second polymer having a hydrophilic portion and a hydrophobic portion,

an agent (e.g., a therapeutic or diagnostic agent), wherein the agent is attached to the first polymer to form a polymer-agent conjugate, and

optionally, the particle comprises one or more of the following:

it further comprises a compound comprising at least one acidic moiety, wherein the compound is a polymer or a small molecule;

it further comprises a surfactant;

the first polymer is a PLGA polymer, wherein the ratio of lactic acid to glycolic acid is from about 25:75 to about 75:25 and the agent is attached to the first polymer;

the first polymer is PLGA polymer, and the weight average molecular weight of the first polymer is from about 1 to about 20 kDa, e.g., is about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 kDa; or

the ratio of the first polymer to the second polymer is such that the particle comprises at least 5%, 8%, 10%, 12%, 15%, 18%, 20%, 23%, 25% or 30% by weight of a polymer having a hydrophobic portion and a hydrophilic portion.

In some embodiments, the particle is a nanoparticle. In some embodiments, the nanoparticle has a diameter of less than or equal to about 220 nm (e.g., less than or equal to about 215 nm, 210 nm, 205 nm, 200 nm, 195 nm, 190 nm, 185 nm, 180 nm, 175 nm, 170 nm, 165 nm, 160 nm, 155 nm, 150 nm, 145 nm, 140 nm, 135 nm, 130 nm, 125 nm, 120 nm, 115 nm, 110 nm, 105 nm, 100 nm, 95 nm, 90 nm, 85 nm, 80 nm, 75 nm, 70 nm, 65 nm, 60 nm, 55 nm or 50 nm).

In some embodiments, the particle further comprises a compound comprising at least one acidic moiety, wherein the compound is a polymer or a small molecule.

In some embodiments, the compound comprising at least one acidic moiety is a polymer comprising an acidic group. In some embodiments, the compound comprising at least one acidic moiety is a hydrophobic polymer. In some embodiments, the first polymer and the compound comprising at least one acidic moiety are the same polymer. In some embodiments, the compound comprising at least one acidic moiety is PLGA. In some embodiments, the ratio of lactic acid monomers to glycolic acid monomers in PLGA is from about 0.1:99.9 to about 99.9:0.1. In some embodiments, the ratio of lactic acid monomers to glycolic acid monomers in PLGA is from about 75:25 to about 25:75, e.g., about 60:40 to about 40:60 (e.g., about 50:50), about 60:40, or about 75:25. In some embodiments, the PLGA comprises a terminal hydroxyl group. In some embodiments, the PLGA comprises a terminal acyl group (e.g., an acetyl group).

In some embodiments, the weight average molecular weight of the compound comprising at least one acidic moiety is from about 1 kDa to about 20 kDa (e.g., from

about 1 kDa to about 15 kDa, from about 2 kDa to about 12 kDa, from about 6 kDa to about 20 kDa, from about 5 kDa to about 15 kDa, from about 7 kDa to about 11 kDa, from about 5 kDa to about 10 kDa, from about 7 kDa to about 10 kDa, from about 5 kDa to about 7 kDa, from about 6 kDa to about 8 kDa, about 6 kDa, about 7 kDa, about 8 kDa, about 9 kDa, about 10 kDa, about 11 kDa, about 12 kDa, about 13 kDa, about 14 kDa, about 15 kDa, about 16 kDa or about 17 kDa). In some embodiments, the compound comprising at least one acidic moiety has a glass transition temperature of from about 20 °C to about 60 °C.

In some embodiments, the compound comprising at least one acidic moiety has a polymer polydispersity index of less than or equal to about 2.5 (e.g., less than or equal to about 2.2, or less than or equal to about 2.0). In some embodiments, the compound comprising at least one acidic moiety has a polymer polydispersity index of about 1.0 to about 2.5, e.g., from about 1.0 to about 2.0, from about 1.0 to about 1.8, from about 1.0 to about 1.7, or from about 1.0 to about 1.6.

In some embodiments, the particle comprises a plurality of compounds comprising at least one acidic moiety. For example, in some embodiments, one compound of the plurality of compounds comprising at least one acidic moiety is a PLGA polymer wherein the hydroxy terminus is functionalized with an acetyl group, and another compound in the plurality is a PLGA polymer wherein the hydroxy terminus is unfunctionalized.

In some embodiments, the percent by weight of the compound comprising at least one acidic moiety within the particle is up to about 50% (e.g., up to about 45% by weight, up to about 40% by weight, up to about 35% by weight, up to about 30% by weight, from about 0 to about 30% by weight, e.g., about 4.5%, about 9%, about 12%, about 15%, about 18%, about 20%, about 22%, about 24%, about 26%, about 28%, or about 30%).

In some embodiments, the compound comprising at least one acidic moiety is a small molecule comprising an acidic group.

In some embodiments, the particle further comprises a surfactant. In some embodiments, the surfactant is PEG, PVA, PVP, poloxamer, a polysorbate, a polyoxyethylene ester, a PEG-lipid (e.g., PEG-ceramide, d-alpha-tocopheryl

polyethylene glycol 1000 succinate), 1,2-Distearoyl-*sn*-Glycero-3-[Phospho-*rac*-(1-glycerol)] or lecithin. In some embodiments, the surfactant is PVA and the PVA is from about 3 kDa to about 50 kDa (e.g., from about 5 kDa to about 45 kDa, about 7 kDa to about 42 kDa, from about 9 kDa to about 30 kDa, or from about 11 to about 28 kDa) and up to about 98% hydrolyzed (e.g., about 75-95%, about 80-90% hydrolyzed, or about 85% hydrolyzed). In some embodiments, the surfactant is polysorbate 80. In some embodiments, the surfactant is Solutol® HS 15. In some embodiments, the surfactant is present in an amount of up to about 35% by weight of the particle (e.g., up to about 20% by weight or up to about 25% by weight, from about 15 % to about 35% by weight, from about 20% to about 30% by weight, or from about 23% to about 26% by weight).

In some embodiments, the particle further comprises a stabilizer or lyoprotectant, e.g., a stabilizer or lyoprotectant described herein. In some embodiments, the stabilizer or lyoprotectant is a carbohydrate (e.g., a carbohydrate described herein, such as, e.g., sucrose, cyclodextrin or a derivative of cyclodextrin (e.g. 2-hydroxypropyl-β-cyclodextrin)), salt, PEG, PVP or crown ether.

In an embodiment the amount of agent in the particle that is not attached to the first polymer is less than about 5% (e.g., less than about 2% or less than about 1%, e.g., in terms of w/w or number/number) of the amount of agent attached to the first polymer.

In some embodiments, the first polymer is a biodegradable polymer (e.g., PLA, PGA, PLGA, PCL, PDO, polyanhydrides, polyorthoesters, or chitosan). In some embodiments, the first polymer is a hydrophobic polymer. In some embodiments, the percent by weight of the first polymer within the particle is from about 20% to about 90% (e.g., from about 20% to about 80%, from about 25% to about 75%, or from about 30% to about 70%). In some embodiments, the first polymer is PLA. In some embodiments, the first polymer is PGA.

In some embodiments, the first polymer is a copolymer of lactic and glycolic acid (e.g., PLGA). In some embodiments, the first polymer is a PLGA-ester. In some embodiments, the first polymer is a PLGA-lauryl ester. In some embodiments, the first polymer comprises a terminal free acid. In some embodiments, the first polymer

comprises a terminal acyl group (e.g., an acetyl group). In some embodiments, the polymer comprises a terminal hydroxyl group. In some embodiments, the ratio of lactic acid monomers to glycolic acid monomers in PLGA is from about 0.1:99.9 to about 99.9:0.1. In some embodiments, the ratio of lactic acid monomers to glycolic acid monomers in PLGA is from about 75:25 to about 25:75, e.g., about 60:40 to about 40:60 (e.g., about 50:50), about 60:40, or about 75:25.

In some embodiments, the weight average molecular weight of the first polymer is from about 1 kDa to about 20 kDa (e.g., from about 1 kDa to about 15 kDa, from about 2 kDa to about 12 kDa, from about 6 kDa to about 20 kDa, from about 5 kDa to about 15 kDa, from about 7 kDa to about 11 kDa, from about 5 kDa to about 10 kDa, from about 7 kDa to about 10 kDa, from about 5 kDa to about 7 kDa, from about 6 kDa to about 8 kDa, about 6 kDa, about 7 kDa, about 8 kDa, about 9 kDa, about 10 kDa, about 11 kDa, about 12 kDa, about 13 kDa, about 14 kDa, about 15 kDa, about 16 kDa or about 17 kDa). In some embodiments, the first polymer has a glass transition temperature of from about 20 °C to about 60 °C. In some embodiments, the first polymer has a polymer polydispersity index of less than or equal to about 2.5 (e.g., less than or equal to about 2.2, or less than or equal to about 2.0). In some embodiments, the first polymer has a polymer polydispersity index of about 1.0 to about 2.5, e.g., from about 1.0 to about 2.0, from about 1.0 to about 1.8, from about 1.0 to about 1.7, or from about 1.0 to about 1.6.

In some embodiments, the percent by weight of the second polymer within the particle is up to about 50% by weight (e.g., from about 4 to any of about 50%, about 5%, about 8%, about 10%, about 15%, about 20%, about 23%, about 25%, about 30%, about 35%, about 40%, about 45% or about 50% by weight). For example, the percent by weight of the second polymer within the particle is from about 3% to 30%, from about 5% to 25% or from about 8% to 23%. In some embodiments, the second polymer has a hydrophilic portion and a hydrophobic portion. In some embodiments, the second polymer is a block copolymer. In some embodiments, the second polymer comprises two regions, the two regions together being at least about 70% by weight of the polymer (e.g., at least about 80%, at least about 90%, at least about 95%). In some embodiments, the second polymer is a block copolymer comprising a

hydrophobic polymer and a hydrophilic polymer. In some embodiments, the second polymer, e.g., a diblock copolymer, comprises a hydrophobic polymer and a hydrophilic polymer. In some embodiments, the second polymer, e.g., a triblock copolymer, comprises a hydrophobic polymer, a hydrophilic polymer and a hydrophobic polymer, e.g., PLA-PEG-PLA, PGA-PEG-PGA, PLGA-PEG-PLGA, PCL-PEG-PCL, PDO-PEG-PDO, PEG-PLGA-PEG, PLA-PEG-PGA, PGA-PEG-PLA, PLGA-PEG-PLA or PGA-PEG-PLGA.

In some embodiments, the hydrophobic portion of the second polymer is a biodegradable polymer (e.g., PLA, PGA, PLGA, PCL, PDO, polyanhydrides, polyorthoesters, or chitosan). In some embodiments, the hydrophobic portion of the second polymer is PLA. In some embodiments, the hydrophobic portion of the second polymer is PGA. In some embodiments, the hydrophobic portion of the second polymer is a copolymer of lactic and glycolic acid (e.g., PLGA). In some embodiments, the hydrophobic portion of the second polymer has a weight average molecular weight of from about 1 kDa to about 20 kDa (e.g., from about 1 kDa to about 18 kDa, 17 kDa, 16 kDa, 15 kDa, 14 kDa or 13 kDa, from about 2 kDa to about 12 kDa, from about 6 kDa to about 20 kDa, from about 5 kDa to about 18 kDa, from about 7 kDa to about 17 kDa, from about 8 kDa to about 13 kDa, from about 9 kDa to about 11 kDa, from about 10 kDa to about 14 kDa, from about 6 kDa to about 8 kDa, about 6 kDa, about 7 kDa, about 8 kDa, about 9 kDa, about 10 kDa, about 11 kDa, about 12 kDa, about 13 kDa, about 14 kDa, about 15 kDa, about 16 kDa or about 17 kDa).

In some embodiments, the hydrophilic polymer portion of the second polymer is PEG. In some embodiments, the hydrophilic portion of the second polymer has a weight average molecular weight of from about 1 kDa to about 21 kDa (e.g., from about 1 kDa to about 3 kDa, e.g., about 2 kDa, or from about 2 kDa to about 5 kDa, e.g., about 3.5 kDa, or from about 4 kDa to about 6 kDa, e.g., about 5 kDa). In some embodiments, the ratio of weight average molecular weight of the hydrophilic to hydrophobic polymer portions of the second polymer is from about 1:1 to about 1:20 (e.g., about 1:4 to about 1:10, about 1:4 to about 1:7, about 1:3 to about 1:7, about 1:3 to about 1:6, about 1:4 to about 1:6.5 (e.g., 1:4, 1:4.5, 1:5, 1:5.5, 1:6, 1:6.5) or about

1:1 to about 1:4 (e.g., about 1:1.4, 1:1.8, 1:2, 1:2.4, 1:2.8, 1:3, 1:3.2, 1:3.5 or 1:4). In one embodiment, the hydrophilic portion of the second polymer has a weight average molecular weight of from about 2 kDa to 3.5 kDa and the ratio of the weight average molecular weight of the hydrophilic to hydrophobic portions of the second polymer is from about 1:4 to about 1:6.5 (e.g., 1:4, 1:4.5, 1:5, 1:5.5, 1:6, 1:6.5). In one embodiment, the hydrophilic portion of the second polymer has a weight average molecular weight of from about 4 kDa to 6 kDa (e.g., 5 kDa) and the ratio of the weight average molecular weight of the hydrophilic to hydrophobic portions of the second polymer is from about 1:1 to about 1:3.5 (e.g., about 1:1.4, 1:1.8, 1:2, 1:2.4, 1:2.8, 1:3, 1:3.2, or 1:3.5).

In some embodiments, the hydrophilic polymer portion of the second polymer has a terminal hydroxyl moiety. In some embodiments, the hydrophilic polymer portion of the second polymer has a terminal alkoxy moiety. In some embodiments, the hydrophilic polymer portion of the second polymer is a methoxy PEG (e.g., a terminal methoxy PEG). In some embodiments, the hydrophilic polymer portion of the second polymer does have a terminal alkoxy moiety. In some embodiments, the terminus of the hydrophilic polymer portion of the second polymer is conjugated to a hydrophobic polymer, e.g., to make a triblock copolymer.

In some embodiments, the hydrophilic polymer portion of the second polymer comprises a terminal conjugate. In some embodiments, the terminal conjugate is a targeting agent or a dye. In some embodiments, the terminal conjugate is a folate or a rhodamine. In some embodiments, the terminal conjugate is a targeting peptide (e.g., an RGD peptide).

In some embodiments, the hydrophilic polymer portion of the second polymer is attached to the hydrophobic polymer portion through a covalent bond. In some embodiments, the hydrophilic polymer is attached to the hydrophobic polymer through an amide, ester, ether, amino, carbamate, or carbonate bond (e.g., an ester or an amide).

In some embodiments, the ratio by weight of the first to the second polymer is from about 1:1 to about 20:1, e.g., about 1:1 to about 10:1, e.g., about 1:1 to 9:1, or about 1.2: to 8:1. In some embodiments, the ratio of the first and second polymer is

from about 85:15 to about 55:45 percent by weight or about 84:16 to about 60:40 percent by weight. In some embodiments, the ratio by weight of the first polymer to the compound comprising at least one acidic moiety is from about 1:3 to about 1000:1, e.g., about 1:1 to about 10:1, or about 1.5:1. In some embodiments, the ratio by weight of the second polymer to the compound comprising at least one acidic moiety is from about 1:10 to about 250:1, e.g., from about 1:5 to about 5:1, or from about 1:3.5 to about 1:1.

In some embodiments the particle is substantially free of a targeting agent (e.g., of a targeting agent covalently linked to a component of the particle, e.g., to the first or second polymer or agent), e.g., a targeting agent able to bind to or otherwise associate with a target biological entity, e.g., a membrane component, a cell surface receptor, prostate specific membrane antigen, or the like. In some embodiments the particle is substantially free of a targeting agent that causes the particle to become localized to a tumor, a disease site, a tissue, an organ, a type of cell, e.g., a cancer cell, within the body of a subject to whom a therapeutically effective amount of the particle is administered. In some embodiments, the particle is substantially free of a targeting agent selected from nucleic acid aptamers, growth factors, hormones, cytokines, interleukins, antibodies, integrins, fibronectin receptors, p-glycoprotein receptors, peptides and cell binding sequences. In some embodiments, no polymer is conjugated to a targeting moiety. In an embodiment substantially free of a targeting agent means substantially free of any moiety other than the first polymer, the second polymer, a third polymer (if present), a surfactant (if present), and the agent, e.g., an anti-cancer agent or other therapeutic or diagnostic agent, that targets the particle. Thus, in such embodiments, any contribution to localization by the first polymer, the second polymer, a third polymer (if present), a surfactant (if present), and the agent is not considered to be "targeting." In an embodiment the particle is free of moieties added for the purpose of selectively targeting the particle to a site in a subject, e.g., by the use of a moiety on the particle having a high and specific affinity for a target in the subject.

In some embodiments the second polymer is other than a lipid, e.g., other than a phospholipid. In some embodiments the particle is substantially free of an

amphiphilic layer that reduces water penetration into the nanoparticle. In some embodiment the particle comprises less than 5 or 10% (e.g., as determined as w/w, v/v) of a lipid, e.g., a phospholipid. In some embodiments the particle is substantially free of a lipid layer, e.g., a phospholipid layer, e.g., that reduces water penetration into the nanoparticle. In some embodiments the particle is substantially free of lipid, e.g., is substantially free of phospholipid.

In some embodiments the therapeutic agent is covalently bound to a PLGA polymer.

In some embodiments the particle is substantially free of a radiopharmaceutical agent, e.g., a radiotherapeutic agent, radiodiagnostic agent, prophylactic agent, or other radioisotope. In some embodiments the particle is substantially free of an immunomodulatory agent, e.g., an immunostimulatory agent or immunosuppressive agent. In some embodiments the particle is substantially free of a vaccine or immunogen, e.g., a peptide, sugar, lipid-based immunogen, B cell antigen or T cell antigen. In some embodiments, the particle is substantially free of water soluble PLGA (e.g., PLGA having a weight average molecular weight of less than about 1 kDa).

In some embodiments, the ratio of the first polymer to the second polymer is such that the particle comprises at least 5%, 8%, 10%, 12%, 15%, 18%, 20%, 23%, 25%, or 30% by weight of a polymer having a hydrophobic portion and a hydrophilic portion.

In some embodiments, the zeta potential of the particle surface, when measured in water, is from about -80 mV to about 50 mV, e.g., about -50 mV to about 30 mV, about -20 mV to about 20 mV, or about -10 mV to about 10 mV. In some embodiments, the zeta potential of the particle surface, when measured in water, is neutral or slightly negative. In some embodiments, the zeta potential of the particle surface, when measured in water, is less than 0, e.g., about 0 mV to about -20 mV.

In some embodiments, the particle comprises less than 5000 ppm of a solvent (e.g., acetone, *tert*-butylmethyl ether, heptane, dichloromethane, dimethylformamide, ethyl acetate, acetonitrile, tetrahydrofuran, ethanol, methanol, isopropyl alcohol, methyl ethyl ketone, butyl acetate, or propyl acetate), (e.g., less than 4500 ppm, less

than 4000 ppm, less than 3500 ppm, less than 3000 ppm, less than 2500 ppm, less than 2000 ppm, less than 1500 ppm, less than 1000 ppm, less than 500 ppm, less than 250 ppm, less than 100 ppm, less than 50 ppm, less than 25 ppm, less than 10 ppm, less than 5 ppm, less than 2 ppm, or less than 1 ppm). In some embodiments, the particle is substantially free of a solvent (e.g., acetone, *tert*-butylmethyl ether, heptane, dichloromethane, dimethylformamide, ethyl acetate, acetonitrile, tetrahydrofuran, ethanol, methanol, isopropyl alcohol, methyl ethyl ketone, butyl acetate, or propyl acetate).

In some embodiments, the particle is substantially free of a class II or class III solvent as defined by the United States Department of Health and Human Services Food and Drug Administration "Q3c -Tables and List." In some embodiments, the particle comprises less than 5000 ppm of acetone. In some embodiments, the particle comprises less than 5000 ppm of *tert*-butylmethyl ether. In some embodiments, the particle comprises less than 5000 ppm of heptane. In some embodiments, the particle comprises less than 600 ppm of dichloromethane. In some embodiments, the particle comprises less than 880 ppm of dimethylformamide. In some embodiments, the particle comprises less than 5000 ppm of ethyl acetate. In some embodiments, the particle comprises less than 410 ppm of acetonitrile. In some embodiments, the particle comprises less than 720 ppm of tetrahydrofuran. In some embodiments, the particle comprises less than 5000 ppm of ethanol. In some embodiments, the particle comprises less than 3000 ppm of methanol. In some embodiments, the particle comprises less than 5000 ppm of isopropyl alcohol. In some embodiments, the particle comprises less than 5000 ppm of methyl ethyl ketone. In some embodiments, the particle comprises less than 5000 ppm of butyl acetate. In some embodiments, the particle comprises less than 5000 ppm of propyl acetate.

In some embodiments, a composition comprising a plurality of particles is substantially free of solvent.

In some embodiments, in a composition of a plurality of particles, the particles have an average diameter of from about 50 nm to about 500 nm (e.g., from about 50 to about 200 nm). In some embodiments, in a composition of a plurality of particles, the particles have a Dv50 (median particle size) from about 50 nm to about 220 nm

(e.g., from about 75 nm to about 200 nm). In some embodiments, in a composition of a plurality of particles, the particles have a Dv90 (particle size below which 90% of the volume of particles exists) of about 50 nm to about 500 nm (e.g., about 75 nm to about 220 nm).

In some embodiments, a single agent is attached to a single first polymer, e.g., to a terminal end of the polymer. In some embodiments, a plurality of agents are attached to a single first polymer (e.g., 2, 3, 4, 5, 6, or more). In some embodiments, the agents are the same agent. In some embodiments, the agents are different agents. In some embodiments, the agent is a diagnostic agent.

In some embodiments, the agent is a therapeutic agent. In some embodiments, the therapeutic agent is an anti-inflammatory agent. In some embodiments, the therapeutic agent is an anti-cancer agent. In some embodiments, the anti-cancer agent is an alkylating agent, a vascular disrupting agent, a microtubule targeting agent, a mitotic inhibitor, a topoisomerase inhibitor, an anti-angiogenic agent or an anti-metabolite. In some embodiments, the anti-cancer agent is a taxane (e.g., paclitaxel, docetaxel, larotaxel or cabazitaxel). In some embodiments, the anti-cancer agent is an anthracycline (e.g., doxorubicin). In some embodiments, the anti-cancer agent is a platinum-based agent (e.g., cisplatin). In some embodiments, the anti-cancer agent is a pyrimidine analog (e.g., gemcitabine).

In some embodiments, the anti-cancer agent is paclitaxel, attached to the polymer via the hydroxyl group at the 2' position, the hydroxyl group at the 1 position and/or the hydroxyl group at the 7 position. In some embodiments, the anti-cancer agent is paclitaxel, attached to the polymer via the hydroxyl group at the 2' position and/or the hydroxyl group at the 7 position.

In some embodiments, the anti-cancer agent is docetaxel, attached to the polymer via the hydroxyl group at the 2' position, the hydroxyl group at the 1 position, the hydroxyl group at the 7 position and/or the hydroxyl group at the 10 position. In some embodiments, the anti-cancer agent is docetaxel, attached to the polymer via the hydroxyl group at the 2' position, the hydroxyl group at the 7 position and/or the hydroxyl group at the 10 position.

In some embodiments, the anti-cancer agent is docetaxel-succinate.

In some embodiments, the anti-cancer agent is a taxane that is attached to the polymer via the hydroxyl group at the 7 position and has an acyl group or a hydroxy protecting group on the hydroxyl group at the 2' position (e.g., wherein the anti-cancer agent is a taxane such as paclitaxel, docetaxel, larotaxel or cabazitaxel). In some embodiments, the anti-cancer agent is larotaxel. In some embodiments, the anti-cancer agent is cabazitaxel.

In some embodiments, the anti-cancer agent is doxorubicin.

In some embodiments, the therapeutic agent is an agent for the treatment or prevention of cardiovascular disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the treatment of cardiovascular disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the prevention of cardiovascular disease, for example as described herein.

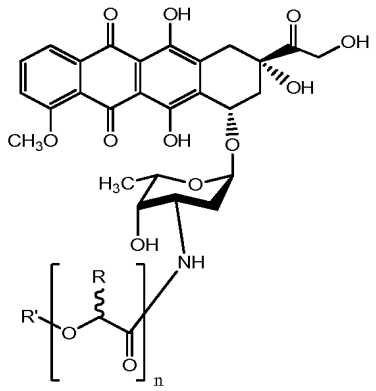
In some embodiments, the therapeutic agent is an agent for the treatment or prevention of an inflammatory or autoimmune disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the treatment of inflammatory or autoimmune disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the prevention of an inflammatory or autoimmune disease, for example as described herein.

In some embodiments, the agent is attached directly to the polymer, e.g., through a covalent bond. In some embodiments, the agent is attached to a terminal end of the polymer via an amide, ester, ether, amino, carbamate or carbonate bond. In some embodiments, the agent is attached to a terminal end of the polymer. In some embodiments, the polymer comprises one or more side chains and the agent is directly attached to the polymer through one or more of the side chains.

In some embodiments, a single agent is attached to the polymer. In some embodiments, multiple agents are attached to the polymer (e.g., 2, 3, 4, 5, 6 or more agents). In some embodiments, the agents are the same agent. In some embodiments, the agents are different agents.

In some embodiments, the agent is doxorubicin, and is covalently attached to the first polymer through an amide bond.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:

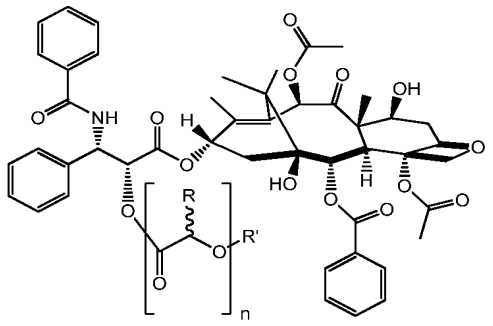


,

wherein about 30% to about 70%, 35% to about 65%, 40% to about 60%, 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, 35% to about 65%, 40% to about 60%, 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is paclitaxel, and is covalently attached to the polymer through an ester bond. In some embodiments, the agent is paclitaxel, and is attached to the polymer via the hydroxyl group at the 2' position.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:

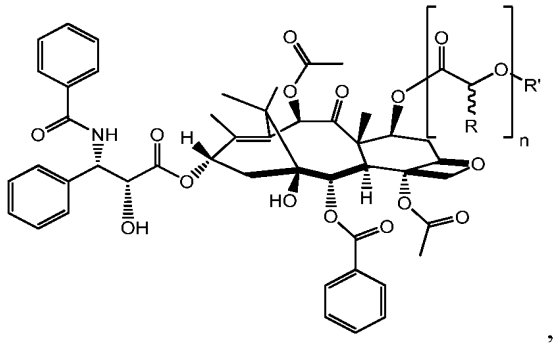


,

wherein about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, 40% to about 60%, 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is paclitaxel, and is attached to the polymer via the hydroxyl group at the 7 position.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:

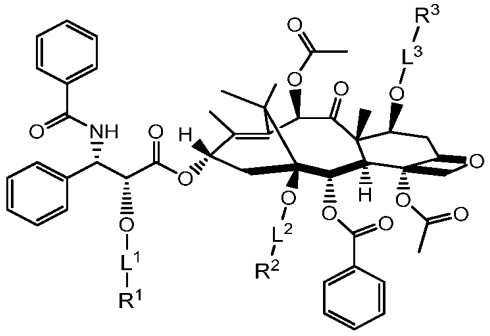


,

wherein about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the particle includes a combination of polymer-paclitaxel conjugates described herein, e.g., polymer-paclitaxel conjugates illustrated above.

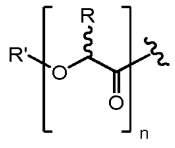
In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, has the following formula (I):



(I),

wherein L^1, L^2 and L^3 are each independently a bond or a linker, e.g., a linker described herein;

wherein R^1, R^2 and R^3 are each independently hydrogen, C_1-C_6 alkyl, acyl, or a polymer of formula (II):



(II),

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)); and

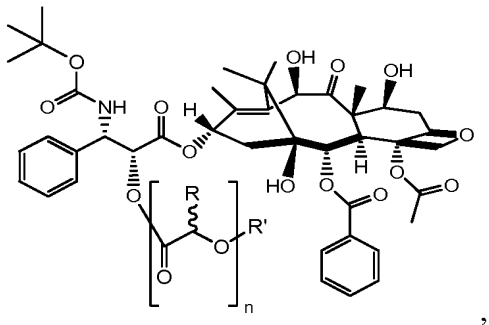
wherein at least one of R^1, R^2 and R^3 is a polymer of formula (II).

In some embodiments, L^2 is a bond and R^2 is hydrogen.

In some embodiments, the agent is paclitaxel, and is covalently attached to the polymer via a carbonate bond.

In some embodiments, the agent is docetaxel, and is covalently attached to the polymer through an ester bond. In some embodiments, the agent is docetaxel, and is attached to the polymer via the hydroxyl group at the 2' position.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:

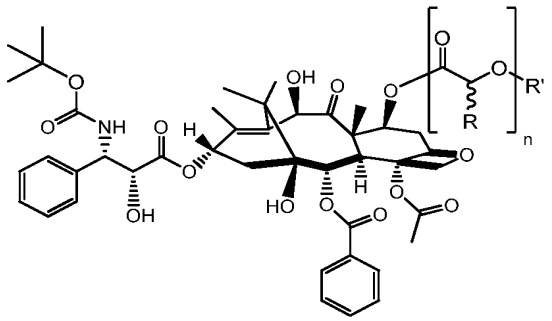


,

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is docetaxel, and is attached to the polymer via the hydroxyl group at the 7 position.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:

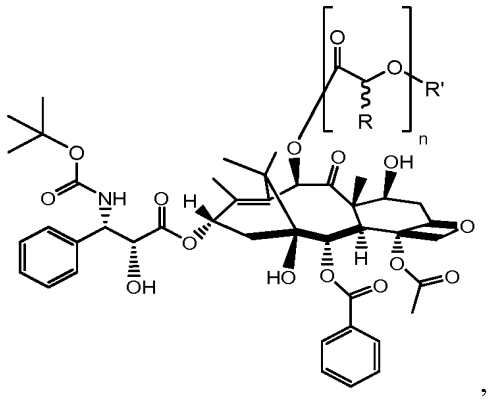


,

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is docetaxel, and is attached to the polymer via the hydroxyl group at the 10 position.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:



,

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about

45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

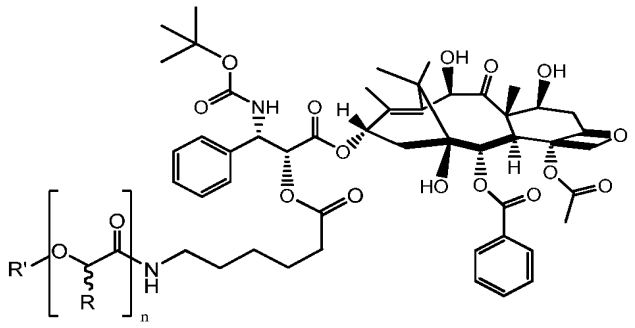
In some embodiments, the agent is docetaxel, and is covalently attached to the polymer through a carbonate bond.

In some embodiments, the particle includes a combination of polymer-docetaxel conjugates described herein, e.g., polymer-docetaxel conjugates illustrated above.

In some embodiments, the agent is attached to the polymer through a linker. In some embodiments, the linker is an alkanoate linker. In some embodiments, the linker is a PEG-based linker. In some embodiments, the linker comprises a disulfide bond. In some embodiments, the linker is a self-immolative linker. In some embodiments, the linker is an amino acid or a peptide (e.g., glutamic acid such as L-glutamic acid, D-glutamic acid, DL-glutamic acid or β-glutamic acid, branched glutamic acid or polyglutamic acid). In some embodiments, the linker is β-alanine glycolate.

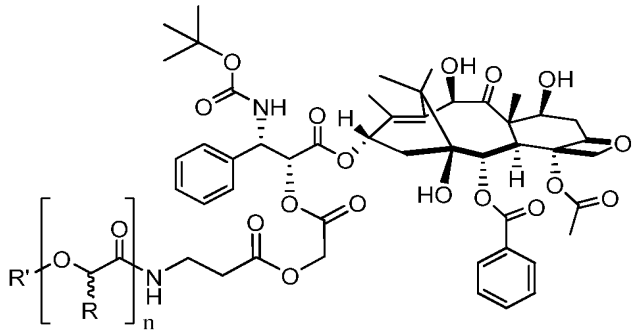
In some embodiments the linker is a multifunctional linker. In some embodiments, the multifunctional linker has 2, 3, 4, 5, 6 or more reactive moieties that may be functionalized with an agent. In some embodiments, all reactive moieties are functionalized with an agent. In some embodiments, not all of the reactive moieties are functionalized with an agent (e.g., the multifunctional linker has two reactive moieties, and only one reacts with an agent; or the multifunctional linker has four reactive moieties, and only one, two or three react with an agent.)

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:



wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

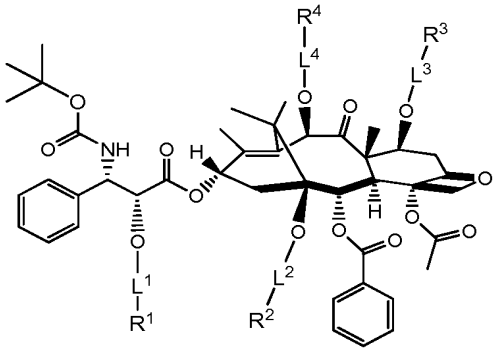
In some embodiments, the polymer-agent conjugate is:



wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g.,

from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

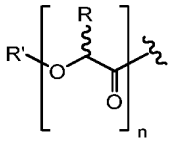
In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, has the following formula (III):



(III)

wherein L^1, L^2, L^3 and L^4 are each independently a bond or a linker, e.g., a linker described herein;

R^1, R^2, R^3 and R^4 are each independently hydrogen, C_1-C_6 alkyl, acyl, a hydroxy protecting group, or a polymer of formula (IV):



(IV)

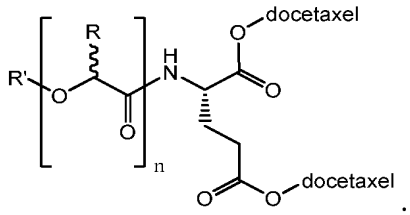
wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)); and

wherein at least one of R^1, R^2, R^3 and R^4 is a polymer of formula (IV).

In some embodiments, L^2 is a bond and R^2 is hydrogen.

In some embodiments, two agents are attached to a polymer via a multifunctional linker. In some embodiments, the two agents are the same agent. In some embodiments, the two agents are different agents. In some embodiments, the agent is docetaxel, and is covalently attached to the polymer via a glutamate linker.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:



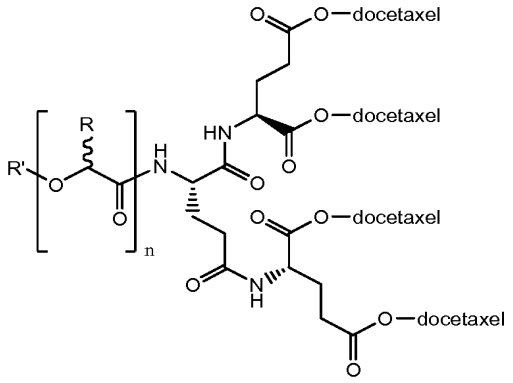
wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 2' position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 7 position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 10 position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 1 position. In some embodiments, each docetaxel is attached via the same hydroxyl group, e.g., the hydroxyl group at the 2' position, the hydroxyl group at the 7 position or the hydroxyl group at the 10 position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 2' position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 7 position. In some embodiments, each docetaxel is attached via the hydroxyl

group at the 10 position. In some embodiments, each docetaxel is attached via a different hydroxyl group, e.g., one docetaxel is attached via the hydroxyl group at the 2' position and the other is attached via the hydroxyl group at the 7 position.

In some embodiments, four agents are attached to a polymer via a multifunctional linker. In some embodiments, the four agents are the same agent. In some embodiments, the four agents are different agents. In some embodiments, the agent is docetaxel, and is covalently attached to the polymer via a tri(glutamate) linker.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:

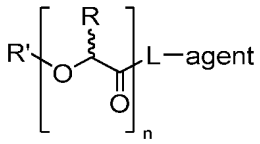


wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 2' position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 7 position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group

at the 10 position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 1 position. In some embodiments, each docetaxel is attached via the same hydroxyl group, e.g., the hydroxyl group at the 2' position, the hydroxyl group at the 7 position or the hydroxyl group at the 10 position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 2' position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 7 position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 10 position. In some embodiments, docetaxel molecules may be attached via different hydroxyl groups, e.g., three docetaxel molecules are attached via the hydroxyl group at the 2' position and the other is attached via the hydroxyl group at the 7 position.

In some embodiments, the polymer-agent conjugate has the following formula:



,

wherein L is a bond or linker, e.g., a linker described herein; and

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is a taxane, e.g., docetaxel, paclitaxel, larotaxel or cabazitaxel.

In some embodiments, L is a bond.

In some embodiments, L is a linker, e.g., a linker described herein.

In some embodiments, the particle comprises a plurality of polymer-agent conjugates. In some embodiments, the plurality of polymer-agent conjugates have the same polymer and the same agent, and differ in the nature of the linkage between the agent and the polymer. For example, in some embodiments, the polymer is PLGA, the agent is paclitaxel, and the plurality of polymer-agent conjugates includes PLGA polymers attached to paclitaxel via the hydroxyl group at the 2' position, and PLGA polymers attached to paclitaxel via the hydroxyl group at the 7 position. In some embodiments, the polymer is PLGA, the agent is paclitaxel, and the plurality of polymer-agent conjugates includes PLGA polymers attached to paclitaxel via the hydroxyl group at the 2' position, PLGA polymers attached to paclitaxel via the hydroxyl group at the 7 position, and/or PLGA polymers attached to paclitaxel via the hydroxyl group at the 1 position. In some embodiments, the polymer is PLGA, the agent is paclitaxel, and the plurality of polymer-agent conjugates includes paclitaxel molecules attached to more than one polymer chain, e.g., paclitaxel molecules with PLGA polymers attached to the hydroxyl group at the 2' position, the hydroxyl group at the 7 position and/or the hydroxyl group at the 1 position.

In some embodiments, the polymer is PLGA, the agent is docetaxel, and the plurality of polymer-agent conjugates includes PLGA attached to docetaxel via the hydroxyl group at the 2' position and PLGA attached to docetaxel via the hydroxyl group at the 7 position. In some embodiments, the polymer is PLGA, the agent is docetaxel, and the plurality of polymer-agent conjugates includes PLGA polymers attached to docetaxel via the hydroxyl group at the 2' position, PLGA polymers attached to docetaxel via the hydroxyl group at the 7 position, and/or PLGA polymers attached to docetaxel via the hydroxyl group at the 10 position. In some embodiments, the polymer is PLGA, the agent is docetaxel, and the plurality of polymer-agent conjugates includes PLGA polymers attached to docetaxel via the hydroxyl group at the 2' position, PLGA polymers attached to docetaxel via the hydroxyl group at the 7 position, PLGA polymers attached to docetaxel via the hydroxyl group at the 10 position and/or PLGA polymers attached to docetaxel via the hydroxyl group at the 1 position. In some embodiments, the polymer is PLGA, the agent is docetaxel, and the plurality of polymer-agent conjugates includes

docetaxel molecules attached to more than one polymer chain, e.g., docetaxel molecules with PLGA polymers attached to the hydroxyl group at the 2' position, the hydroxyl group at the 7 position, the hydroxyl group at the 10 position and/or the hydroxyl group at the 1 position.

In some embodiments, the plurality of polymer-agent conjugates have the same polymer and the same agent, but the agent may be attached to the polymer via different linkers. In some embodiments, the plurality of polymer-agent conjugates includes a polymer directly attached to an agent and a polymer attached to an agent via a linker. In an embodiment, one agent is released from one polymer-agent conjugate in the plurality with a first release profile and a second agent is released from a second polymer-agent conjugate in the plurality with a second release profile. E.g., a bond between the first agent and the first polymer is more rapidly broken than a bond between the second agent and the second polymer. E.g., the first polymer-agent conjugate can comprise a first linker linking the first agent to the first polymer and the second polymer-agent conjugate can comprise a second linker linking the second agent to the second polymer, wherein the linkers provide for different profiles for release of the first and second agents from their respective agent-polymer conjugates.

In some embodiments, the plurality of polymer-agent conjugates includes different polymers. In some embodiments, the plurality of polymer-agent conjugates includes different agents.

In some embodiments, the agent is present in the particle in an amount of from about 1 to about 30% by weight (e.g., from about 3 to about 30% by weight, from about 4 to about 25 % by weight, or from about 5 to about 13%, 14%, 15%, 16%, 17%, 18%, 19% or 20% by weight).

In an embodiment the particle comprises the enumerated elements.

In an embodiment the particle consists of the enumerated elements.

In an embodiment the particle consists essentially of the enumerated elements.

In another aspect, the invention features a particle. The particle comprises:

a first polymer,

a second polymer having a hydrophilic portion and a hydrophobic portion,

a first agent (e.g., a therapeutic or diagnostic agent) attached to the first polymer or second polymer to form a polymer-agent conjugate, and

a second agent embedded in the particle.

In some embodiments, the second agent embedded in the particle makes up from about 0.1 to about 10% by weight of the particle (e.g., about 0.5% wt., about 1% wt., about 2% wt., about 3% wt., about 4% wt., about 5% wt., about 6% wt., about 7% wt., about 8% wt., about 9% wt., about 10% wt.).

In some embodiments, the second agent embedded in the particle is substantially absent from the surface of the particle. In some embodiments, the second agent embedded in the particle is substantially uniformly distributed throughout the particle. In some embodiments, the second agent embedded in the particle is not uniformly distributed throughout the particle. In some embodiments, the particle includes hydrophobic pockets and the embedded second agent is concentrated in hydrophobic pockets of the particle.

In some embodiments, the second agent embedded in the particle forms one or more non-covalent interactions with a polymer in the particle. In some embodiments, the second agent forms one or more hydrophobic interactions with a hydrophobic polymer in the particle. In some embodiments, the second agent forms one or more hydrogen bonds with a polymer in the particle.

In some embodiments, the particle is a nanoparticle. In some embodiments, the nanoparticle has a diameter of less than or equal to about 220 nm (e.g., less than or equal to about 215 nm, 210 nm, 205 nm, 200 nm, 195 nm, 190 nm, 185 nm, 180 nm, 175 nm, 170 nm, 165 nm, 160 nm, 155 nm, 150 nm, 145 nm, 140 nm, 135 nm, 130 nm, 125 nm, 120 nm, 115 nm, 110 nm, 105 nm, 100 nm, 95 nm, 90 nm, 85 nm, 80 nm, 75 nm, 70 nm, 65 nm, 60 nm, 55 nm or 50 nm).

In some embodiments, the particle further comprises a compound comprising at least one acidic moiety, wherein the compound is a polymer or a small molecule.

In some embodiments, the compound comprising at least one acidic moiety is a polymer comprising an acidic group. In some embodiments, the compound comprising at least one acidic moiety is a hydrophobic polymer. In some

embodiments, the first polymer and the compound comprising at least one acidic moiety are the same polymer. In some embodiments, the compound comprising at least one acidic moiety is PLGA. In some embodiments, the ratio of lactic acid monomers to glycolic acid monomers in PLGA is from about 0.1:99.9 to about 99.9:0.1. In some embodiments, the ratio of lactic acid monomers to glycolic acid monomers in PLGA is from about 75:25 to about 25:75, e.g., about 60:40 to about 40:60 (e.g., about 50:50), about 60:40, or about 75:25. In some embodiments, the PLGA comprises a terminal hydroxyl group. In some embodiments, the PLGA comprises a terminal acyl group (e.g., an acetyl group).

In some embodiments, the weight average molecular weight of the compound comprising at least one acidic moiety is from about 1 kDa to about 20 kDa (e.g., from about 1 kDa to about 15 kDa, from about 2 kDa to about 12 kDa, from about 6 kDa to about 20 kDa, from about 5 kDa to about 15 kDa, from about 7 kDa to about 11 kDa, from about 5 kDa to about 10 kDa, from about 7 kDa to about 10 kDa, from about 5 kDa to about 7 kDa, from about 6 kDa to about 8 kDa, about 6 kDa, about 7 kDa, about 8 kDa, about 9 kDa, about 10 kDa, about 11 kDa, about 12 kDa, about 13 kDa, about 14 kDa, about 15 kDa, about 16 kDa or about 17 kDa). In some embodiments, the compound comprising at least one acidic moiety has a glass transition temperature of from about 20 °C to about 60 °C.

In some embodiments, the compound comprising at least one acidic moiety has a polymer polydispersity index of less than or equal to about 2.5 (e.g., less than or equal to about 2.2, or less than or equal to about 2.0). In some embodiments, the compound comprising at least one acidic moiety has a polymer polydispersity index of about 1.0 to about 2.5, e.g., from about 1.0 to about 2.0, from about 1.0 to about 1.8, from about 1.0 to about 1.7, or from about 1.0 to about 1.6.

In some embodiments, the particle comprises a plurality of compounds comprising at least one acidic moiety. For example, in some embodiments, one compound of the plurality of compounds comprising at least one acidic moiety is a PLGA polymer wherein the hydroxy terminus is functionalized with an acetyl group, and another compound in the plurality is a PLGA polymer wherein the hydroxy terminus is unfunctionalized.

In some embodiments, the percent by weight of the compound comprising at least one acidic moiety within the particle is up to about 50% (e.g., up to about 45% by weight, up to about 40% by weight, up to about 35% by weight, up to about 30% by weight, from about 0 to about 30% by weight, e.g., about 4.5%, about 9%, about 12%, about 15%, about 18%, about 20%, about 22%, about 24%, about 26%, about 28% or about 30%).

In some embodiments, the compound comprising at least one acidic moiety is a small molecule comprising an acidic group.

In some embodiments, the particle further comprises a surfactant. In some embodiments, the surfactant is PEG, PVA, PVP, poloxamer, a polysorbate, a polyoxyethylene ester, a PEG-lipid (e.g., PEG-ceramide, d-alpha-tocopheryl polyethylene glycol 1000 succinate), 1,2-Distearoyl-*sn*-Glycero-3-[Phospho-*rac*-(1-glycerol)] or lecithin. In some embodiments, the surfactant is PVA and the PVA is from about 3 kDa to about 50 kDa (e.g., from about 5 kDa to about 45 kDa, about 7 kDa to about 42 kDa, from about 9 kDa to about 30 kDa, or from about 11 to about 28 kDa) and up to about 98% hydrolyzed (e.g., about 75-95%, about 80-90% hydrolyzed, or about 85% hydrolyzed). In some embodiments, the surfactant is polysorbate 80. In some embodiments, the surfactant is Solutol® HS 15. In some embodiments, the surfactant is present in an amount of up to about 35% by weight of the particle (e.g., up to about 20% by weight or up to about 25% by weight, from about 15 % to about 35% by weight, from about 20% to about 30% by weight, or from about 23% to about 26% by weight).

In some embodiments, the particle further comprises a stabilizer or lyoprotectant, e.g., a stabilizer or lyoprotectant described herein. In some embodiments, the stabilizer or lyoprotectant is a carbohydrate (e.g., a carbohydrate described herein, such as, e.g., sucrose, cyclodextrin or a derivative of cyclodextrin (e.g. 2-hydroxypropyl-β-cyclodextrin)), salt, PEG, PVP or crown ether.

In some embodiments, the first agent and the second agent are the same agent (e.g., both the first and second agents are docetaxel). In some embodiments, the first agent and the second agent are different agents (e.g., one agent is docetaxel and the other is doxorubicin).

In some embodiments, the first agent is attached to the first polymer to form a polymer-agent conjugate. In some embodiments, first agent is attached to the second polymer to form a polymer-agent conjugate.

In some embodiments, the second agent is not covalently bound to the first or second polymer.

In an embodiment the amount of the first agent in the particle that is not attached to the first polymer is less than about 5% (e.g., less than about 2% or less than about 1%, e.g., in terms of w/w or number/number) of the amount of the first agent attached to the first polymer.

In some embodiments, the first polymer is a biodegradable polymer (e.g., PLA, PGA, PLGA, PCL, PDO, polyanhydrides, polyorthoesters or chitosan). In some embodiments, the first polymer is a hydrophobic polymer. In some embodiments, the percent by weight of the first polymer within the particle is from about 40% to about 90%, e.g., about 30% to about 70%. In some embodiments, the first polymer is PLA. In some embodiments, the first polymer is PGA.

In some embodiments, the first polymer is a copolymer of lactic and glycolic acid (e.g., PLGA). In some embodiments, the first polymer is a PLGA-ester. In some embodiments, the first polymer is a PLGA-lauryl ester. In some embodiments, the first polymer comprises a terminal free acid. In some embodiments, the first polymer comprises a terminal acyl group (e.g., an acetyl group). In some embodiments, the polymer comprises a terminal hydroxyl group. In some embodiments, the ratio of lactic acid monomers to glycolic acid monomers in PLGA is from about 0.1:99.9 to about 99.9:0.1. In some embodiments, the ratio of lactic acid monomers to glycolic acid monomers in PLGA is from about 75:25 to about 25:75, e.g., about 60:40 to about 40:60 (e.g., about 50:50), about 60:40, or about 75:25.

In some embodiments, the weight average molecular weight of the first polymer is from about 1 kDa to about 20 kDa (e.g., from about 1 kDa to about 15 kDa, from about 2 kDa to about 12 kDa, from about 6 kDa to about 20 kDa, from about 5 kDa to about 15 kDa, from about 7 kDa to about 11 kDa, from about 5 kDa to about 10 kDa, from about 7 kDa to about 10 kDa, from about 5 kDa to about 7 kDa, from about 6 kDa to about 8 kDa, about 6 kDa, about 7 kDa, about 8 kDa, about 9

kDa, about 10 kDa, about 11 kDa, about 12 kDa, about 13 kDa, about 14 kDa, about 15 kDa, about 16 kDa or about 17 kDa). In some embodiments, the first polymer has a glass transition temperature of from about 20 °C to about 60 °C. In some embodiments, the first polymer has a polymer polydispersity index of less than or equal to about 2.5 (e.g., less than or equal to about 2.2, or less than or equal to about 2.0). In some embodiments, the first polymer has a polymer polydispersity index of about 1.0 to about 2.5, e.g., from about 1.0 to about 2.0, from about 1.0 to about 1.8, from about 1.0 to about 1.7, or from about 1.0 to about 1.6.

In some embodiments, the percent by weight of the second polymer within the particle is up to about 50% by weight (e.g., from about 4 to any of about 50%, about 5%, about 8%, about 10%, about 15%, about 20%, about 23%, about 25%, about 30%, about 35%, about 40%, about 45% or about 50% by weight). For example, the percent by weight of the second polymer within the particle is from about 3% to 30%, from about 5% to 25% or from about 8% to 23%. In some embodiments, the second polymer has a hydrophilic portion and a hydrophobic portion. In some embodiments, the second polymer is a block copolymer. In some embodiments, the second polymer comprises two regions, the two regions together being at least about 70% by weight of the polymer (e.g., at least about 80%, at least about 90%, at least about 95%). In some embodiments, the second polymer is a block copolymer comprising a hydrophobic polymer and a hydrophilic polymer. In some embodiments, the second polymer is diblock copolymer comprising a hydrophobic polymer and a hydrophilic polymer. In some embodiments, the second polymer, e.g., a diblock copolymer, comprises a hydrophobic polymer and a hydrophilic polymer. In some embodiments, the second polymer, e.g., a triblock copolymer, comprises a hydrophobic polymer, a hydrophilic polymer and a hydrophobic polymer, e.g., PLA-PEG-PLA, PGA-PEG-PGA, PLGA-PEG-PLGA, PCL-PEG-PCL, PDO-PEG-PDO, PEG-PLGA-PEG, PLA-PEG-PGA, PGA-PEG-PLA, PLGA-PEG-PLA or PGA-PEG-PLGA.

In some embodiments, the hydrophobic portion of the second polymer is a biodegradable polymer (e.g., PLA, PGA, PLGA, PCL, PDO, polyanhydrides, polyorthoesters or chitosan). In some embodiments, the hydrophobic portion of the second polymer is PLA. In some embodiments, the hydrophobic portion of the

second polymer is PGA. In some embodiments, the hydrophobic portion of the second polymer is a copolymer of lactic and glycolic acid (e.g., PLGA). In some embodiments, the hydrophobic portion of the second polymer has a weight average molecular weight of from about 1 kDa to about 20 kDa (e.g., from about 1 kDa to about 18 kDa, 17 kDa, 16 kDa, 15 kDa, 14 kDa or 13 kDa, from about 2 kDa to about 12 kDa, from about 6 kDa to about 20 kDa, from about 5 kDa to about 18 kDa, from about 7 kDa to about 17 kDa, from about 8 kDa to about 13 kDa, from about 9 kDa to about 11 kDa, from about 10 kDa to about 14 kDa, from about 6 kDa to about 8 kDa, about 6 kDa, about 7 kDa, about 8 kDa, about 9 kDa, about 10 kDa, about 11 kDa, about 12 kDa, about 13 kDa, about 14 kDa, about 15 kDa, about 16 kDa or about 17 kDa).

In some embodiments, the hydrophilic polymer portion of the second polymer is PEG. In some embodiments, the hydrophilic portion of the second polymer has a weight average molecular weight of from about 1 kDa to about 21 kDa (e.g., from about 1 kDa to about 3 kDa, e.g., about 2 kDa, or from about 2 kDa to about 5 kDa, e.g., about 3.5 kDa, or from about 4 kDa to about 6 kDa, e.g., about 5 kDa). In some embodiments, the ratio of weight average molecular weight of the hydrophilic to hydrophobic polymer portions of the second polymer is from about 1:1 to about 1:20 (e.g., about 1:4 to about 1:10, about 1:4 to about 1:7, about 1:3 to about 1:7, about 1:3 to about 1:6, about 1:4 to about 1:6.5 (e.g., 1:4, 1:4.5, 1:5, 1:5.5, 1:6, 1:6.5) or about 1:1 to about 1:4 (e.g., about 1:1.4, 1:1.8, 1:2, 1:2.4, 1:2.8, 1:3, 1:3.2, 1:3.5 or 1:4). In one embodiment, the hydrophilic portion of the second polymer has a weight average molecular weight of from about 2 kDa to 3.5 kDa and the ratio of the weight average molecular weight of the hydrophilic to hydrophobic portions of the second polymer is from about 1:4 to about 1:6.5 (e.g., 1:4, 1:4.5, 1:5, 1:5.5, 1:6, 1:6.5). In one embodiment, the hydrophilic portion of the second polymer has a weight average molecular weight of from about 4 kDa to 6 kDa (e.g., 5 kDa) and the ratio of the weight average molecular weight of the hydrophilic to hydrophobic portions of the second polymer is from about 1:1 to about 1:3.5 (e.g., about 1:1.4, 1:1.8, 1:2, 1:2.4, 1:2.8, 1:3, 1:3.2, or 1:3.5).

In some embodiments, the hydrophilic polymer portion of the second polymer has a terminal hydroxyl moiety. In some embodiments, the hydrophilic polymer portion of the second polymer has a terminal alkoxy moiety. In some embodiments, the hydrophilic polymer portion of the second polymer is a methoxy PEG (e.g., a terminal methoxy PEG). In some embodiments, the hydrophilic polymer portion of the second polymer does not have a terminal alkoxy moiety. In some embodiments, the terminus of the hydrophilic polymer portion of the second polymer is conjugated to a hydrophobic polymer, e.g., to make a triblock copolymer.

In some embodiments, the hydrophilic polymer portion of the second polymer comprises a terminal conjugate. In some embodiments, the terminal conjugate is a targeting agent or a dye. In some embodiments, the terminal conjugate is a folate or a rhodamine. In some embodiments, the terminal conjugate is a targeting peptide (e.g., an RGD peptide).

In some embodiments, the hydrophilic polymer portion of the second polymer is attached to the hydrophobic polymer portion through a covalent bond. In some embodiments, the hydrophilic polymer is attached to the hydrophobic polymer through an amide, ester, ether, amino, carbamate, or carbonate bond (e.g., an ester or an amide).

In some embodiments, the ratio by weight of the first to the second polymer is from about 1:1 to about 20:1, e.g., about 1:1 to about 10:1, e.g., about 1:1 to 9:1, or about 1.2: to 8:1. In some embodiments, the ratio of the first and second polymer is from about 85:15 to about 55:45 percent by weight or about 84:16 to about 60:40 percent by weight. In some embodiments, the ratio by weight of the first polymer to the compound comprising at least one acidic moiety is from about 1:3 to about 1000:1, e.g., about 1:1 to about 10:1, or about 1.5:1. In some embodiments, the ratio by weight of the second polymer to the compound comprising at least one acidic moiety is from about 1:10 to about 250:1, e.g., from about 1:5 to about 5:1, or from about 1:3.5 to about 1:1.

In some embodiments the particle is substantially free of a targeting agent (e.g., of a targeting agent covalently linked to a component of the particle, e.g., to the first or second polymer or agent), e.g., a targeting agent able to bind to or otherwise

associate with a target biological entity, e.g., a membrane component, a cell surface receptor, prostate specific membrane antigen, or the like. In some embodiments the particle is substantially free of a targeting agent that causes the particle to become localized to a tumor, a disease site, a tissue, an organ, a type of cell, e.g., a cancer cell, within the body of a subject to whom a therapeutically effective amount of the particle is administered. In some embodiments, the particle is substantially free of a targeting agent selected from nucleic acid aptamers, growth factors, hormones, cytokines, interleukins, antibodies, integrins, fibronectin receptors, p-glycoprotein receptors, peptides and cell binding sequences. In some embodiments, no polymer is conjugated to a targeting moiety. In an embodiment substantially free of a targeting agent means substantially free of any moiety other than the first polymer, the second polymer, a third polymer (if present), a surfactant (if present), and the agent, e.g., an anti-cancer agent or other therapeutic or diagnostic agent, that targets the particle. Thus, in such embodiments, any contribution to localization by the first polymer, the second polymer, a third polymer (if present), a surfactant (if present), and the agent is not considered to be "targeting." In an embodiment the particle is free of moieties added for the purpose of selectively targeting the particle to a site in a subject, e.g., by the use of a moiety on the particle having a high and specific affinity for a target in the subject.

In some embodiments the second polymer is other than a lipid, e.g., other than a phospholipid. In some embodiments the particle is substantially free of an amphiphilic layer that reduces water penetration into the nanoparticle. In some embodiment the particle comprises less than 5 or 10% (e.g., as determined as w/w, v/v) of a lipid, e.g., a phospholipid. In some embodiments the particle is substantially free of a lipid layer, e.g., a phospholipid layer, e.g., that reduces water penetration into the nanoparticle. In some embodiments the particle is substantially free of lipid, e.g., is substantially free of phospholipid.

In some embodiments the first agent is covalently bound to a PLGA polymer.

In some embodiments the particle is substantially free of a radiopharmaceutical agent, e.g., a radiotherapeutic agent, radiodiagnostic agent, prophylactic agent, or other radioisotope. In some embodiments the particle is

substantially free of an immunomodulatory agent, e.g., an immunostimulatory agent or immunosuppressive agent. In some embodiments the particle is substantially free of a vaccine or immunogen, e.g., a peptide, sugar, lipid-based immunogen, B cell antigen or T cell antigen. In some embodiments, the particle is substantially free of water soluble PLGA (e.g., PLGA having a weight average molecular weight of less than about 1 kDa).

In some embodiments, the ratio of the first polymer to the second polymer is such that the particle comprises at least 5%, 8%, 10%, 12%, 15%, 18%, 20%, 23%, 25% or 30% by weight of a polymer having a hydrophobic portion and a hydrophilic portion.

In some embodiments, the zeta potential of the particle surface, when measured in water, is from about -80 mV to about 50 mV, e.g., about -50 mV to about 30 mV, about -20 mV to about 20 mV, or about -10 mV to about 10 mV. In some embodiments, the zeta potential of the particle surface, when measured in water, is neutral or slightly negative. In some embodiments, the zeta potential of the particle surface, when measured in water, is less than 0, e.g., about 0 mV to about -20 mV.

In some embodiments, the particle comprises less than 5000 ppm of a solvent (e.g., acetone, *tert*-butylmethyl ether, heptane, dichloromethane, dimethylformamide, ethyl acetate, acetonitrile, tetrahydrofuran, ethanol, methanol, isopropyl alcohol, methyl ethyl ketone, butyl acetate, or propyl acetate), e.g., less than 4500 ppm, less than 4000 ppm, less than 3500 ppm, less than 3000 ppm, less than 2500 ppm, less than 2000 ppm, less than 1500 ppm, less than 1000 ppm, less than 500 ppm, less than 250 ppm, less than 100 ppm, less than 50 ppm, less than 25 ppm, less than 10 ppm, less than 5 ppm, less than 2 ppm, or less than 1 ppm). In some embodiments, the particle is substantially free of a solvent (e.g., acetone, *tert*-butylmethyl ether, heptane, dichloromethane, dimethylformamide, ethyl acetate, acetonitrile, tetrahydrofuran, ethanol, methanol, isopropyl alcohol, methyl ethyl ketone, butyl acetate, or propyl acetate).

In some embodiments, the particle is substantially free of a class II or class III solvent as defined by the United States Department of Health and Human Services Food and Drug Administration "Q3c -Tables and List." In some embodiments, the

particle comprises less than 5000 ppm of acetone. In some embodiments, the particle comprises less than 5000 ppm of *tert*-butylmethyl ether. In some embodiments, the particle comprises less than 5000 ppm of heptane. In some embodiments, the particle comprises less than 600 ppm of dichloromethane. In some embodiments, the particle comprises less than 880 ppm of dimethylformamide. In some embodiments, the particle comprises less than 5000 ppm of ethyl acetate. In some embodiments, the particle comprises less than 410 ppm of acetonitrile. In some embodiments, the particle comprises less than 720 ppm of tetrahydrofuran. In some embodiments, the particle comprises less than 5000 ppm of ethanol. In some embodiments, the particle comprises less than 3000 ppm of methanol. In some embodiments, the particle comprises less than 5000 ppm of isopropyl alcohol. In some embodiments, the particle comprises less than 5000 ppm of methyl ethyl ketone. In some embodiments, the particle comprises less than 5000 ppm of butyl acetate. In some embodiments, the particle comprises less than 5000 ppm of propyl acetate.

In some embodiments, a composition comprising a plurality of particles is substantially free of solvent.

In some embodiments, in a composition of a plurality of particles, the particles have an average diameter of from about 50 to about 500 nm (e.g., from about 50 to about 200 nm). In some embodiments, in a composition of a plurality of particles, the particles have a Dv50 (median particle size) from about 50 nm to about 220 nm (e.g., from about 75 nm to about 200 nm). In some embodiments, in a composition of a plurality of particles, the particles have a Dv90 (particle size below which 90% of the volume of particles exists) of about 50 nm to about 500 nm (e.g., about 75 nm to about 220 nm).

In some embodiments, a single first agent is attached to a single first polymer, e.g., to a terminal end of the polymer. In some embodiments, a plurality of first agents are attached to a single first polymer (e.g., 2, 3, 4, 5, 6, or more). In some embodiments, the first agent is a diagnostic agent.

In some embodiments, the first agent is a therapeutic agent. In some embodiments, the therapeutic agent is an anti-inflammatory agent. In some embodiments, the therapeutic agent is an anti-cancer agent. In some embodiments,

the anti-cancer agent is an alkylating agent, a vascular disrupting agent, a microtubule targeting agent, a mitotic inhibitor, a topoisomerase inhibitor, an anti-angiogenic agent, or an anti-metabolite. In some embodiments, the anti-cancer agent is a taxane (e.g., paclitaxel, docetaxel, larotaxel or cabazitaxel). In some embodiments, the anti-cancer agent is an anthracycline (e.g., doxorubicin). In some embodiments, the anti-cancer agent is a platinum-based agent (e.g., cisplatin). In some embodiments, the anti-cancer agent is a pyrimidine analog (e.g., gemcitabine).

In some embodiments, the anti-cancer agent is paclitaxel, attached to the first polymer via the hydroxyl group at the 2' position, the hydroxyl group at the 1 position and/or the hydroxyl group at the 7 position. In some embodiments, the anti-cancer agent is paclitaxel, attached to the first polymer via the hydroxyl group at the 2' position and/or the hydroxyl group at the 7 position.

In some embodiments, the anti-cancer agent is docetaxel, attached to the first polymer via the hydroxyl group at the 2' position, the hydroxyl group at the 7 position, the hydroxyl group at the 10 position, and/or the hydroxyl group at the 1 position. In some embodiments, the anti-cancer agent is docetaxel, attached to the first polymer via the hydroxyl group at the 2' position, the hydroxyl group at the 7 position and/or the hydroxyl group at the 10 position.

In some embodiments, the anti-cancer agent is docetaxel-succinate.

In some embodiments, the anti-cancer agent is a taxane that is attached to the polymer via the hydroxyl group at the 7 position and has an acyl group or a hydroxy protecting group on the hydroxyl group at the 2' position (e.g., wherein the anti-cancer agent is a taxane such as paclitaxel, docetaxel, larotaxel or cabazitaxel). In some embodiments, the anti-cancer agent is larotaxel. In some embodiments, the anti-cancer agent is cabazitaxel.

In some embodiments, the anti-cancer agent is doxorubicin.

In some embodiments, the therapeutic agent is an agent for the treatment or prevention of cardiovascular disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the treatment of cardiovascular disease, for example as described herein. In some embodiments, the therapeutic agent

is an agent for the prevention of cardiovascular disease, for example as described herein.

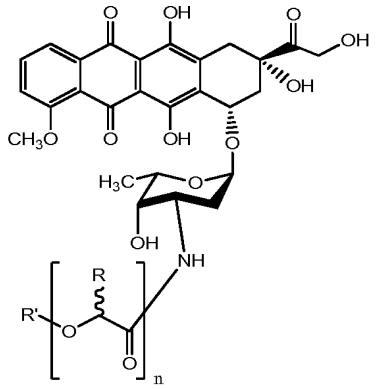
In some embodiments, the therapeutic agent is an agent for the treatment or prevention of an inflammatory or autoimmune disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the treatment of inflammatory or autoimmune disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the prevention of an inflammatory or autoimmune disease, for example as described herein.

In some embodiments, the agent is attached directly to the polymer, e.g., through a covalent bond. In some embodiments, the agent is attached to a terminal end of the polymer via an amide, ester, ether, amino, carbamate or carbonate bond. In some embodiments, the agent is attached to a terminal end of the polymer. In some embodiments, the polymer comprises one or more side chains and the agent is directly attached to the polymer through one or more of the side chains.

In some embodiments, the first agent is attached to the first polymer to form a polymer-agent conjugate. In some embodiments, a single first agent is attached to the first polymer. In some embodiments, multiple agents are attached to the first polymer (e.g., 2, 3, 4, 5, 6 or more agents). In some embodiments, the agents are the same agent. In some embodiments, the agents are different agents.

In some embodiments, the agent is doxorubicin, and is covalently attached to the first polymer through an amide bond.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:

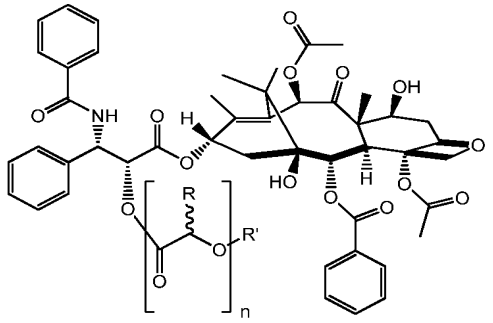


,

wherein about 30% to about 70%, 35% to about 65%, 40% to about 60%, 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, 35% to about 65%, 40% to about 60%, 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the therapeutic agent is paclitaxel, and is covalently attached to the first polymer through an ester bond. In some embodiments, the agent is paclitaxel, and is attached to the polymer via the hydroxyl group at the 2' position.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:

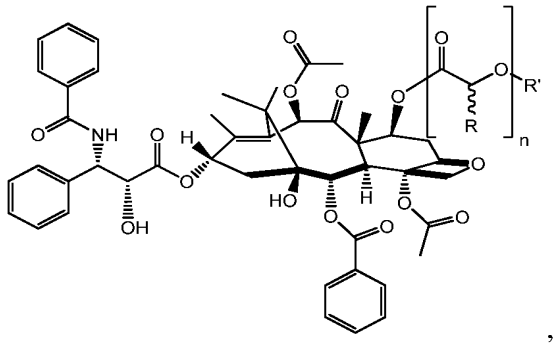


,

wherein about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, 40% to about 60%, 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is paclitaxel, and is attached to the polymer via the hydroxyl group at the 7 position.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:

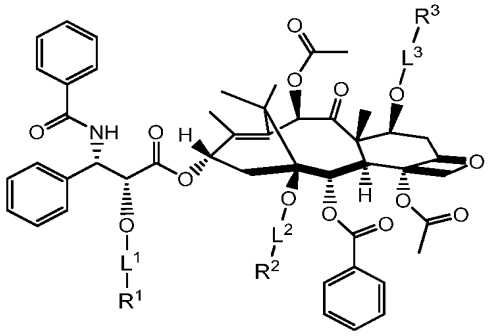


,

wherein about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the particle includes a combination of polymer-paclitaxel conjugates described herein, e.g., polymer-paclitaxel conjugates illustrated above.

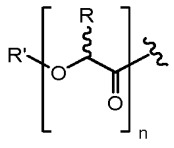
In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, has the following formula (I):



(I),

wherein L^1, L^2 and L^3 are each independently a bond or a linker, e.g., a linker described herein;

wherein R^1, R^2 and R^3 are each independently hydrogen, C_1-C_6 alkyl, acyl, or a polymer of formula (II):



(II),

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)); and

wherein at least one of R^1, R^2 and R^3 is a polymer of formula (II).

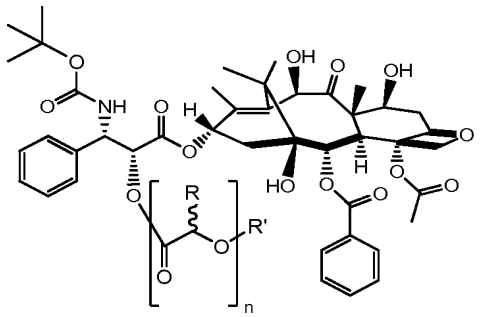
In some embodiments, L^2 is a bond and R^2 is hydrogen.

In some embodiments, the therapeutic agent is paclitaxel, and is covalently attached to the first polymer via a carbonate bond.

In some embodiments, the therapeutic agent is docetaxel, and is covalently attached to the first polymer through an ester bond.

In some embodiments, the agent is docetaxel, and is attached to the polymer via the hydroxyl group at the 2' position.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:

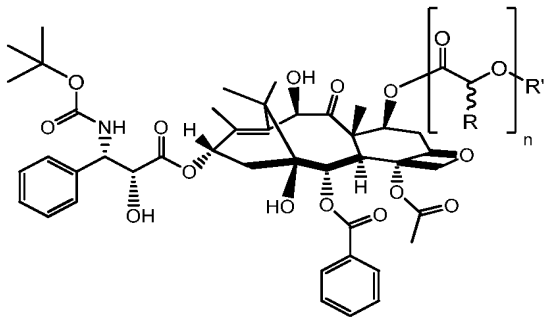


,

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is docetaxel, and is attached to the polymer via the hydroxyl group at the 7 position.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:



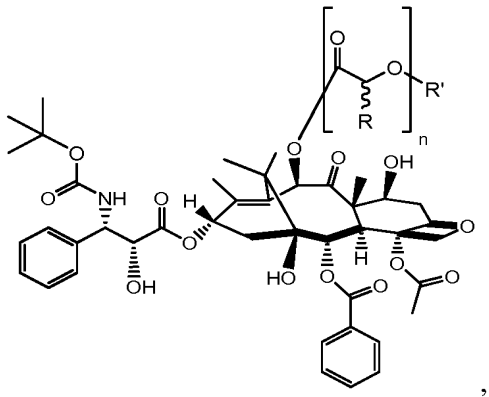
,

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about

77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is docetaxel, and is attached to the polymer via the hydroxyl group at the 10 position.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:



,

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

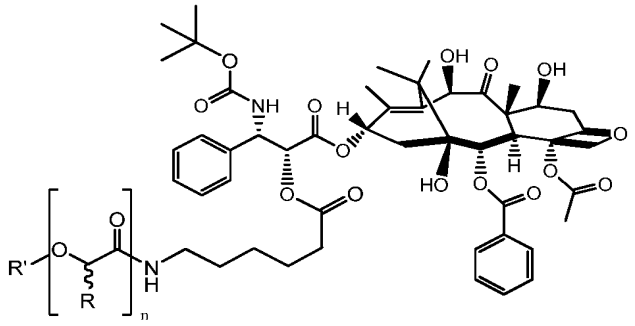
In some embodiments, the agent is docetaxel, and is covalently attached to the first polymer through a carbonate bond.

In some embodiments, the particle includes a combination of polymer-docetaxel conjugates described herein, e.g., polymer-docetaxel conjugates illustrated above.

In some embodiments, the agent is attached to the polymer through a linker. In some embodiments, the linker is an alkanoate linker. In some embodiments, the linker is a PEG-based linker. In some embodiments, the linker comprises a disulfide bond. In some embodiments, the linker is a self-immolative linker. In some embodiments, the linker is an amino acid or a peptide (e.g., glutamic acid such as L-glutamic acid, D-glutamic acid, DL-glutamic acid or β-glutamic acid, branched glutamic acid or polyglutamic acid). In some embodiments, the linker is β-alanine glycolate.

In some embodiments the linker is a multifunctional linker. In some embodiments, the multifunctional linker has 2, 3, 4, 5, 6 or more reactive moieties that may be functionalized with an agent. In some embodiments, all reactive moieties are functionalized with an agent. In some embodiments, not all of the reactive moieties are functionalized with an agent (e.g., the multifunctional linker has two reactive moieties, and only one reacts with an agent; or the multifunctional linker has four reactive moieties, and only one, two or three react with an agent.)

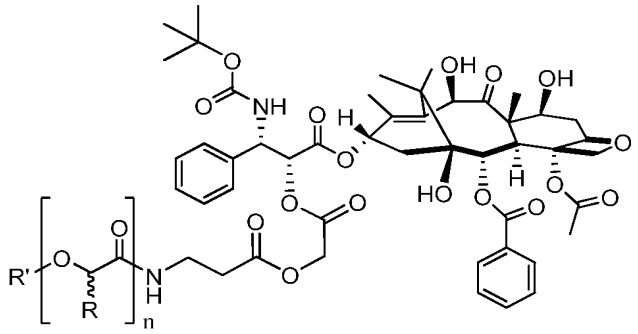
In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:



wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g.,

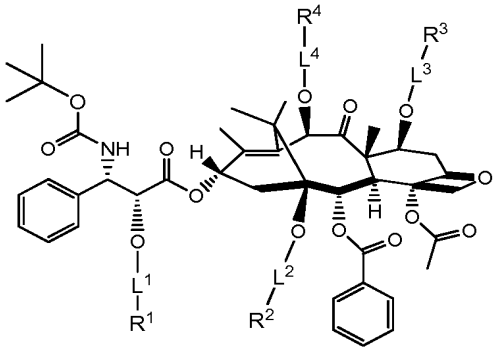
from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the polymer-agent conjugate is:



wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

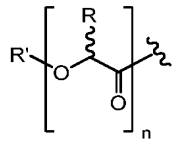
In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, has the following formula (III):



(III)

wherein L^1, L^2, L^3 and L^4 are each independently a bond or a linker, e.g., a linker described herein;

R^1, R^2, R^3 and R^4 are each independently hydrogen, C_1-C_6 alkyl, acyl, a hydroxy protecting group, or a polymer of formula (IV):



(IV)

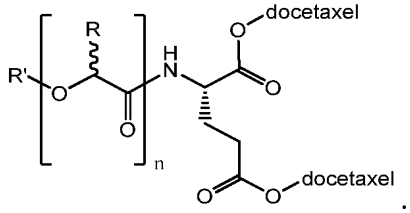
wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)); and

wherein at least one of R^1, R^2, R^3 and R^4 is a polymer of formula (IV).

In some embodiments, L^2 is a bond and R^2 is hydrogen.

In some embodiments, two agents are attached to a polymer via a multifunctional linker. In some embodiments, the two agents are the same agent. In some embodiments, the two agents are different agents. In some embodiments, the agent is docetaxel, and is covalently attached to the polymer via a glutamate linker.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:



.

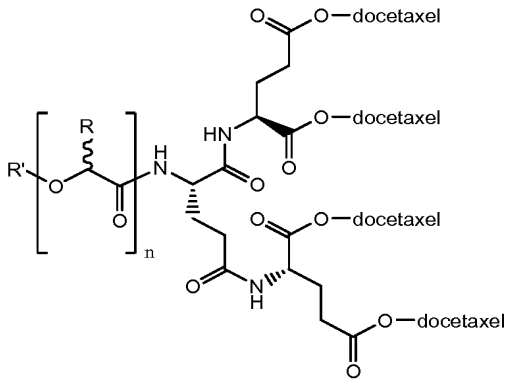
wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and

acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 2' position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 7 position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 10 position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 1 position. In some embodiments, each docetaxel is attached via the same hydroxyl group, e.g., the hydroxyl group at the 2' position, the hydroxyl group at the 7 position or the hydroxyl group at the 10 position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 2' position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 7 position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 10 position. In some embodiments, each docetaxel is attached via a different hydroxyl group, e.g., one docetaxel is attached via the hydroxyl group at the 2' position and the other is attached via the hydroxyl group at the 7 position.

In some embodiments, four agents are attached to a polymer via a multifunctional linker. In some embodiments, the four agents are the same agent. In some embodiments, the four agents are different agents. In some embodiments, the agent is docetaxel, and is covalently attached to the polymer via a tri(glutamate) linker.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:

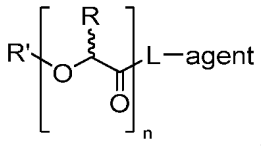


wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 2' position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 7 position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 10 position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 1 position. In some embodiments, each docetaxel is attached via the same hydroxyl group, e.g., the hydroxyl group at the 2' position, the hydroxyl group at the 7 position or the hydroxyl group at the 10 position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 2' position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 7 position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 10 position. In some embodiments, docetaxel molecules may be attached via different hydroxyl groups, e.g., three docetaxel molecules are attached via the

hydroxyl group at the 2' position and the other is attached via the hydroxyl group at the 7 position.

In some embodiments, the polymer-agent conjugate has the following formula:



,

wherein L is a bond or linker, e.g., a linker described herein; and

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is a taxane, e.g., docetaxel, paclitaxel, larotaxel or cabazitaxel.

In some embodiments, L is a bond.

In some embodiments, L is a linker, e.g., a linker described herein.

In some embodiments, the particle comprises a plurality of polymer-agent conjugates. In some embodiments, the plurality of polymer-agent conjugates have the same polymer and the same agent, and differ in the nature of the linkage between the agent and the polymer. For example, in some embodiments, the polymer is PLGA, the agent is paclitaxel, and the plurality of polymer-agent conjugates includes PLGA polymers attached to paclitaxel via the hydroxyl group at the 2' position, and PLGA polymers attached to paclitaxel via the hydroxyl group at the 7 position. In some embodiments, the polymer is PLGA, the agent is paclitaxel, and the plurality of polymer-agent conjugates includes PLGA polymers attached to paclitaxel via the

hydroxyl group at the 2' position, PLGA polymers attached to paclitaxel via the hydroxyl group at the 7 position, and/or PLGA polymers attached to paclitaxel via the hydroxyl group at the 1 position. In some embodiments, the polymer is PLGA, the agent is paclitaxel, and the plurality of polymer-agent conjugates includes paclitaxel molecules attached to more than one polymer chain, e.g., paclitaxel molecules with PLGA polymers attached to the hydroxyl group at the 2' position, the hydroxyl group at the 7 position and/or the hydroxyl group at the 1 position.

In some embodiments, the polymer is PLGA, the agent is docetaxel, and the plurality of polymer-agent conjugates includes PLGA attached to docetaxel via the hydroxyl group at the 2' position and PLGA attached to docetaxel via the hydroxyl group at the 7 position. In some embodiments, the polymer is PLGA, the agent is docetaxel, and the plurality of polymer-agent conjugates includes PLGA polymers attached to docetaxel via the hydroxyl group at the 2' position, PLGA polymers attached to docetaxel via the hydroxyl group at the 7 position, and/or PLGA polymers attached to docetaxel via the hydroxyl group at the 10 position. In some embodiments, the polymer is PLGA, the agent is docetaxel, and the plurality of polymer-agent conjugates includes PLGA polymers attached to docetaxel via the hydroxyl group at the 2' position, PLGA polymers attached to docetaxel via the hydroxyl group at the 7 position, PLGA polymers attached to docetaxel via the hydroxyl group at the 10 position and/or PLGA polymers attached to docetaxel via the hydroxyl group at the 1 position. In some embodiments, the polymer is PLGA, the agent is docetaxel, and the plurality of polymer-agent conjugates includes docetaxel molecules attached to more than one polymer chain, e.g., docetaxel molecules with PLGA polymers attached to the hydroxyl group at the 2' position, the hydroxyl group at the 7 position, the hydroxyl group at the 10 position and/or the hydroxyl group at the 1 position.

In some embodiments, the plurality of polymer-agent conjugates have the same polymer and the same agent, but the agent may be attached to the polymer via different linkers. In some embodiments, the plurality of polymer-agent conjugates includes a polymer directly attached to an agent and a polymer attached to an agent via a linker. In an embodiment, one agent is released from one polymer-agent

conjugate in the plurality with a first release profile and a second agent is released from a second polymer-agent conjugate in the plurality with a second release profile. E.g., a bond between the first agent and the first polymer is more rapidly broken than a bond between the second agent and the second polymer. E.g., the first polymer-agent conjugate can comprise a first linker linking the first agent to the first polymer and the second polymer-agent conjugate can comprise a second linker linking the second agent to the second polymer, wherein the linkers provide for different profiles for release of the first and second agents from their respective agent-polymer conjugates.

In some embodiments, the plurality of polymer-agent conjugates includes different polymers. In some embodiments, the plurality of polymer-agent conjugates includes different agents.

In some embodiments, the first agent is present in the particle in an amount of from about 1 to about 30% by weight (e.g., from about 3 to about 30% by weight, from about 4 to about 25 % by weight, or from about 5 to about 13%, 14%, 15%, 16%, 17%, 18%, 19% or 20% by weight).

In some embodiments, the second agent is a diagnostic agent. In some embodiments, the second agent is a therapeutic agent. In some embodiments, the therapeutic agent is in the form of a salt (e.g., an insoluble salt). In some embodiments, the therapeutic agent is a salt of doxorubicin (e.g., a tosylate salt of doxorubicin). In some embodiments, the therapeutic agent is in the form of a prodrug (i.e., the prodrug releases the therapeutic agent *in vivo*). In some embodiments, the prodrug of the therapeutic agent is conjugated to a hydrophobic moiety that is cleaved in vivo (e.g., a polymer or oligomer).

In some embodiments, the second agent is an anti-inflammatory agent. In some embodiments, the second agent is an anti-cancer agent. In some embodiments, the anti-cancer agent is an alkylating agent, a vascular disrupting agent, a microtubule targeting agent, a mitotic inhibitor, a topoisomerase inhibitor, an anti-angiogenic agent or an anti-metabolite. In some embodiments, the anti-cancer agent is a taxane (e.g., paclitaxel, docetaxel, larotaxel or cabazitaxel). In some embodiments, the anti-cancer agent is an anthracycline (e.g., doxorubicin). In some embodiments, the anti-

cancer agent is a platinum-based agent (e.g., cisplatin). In some embodiments, the anti-cancer agent is a pyrimidine analog (e.g., gemcitabine).

In some embodiments, the anti-cancer agent is paclitaxel. In some embodiments, the anti-cancer agent is docetaxel. In some embodiments, the anti-cancer agent is docetaxel-succinate. In some embodiments, the anti-cancer agent is selected from doxorubicin, doxorubicin hexanoate and doxorubicin hydrazone hexanoate. In some embodiments, the anti-cancer agent is larotaxel. In some embodiments, the anti-cancer agent is cabazitaxel. In some embodiments, the anti-cancer agent is selected from gemcitabine, 5FU and cisplatin or a prodrug thereof.

In some embodiments, the second agent is an agent for the treatment or prevention of cardiovascular disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the treatment of cardiovascular disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the prevention of cardiovascular disease, for example as described herein.

In some embodiments, the second agent is an agent for the treatment or prevention of an inflammatory or autoimmune disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the treatment of inflammatory or autoimmune disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the prevention of an inflammatory or autoimmune disease, for example as described herein.

In some embodiments, the first agent is docetaxel and the second agent is doxorubicin.

In some embodiments, at least about 50% of the second agent is embedded in the particle (e.g., embedded in the first polymer, second polymer, and/or compound comprising at least one acidic moiety). In some embodiments, substantially all of the second agent is embedded in the particle (e.g., embedded in the first polymer, second polymer, and/or compound comprising at least one acidic moiety).

In an embodiment the particle comprises the enumerated elements.

In an embodiment the particle consists of the enumerated elements.

In an embodiment the particle consists essentially of the enumerated elements.

In another aspect, the invention features a particle. The particle comprises:

a first polymer,

a second polymer having a hydrophilic portion and a hydrophobic portion, and

an agent (e.g., a therapeutic or diagnostic agent) embedded in the particle.

In some embodiments, the agent embedded in the particle makes up from about 0.1 to about 10% by weight of the particle (e.g., about 0.5% wt., about 1% wt., about 2% wt., about 3% wt., about 4% wt., about 5% wt., about 6% wt., about 7% wt., about 8% wt., about 9% wt., about 10% wt.).

In some embodiments, the agent is substantially absent from the surface of the particle. In some embodiments, the agent is substantially uniformly distributed throughout the particle. In some embodiments, the agent is not uniformly distributed throughout the particle. In some embodiments, the particle includes hydrophobic pockets and the agent is concentrated in hydrophobic pockets of the particle.

In some embodiments, the agent forms one or more non-covalent interactions with a polymer in the particle. In some embodiments, the agent forms one or more hydrophobic interactions with a hydrophobic polymer in the particle. In some embodiments, the agent forms one or more hydrogen bonds with a polymer in the particle.

In some embodiments, the agent is not covalently bound to the first or second polymer.

In some embodiments, the particle is a nanoparticle. In some embodiments, the nanoparticle has a diameter of less than or equal to about 220 nm (e.g., less than or equal to about 215 nm, 210 nm, 205 nm, 200 nm, 195 nm, 190 nm, 185 nm, 180 nm, 175 nm, 170 nm, 165 nm, 160 nm, 155 nm, 150 nm, 145 nm, 140 nm, 135 nm, 130 nm, 125 nm, 120 nm, 115 nm, 110 nm, 105 nm, 100 nm, 95 nm, 90 nm, 85 nm, 80 nm, 75 nm, 70 nm, 65 nm, 60 nm, 55 nm or 50 nm).

In some embodiments, the particle further comprises a surfactant. In some embodiments, the surfactant is PEG, PVA, PVP, poloxamer, a polysorbate, a polyoxyethylene ester, a PEG-lipid (e.g., PEG-ceramide, d-alpha-tocopheryl polyethylene glycol 1000 succinate), 1,2-Distearoyl-*sn*-Glycero-3-[Phospho-*rac*-(1-

glycerol)] or lecithin. In some embodiments, the surfactant is PVA and the PVA is from about 3 kDa to about 50 kDa (e.g., from about 5 kDa to about 45 kDa, about 7 kDa to about 42 kDa, from about 9 kDa to about 30 kDa, or from about 11 to about 28 kDa) and up to about 98% hydrolyzed (e.g., about 75-95%, about 80-90% hydrolyzed, or about 85% hydrolyzed). In some embodiments, the surfactant is polysorbate 80. In some embodiments, the surfactant is Solutol® HS 15. In some embodiments, the surfactant is present in an amount of up to about 35% by weight of the particle (e.g., up to about 20% by weight or up to about 25% by weight, from about 15 % to about 35% by weight, from about 20% to about 30% by weight, or from about 23% to about 26% by weight).

In some embodiments, the particle further comprises a stabilizer or lyoprotectant, e.g., a stabilizer or lyoprotectant described herein. In some embodiments, the stabilizer or lyoprotectant is a carbohydrate (e.g., a carbohydrate described herein, such as, e.g., sucrose, cyclodextrin or a derivative of cyclodextrin (e.g. 2-hydroxypropyl-β-cyclodextrin)), salt, PEG, PVP or crown ether.

In some embodiments, the first polymer is a biodegradable polymer (e.g., PLA, PGA, PLGA, PCL, PDO, polyanhydrides, polyorthoesters or chitosan). In some embodiments, the first polymer is a hydrophobic polymer. In some embodiments, the percent by weight of the first polymer within the particle is from about 40% to about 90%. In some embodiments, the first polymer is PLA. In some embodiments, the first polymer is PGA.

In some embodiments, the first polymer is a copolymer of lactic and glycolic acid (e.g., PLGA). In some embodiments, the first polymer is a PLGA-ester. In some embodiments, the first polymer is a PLGA-lauryl ester. In some embodiments, the first polymer comprises a terminal free acid. In some embodiments, the first polymer comprises a terminal acyl group (e.g., an acetyl group). In some embodiments, the polymer comprises a terminal hydroxyl group. In some embodiments, the ratio of lactic acid monomers to glycolic acid monomers in PLGA is from about 0.1:99.9 to about 99.9:0.1. In some embodiments, the ratio of lactic acid monomers to glycolic acid monomers in PLGA is from about 75:25 to about 25:75, e.g., about 60:40 to about 40:60 (e.g., about 50:50), about 60:40, or about 75:25.

In some embodiments, the weight average molecular weight of the first polymer is from about 1 kDa to about 20 kDa (e.g., from about 1 kDa to about 15 kDa, from about 2 kDa to about 12 kDa, from about 6 kDa to about 20 kDa, from about 5 kDa to about 15 kDa, from about 7 kDa to about 11 kDa, from about 5 kDa to about 10 kDa, from about 7 kDa to about 10 kDa, from about 5 kDa to about 7 kDa, from about 6 kDa to about 8 kDa, about 6 kDa, about 7 kDa, about 8 kDa, about 9 kDa, about 10 kDa, about 11 kDa, about 12 kDa, about 13 kDa, about 14 kDa, about 15 kDa, about 16 kDa or about 17 kDa). In some embodiments, the first polymer has a glass transition temperature of from about 20 °C to about 60 °C. In some embodiments, the first polymer has a polymer polydispersity index of less than or equal to about 2.5 (e.g., less than or equal to about 2.2, or less than or equal to about 2.0). In some embodiments, the first polymer has a polymer polydispersity index of about 1.0 to about 2.5, e.g., from about 1.0 to about 2.0, from about 1.0 to about 1.8, from about 1.0 to about 1.7, or from about 1.0 to about 1.6.

In some embodiments, the percent by weight of the second polymer within the particle is up to about 50% by weight (e.g., from about 4 to any of about 50%, about 5%, about 8%, about 10%, about 15%, about 20%, about 23%, about 25%, about 30%, about 35%, about 40%, about 45% or about 50% by weight). For example, the percent by weight of the second polymer within the particle is from about 3% to 30%, from about 5% to 25% or from about 8% to 23%. In some embodiments, the second polymer has a hydrophilic portion and a hydrophobic portion. In some embodiments, the second polymer is a block copolymer. In some embodiments, the second polymer comprises two regions, the two regions together being at least about 70% by weight of the polymer (e.g., at least about 80%, at least about 90%, at least about 95%). In some embodiments, the second polymer is a block copolymer comprising a hydrophobic polymer and a hydrophilic polymer. In some embodiments, the second polymer is diblock copolymer comprising a hydrophobic polymer and a hydrophilic polymer. In some embodiments, the second polymer, e.g., a diblock copolymer, comprises a hydrophobic polymer and a hydrophilic polymer. In some embodiments, the second polymer, e.g., a triblock copolymer, comprises a hydrophobic polymer, a hydrophilic polymer and a hydrophobic polymer, e.g., PLA-PEG-PLA, PGA-PEG-

PGA, PLGA-PEG-PLGA, PCL-PEG-PCL, PDO-PEG-PDO, PEG-PLGA-PEG, PLA-PEG-PGA, PGA-PEG-PLA, PLGA-PEG-PLA or PGA-PEG-PLGA.

In some embodiments, the hydrophobic portion of the second polymer is a biodegradable polymer (e.g., PLA, PGA, PLGA, PCL, PDO, polyanhydrides, polyorthoesters or chitosan). In some embodiments, the hydrophobic portion of the second polymer is PLA. In some embodiments, the hydrophobic portion of the second polymer is PGA. In some embodiments, the hydrophobic portion of the second polymer is a copolymer of lactic and glycolic acid (e.g., PLGA). In some embodiments, the hydrophobic portion of the second polymer has a weight average molecular weight of from about 1 kDa to about 20 kDa (e.g., from about 1 kDa to about 18 kDa, 17 kDa, 16 kDa, 15 kDa, 14 kDa or 13 kDa, from about 2 kDa to about 12 kDa, from about 6 kDa to about 20 kDa, from about 5 kDa to about 18 kDa, from about 7 kDa to about 17 kDa, from about 8 kDa to about 13 kDa, from about 9 kDa to about 11 kDa, from about 10 kDa to about 14 kDa, from about 6 kDa to about 8 kDa, about 6 kDa, about 7 kDa, about 8 kDa, about 9 kDa, about 10 kDa, about 11 kDa, about 12 kDa, about 13 kDa, about 14 kDa, about 15 kDa, about 16 kDa or about 17 kDa).

In some embodiments, the hydrophilic polymer portion of the second polymer is PEG. In some embodiments, the hydrophilic portion of the second polymer has a weight average molecular weight of from about 1 kDa to about 21 kDa (e.g., from about 1 kDa to about 3 kDa, e.g., about 2 kDa, or from about 2 kDa to about 5 kDa, e.g., about 3.5 kDa, or from about 4 kDa to about 6 kDa, e.g., about 5 kDa). In some embodiments, the ratio of weight average molecular weight of the hydrophilic to hydrophobic polymer portions of the second polymer is from about 1:1 to about 1:20 (e.g., about 1:4 to about 1:10, about 1:4 to about 1:7, about 1:3 to about 1:7, about 1:3 to about 1:6, about 1:4 to about 1:6.5 (e.g., 1:4, 1:4.5, 1:5, 1:5.5, 1:6, 1:6.5) or about 1:1 to about 1:4 (e.g., about 1:1.4, 1:1.8, 1:2, 1:2.4, 1:2.8, 1:3, 1:3.2, 1:3.5 or 1:4). In one embodiment, the hydrophilic portion of the second polymer has a weight average molecular weight of from about 2 kDa to 3.5 kDa and the ratio of the weight average molecular weight of the hydrophilic to hydrophobic portions of the second polymer is from about 1:4 to about 1:6.5 (e.g., 1:4, 1:4.5, 1:5, 1:5.5, 1:6, 1:6.5). In one

embodiment, the hydrophilic portion of the second polymer has a weight average molecular weight of from about 4 kDa to 6 kDa (e.g., 5 kDa) and the ratio of the weight average molecular weight of the hydrophilic to hydrophobic portions of the second polymer is from about 1:1 to about 1:3.5 (e.g., about 1:1.4, 1:1.8, 1:2, 1:2.4, 1:2.8, 1:3, 1:3.2, or 1:3.5).

In some embodiments, the hydrophilic polymer portion of the second polymer has a terminal hydroxyl moiety. In some embodiments, the hydrophilic polymer portion of the second polymer has a terminal alkoxy moiety. In some embodiments, the hydrophilic polymer portion of the second polymer is a methoxy PEG (e.g., a terminal methoxy PEG). In some embodiments, the hydrophilic polymer portion of the second polymer does not hae a terminal alkoxy moiety. In some embodiments, the terminus of the hydrophilic polymer portion of the second polymer is conjugated to a hydrophobic polymer, e.g., to make a triblock copolymer.

In some embodiments, the hydrophilic polymer portion of the second polymer comprises a terminal conjugate. In some embodiments, the terminal conjugate is a targeting agent or a dye. In some embodiments, the terminal conjugate is a folate or a rhodamine. In some embodiments, the terminal conjugate is a targeting peptide (e.g., an RGD peptide).

In some embodiments, the hydrophilic polymer portion of the second polymer is attached to the hydrophobic polymer portion through a covalent bond. In some embodiments, the hydrophilic polymer is attached to the hydrophobic polymer through an amide, ester, ether, amino, carbamate, or carbonate bond (e.g., an ester or an amide).

In some embodiments, the ratio of the first and second polymer is from about 1:1 to about 20:1, e.g., about 1:1 to about 10:1, e.g., about 1:1 to 9:1, or about 1.2: to 8:1. In some embodiments, the ratio of the first and second polymer is from about 85:15 to about 55:45 percent by weight or about 84:16 to about 60:40 percent by weight.

In some embodiments the particle is substantially free of a targeting agent (e.g., of a targeting agent covalently linked to a component of the particle, e.g., to the first or second polymer or agent), e.g., a targeting agent able to bind to or otherwise

associate with a target biological entity, e.g., a membrane component, a cell surface receptor, prostate specific membrane antigen, or the like. In some embodiments the particle is substantially free of a targeting agent that causes the particle to become localized to a tumor, a disease site, a tissue, an organ, a type of cell, e.g., a cancer cell, within the body of a subject to whom a therapeutically effective amount of the particle is administered. In some embodiments, the particle is substantially free of a targeting agent selected from nucleic acid aptamers, growth factors, hormones, cytokines, interleukins, antibodies, integrins, fibronectin receptors, p-glycoprotein receptors, peptides and cell binding sequences. In some embodiments, no polymer is conjugated to a targeting moiety. In an embodiment substantially free of a targeting agent means substantially free of any moiety other than the first polymer, the second polymer, a surfactant (if present), and the agent, e.g., an anti-cancer agent or other therapeutic or diagnostic agent, that targets the particle. Thus, in such embodiments, any contribution to localization by the first polymer, the second polymer, a surfactant (if present), and the agent is not considered to be "targeting." In an embodiment the particle is free of moieties added for the purpose of selectively targeting the particle to a site in a subject, e.g., by the use of a moiety on the particle having a high and specific affinity for a target in the subject.

In some embodiments the second polymer is other than a lipid, e.g., other than a phospholipid. In some embodiments the particle is substantially free of an amphiphilic layer that reduces water penetration into the nanoparticle. In some embodiment the particle comprises less than 5 or 10% (e.g., as determined as w/w, v/v) of a lipid, e.g., a phospholipid. In some embodiments the particle is substantially free of a lipid layer, e.g., a phospholipid layer, e.g., that reduces water penetration into the nanoparticle. In some embodiments the particle is substantially free of lipid, e.g., is substantially free of phospholipid.

In some embodiments the particle is substantially free of a radiopharmaceutical agent, e.g., a radiotherapeutic agent, radiodiagnostic agent, prophylactic agent, or other radioisotope. In some embodiments the particle is substantially free of an immunomodulatory agent, e.g., an immunostimulatory agent or immunosuppressive agent. In some embodiments the particle is substantially free

of a vaccine or immunogen, e.g., a peptide, sugar, lipid-based immunogen, B cell antigen or T cell antigen. In some embodiments, the particle is substantially free of water soluble PLGA (e.g., PLGA having a weight average molecular weight of less than about 1 kDa).

In some embodiments, the ratio of the first polymer to the second polymer is such that the particle comprises at least 5%, 8%, 10%, 12%, 15%, 18%, 20%, 23%, 25%, or 30% by weight of a polymer having a hydrophobic portion and a hydrophilic portion.

In some embodiments, the zeta potential of the particle surface, when measured in water, is from about -80 mV to about 50 mV, e.g., about -50 mV to about 30 mV, about -20 mV to about 20 mV, or about -10 mV to about 10 mV. In some embodiments, the zeta potential of the particle surface, when measured in water, is neutral or slightly negative. In some embodiments, the zeta potential of the particle surface, when measured in water, is less than 0, e.g., about 0 mV to about -20 mV.

In some embodiments, the particle comprises less than 5000 ppm of a solvent (e.g., acetone, *tert*-butylmethyl ether, heptane, dichloromethane, dimethylformamide, ethyl acetate, acetonitrile, tetrahydrofuran, ethanol, methanol, isopropyl alcohol, methyl ethyl ketone, butyl acetate, or propyl acetate), e.g., less than 4500 ppm, less than 4000 ppm, less than 3500 ppm, less than 3000 ppm, less than 2500 ppm, less than 2000 ppm, less than 1500 ppm, less than 1000 ppm, less than 500 ppm, less than 250 ppm, less than 100 ppm, less than 50 ppm, less than 25 ppm, less than 10 ppm, less than 5 ppm, less than 2 ppm, or less than 1 ppm). In some embodiments, the particle is substantially free of a solvent (e.g., acetone, *tert*-butylmethyl ether, heptane, dichloromethane, dimethylformamide, ethyl acetate, acetonitrile, tetrahydrofuran, ethanol, methanol, isopropyl alcohol, methyl ethyl ketone, butyl acetate, or propyl acetate).

In some embodiments, the particle is substantially free of a class II or class III solvent as defined by the United States Department of Health and Human Services Food and Drug Administration "Q3c -Tables and List." In some embodiments, the particle comprises less than 5000 ppm of acetone. In some embodiments, the particle comprises less than 5000 ppm of *tert*-butylmethyl ether. In some embodiments, the

particle comprises less than 5000 ppm of heptane. In some embodiments, the particle comprises less than 600 ppm of dichloromethane. In some embodiments, the particle comprises less than 880 ppm of dimethylformamide. In some embodiments, the particle comprises less than 5000 ppm of ethyl acetate. In some embodiments, the particle comprises less than 410 ppm of acetonitrile. In some embodiments, the particle comprises less than 720 ppm of tetrahydrofuran. In some embodiments, the particle comprises less than 5000 ppm of ethanol. In some embodiments, the particle comprises less than 3000 ppm of methanol. In some embodiments, the particle comprises less than 5000 ppm of isopropyl alcohol. In some embodiments, the particle comprises less than 5000 ppm of methyl ethyl ketone. In some embodiments, the particle comprises less than 5000 ppm of butyl acetate. In some embodiments, the particle comprises less than 5000 ppm of propyl acetate.

In some embodiments, a composition comprising a plurality of particles is substantially free of solvent.

In some embodiments, in a composition of a plurality of particles, the particles have an average diameter of from about 50 to about 500 nm (e.g., from about 50 to about 200 nm). In some embodiments, in a composition of a plurality of particles, the particles have a Dv50 (median particle size) from about 50 nm to about 220 nm (e.g., from about 75 nm to about 200 nm). In some embodiments, in a composition of a plurality of particles, the particles have a Dv90 (particle size below which 90% of the volume of particles exists) of about 50 nm to about 500 nm (e.g., about 75 nm to about 220 nm).

In some embodiments, the agent is a diagnostic agent. In some embodiments, the agent is a therapeutic agent. In some embodiments, the therapeutic agent is in the form of a salt (e.g., an insoluble salt). In some embodiments, the therapeutic agent is a salt of doxorubicin (e.g., a tosylate salt of doxorubicin). In some embodiments, the therapeutic agent is in the form of a prodrug (i.e., the prodrug releases the therapeutic agent *in vivo*).

In some embodiments, the therapeutic agent is an anti-inflammatory agent. In some embodiments, the therapeutic agent is an anti-cancer agent. In some embodiments, the anti-cancer agent is an alkylating agent, a vascular disrupting agent,

a microtubule targeting agent, a mitotic inhibitor, a topoisomerase inhibitor, an anti-angiogenic agent, or an anti-metabolite. In some embodiments, the anti-cancer agent is a taxane (e.g., paclitaxel, docetaxel, larotaxel or cabazitaxel). In some embodiments, the anti-cancer agent is an anthracycline (e.g., doxorubicin). In some embodiments, the anti-cancer agent is a platinum-based agent (e.g., cisplatin). In some embodiments, the anti-cancer agent is a pyrimidine analog (e.g., gemcitabine). In some embodiments, the anti-cancer agent is selected from gemcitabine, 5FU and cisplatin or a prodrug thereof. In some embodiments, the anti-cancer agent is docetaxel-succinate. In some embodiments, the anti-cancer agent is selected from doxorubicin hexanoate and doxorubicin hydrazone hexanoate.

In some embodiments, the therapeutic agent is an agent for the treatment or prevention of cardiovascular disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the treatment of cardiovascular disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the prevention of cardiovascular disease, for example as described herein.

In some embodiments, the therapeutic agent is an agent for the treatment or prevention of an inflammatory or autoimmune disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the treatment of inflammatory or autoimmune disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the prevention of an inflammatory or autoimmune disease, for example as described herein.

In some embodiments, the agent is present in the particle in an amount of from about 1 to about 30% by weight (e.g., from about 3 to about 30% by weight, from about 4 to about 25 % by weight, or from about 5 to about 13%, 14%, 15%, 16%, 17%, 18%, 19% or 20% by weight).

In some embodiments, at least about 50% of the agent is embedded in the particle (e.g., embedded in the first polymer and/or the second polymer). In some embodiments, substantially all of the agent is embedded in particle (e.g., embedded in the first polymer and/or the second polymer).

In an embodiment the particle comprises the enumerated elements.

In an embodiment the particle consists of the enumerated elements.

In an embodiment the particle consists essentially of the enumerated elements.

In another aspect, the invention features a particle. The particle comprises:

a first polymer and a second polymer;

a first agent and a second agent, wherein the first agent is attached to the first polymer to form a first polymer-agent conjugate, and the second agent is attached to the second polymer to form a second polymer-agent conjugate; and

a third polymer, the third polymer comprising a hydrophilic portion and a hydrophobic portion.

In some embodiments, the particle is a nanoparticle. In some embodiments, the nanoparticle has a diameter of less than or equal to about 220 nm (e.g., less than or equal to about 215 nm, 210 nm, 205 nm, 200 nm, 195 nm, 190 nm, 185 nm, 180 nm, 175 nm, 170 nm, 165 nm, 160 nm, 155 nm, 150 nm, 145 nm, 140 nm, 135 nm, 130 nm, 125 nm, 120 nm, 115 nm, 110 nm, 105 nm, 100 nm, 95 nm, 90 nm, 85 nm, 80 nm, 75 nm, 70 nm, 65 nm, 60 nm, 55 nm or 50 nm).

In some embodiments, the first polymer is a PLGA polymer. In some embodiments, the second polymer is a PLGA polymer. In some embodiments, both the first and second polymers are PLGA polymers.

In some embodiments, the first agent is a therapeutic agent (e.g., an anti-cancer agent). In some embodiments, the second agent is a therapeutic agent (e.g., an anti-cancer agent). In some embodiments, the first and second agent have the same chemical structure. In some embodiments, the first agent and second agent have the same chemical structure and are attached to the respective polymers via the same point of attachment. In some embodiments, the first agent and second agent have the same chemical structure and are attached to the respective polymers through different points of attachment. In some embodiments, the first and second agent have different chemical structures.

In some embodiments, the particle has one or more of the following properties:

it further comprises a compound comprising at least one acidic moiety, wherein the compound is a polymer or a small molecule;

it further comprises a surfactant;

the first or second polymer is a PLGA polymer, wherein the ratio of lactic acid to glycolic acid is from about 25:75 to about 75:25;

the first or second polymer is a PLGA polymer, and the weight average molecular weight of the first polymer is from about 1 to about 20 kDa, e.g., is about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 kDa; or

the ratio of the combined first and second polymer to the third polymer is such that the particle comprises at least 5%, 10%, 15%, 20%, 25% by weight of a polymer having a hydrophobic portion and a hydrophilic portion.

In an embodiment the first agent is attached to a first polymer, the second agent is attached to a second polymer and:

the first and second agents are the same, e.g., the same anti-cancer agent;

the first and second agents are the same, e.g., the same anti-cancer agent, and the first and second polymers are different from one another. E.g., the first and second polymers differ by molecular weight, subunit composition (e.g., the first and second polymers are PLGA polymers having different ratios of ratio of lactic acid monomers to glycolic acid monomers), or subunit identity, e.g. a chitosan polymer and a PLGA polymer;

the first and second agents are different agents, e.g., two different anti-cancer agents;

the first and second agents are different agents, e.g., two different anti-cancer agents, and the first and second polymers have the same structure, e.g., they are the same PLGA polymer;

the first and second agents are different agents, e.g., two different anti-cancer agents, and the first and second polymers are different from one another. E.g., the first and second polymers differ by molecular weight, subunit composition (e.g., the first and second polymers are PLGA polymers having different ratios of ratio of lactic acid monomers to glycolic acid monomers), or subunit identity, e.g. a chitosan polymer and a PLGA polymer;

In an embodiment the first agent is released from the first polymer-agent conjugate with a first release profile and the second agent is released from the second polymer-agent conjugate with a second release profile. E.g., a bond between the first agent and the first polymer is more rapidly broken than a bond between the second agent and the second polymer. E.g., the first polymer-agent conjugate can comprise a first linker (e.g., a linker or a bond) linking the first agent to the first polymer and the second polymer-agent conjugate can comprise a second linker (e.g., a linker or a bond) linking the second agent to the second polymer, wherein the linkers provide for different profiles for release of the first and second agents from their respective agent-polymer conjugates. As described above, the first and second agents can differ or be the same. Similarly, the first and second polymers can differ or be the same. Thus, the release profile of one or more agents can be optimized.

In some embodiments, the particle further comprises a compound comprising at least one acidic moiety, wherein the compound is a polymer or a small molecule.

In some embodiments, the compound comprising at least one acidic moiety is a polymer comprising an acidic group. In some embodiments, the compound comprising at least one acidic moiety is a hydrophobic polymer. In some embodiments, the first polymer and the compound comprising at least one acidic moiety are the same polymer. In some embodiments, the compound comprising at least one acidic moiety is PLGA. In some embodiments, the ratio of lactic acid monomers to glycolic acid monomers in PLGA is from about 0.1:99.9 to about 99.9:0.1. In some embodiments, the ratio of lactic acid monomers to glycolic acid monomers in PLGA is from about 75:25 to about 25:75, e.g., about 60:40 to about 40:60 (e.g., about 50:50), about 60:40, or about 75:25. In some embodiments, the PLGA comprises a terminal hydroxyl group. In some embodiments, the PLGA comprises a terminal acyl group (e.g., an acetyl group).

In some embodiments, the weight average molecular weight of the compound comprising at least one acidic moiety is from about 1 kDa to about 20 kDa (e.g., from about 1 kDa to about 15 kDa, from about 2 kDa to about 12 kDa, from about 6 kDa to about 20 kDa, from about 5 kDa to about 15 kDa, from about 7 kDa to about 11 kDa, from about 5 kDa to about 10 kDa, from about 7 kDa to about 10 kDa, from about 5

kDa to about 7 kDa, from about 6 kDa to about 8 kDa, about 6 kDa, about 7 kDa, about 8 kDa, about 9 kDa, about 10 kDa, about 11 kDa, about 12 kDa, about 13 kDa, about 14 kDa, about 15 kDa, about 16 kDa or about 17 kDa). In some embodiments, the compound comprising at least one acidic moiety has a glass transition temperature of from about 20 ℃ to about 60 ℃.

In some embodiments, the compound comprising at least one acidic moiety has a polymer polydispersity index of less than or equal to about 2.5 (e.g., less than or equal to about 2.2, or less than or equal to about 2.0). In some embodiments, the compound comprising at least one acidic moiety has a polymer polydispersity index of about 1.0 to about 2.5, e.g., from about 1.0 to about 2.0, from about 1.0 to about 1.8, from about 1.0 to about 1.7, or from about 1.0 to about 1.6.

In some embodiments, the particle comprises a plurality of compounds comprising at least one acidic moiety. For example, in some embodiments, one compound of the plurality of compounds comprising at least one acidic moiety is a PLGA polymer wherein the hydroxy terminus is functionalized with an acetyl group, and another compound in the plurality is a PLGA polymer wherein the hydroxy terminus is unfunctionalized.

In some embodiments, the percent by weight of the compound comprising at least one acidic moiety within the particle is up to about 50% (e.g., up to about 45% by weight, up to about 40% by weight, up to about 35% by weight, up to about 30% by weight, from about 0 to about 30% by weight, e.g., about 4.5%, about 9%, about 12%, about 15%, about 18%, about 20%, about 22%, about 24%, about 26%, about 28% or about 30%).

In some embodiments, the compound comprising at least one acidic moiety is a small molecule comprising an acidic group.

In some embodiments, the particle further comprises a surfactant. In some embodiments, the surfactant is PEG, PVA, PVP, poloxamer, a polysorbate, a polyoxyethylene ester, a PEG-lipid (e.g., PEG-ceramide, d-alpha-tocopheryl polyethylene glycol 1000 succinate), 1,2-Distearoyl-*sn*-Glycero-3-[Phospho-*rac*-(1-glycerol)] or lecithin. In some embodiments, the surfactant is PVA and the PVA is from about 3 kDa to about 50 kDa (e.g., from about 5 kDa to about 45 kDa, about 7

kDa to about 42 kDa, from about 9 kDa to about 30 kDa, or from about 11 to about 28 kDa) and up to about 98% hydrolyzed (e.g., about 75-95%, about 80-90% hydrolyzed, or about 85% hydrolyzed). In some embodiments, the surfactant is polysorbate 80. In some embodiments, the surfactant is Solutol® HS 15. In some embodiments, the surfactant is present in an amount of up to about 35% by weight of the particle (e.g., up to about 20% by weight or up to about 25% by weight, from about 15 % to about 35% by weight, from about 20% to about 30% by weight, or from about 23% to about 26% by weight).

In some embodiments, the particle further comprises a stabilizer or lyoprotectant, e.g., a stabilizer or lyoprotectant described herein. In some embodiments, the stabilizer or lyoprotectant is a carbohydrate (e.g., a carbohydrate described herein, such as, e.g., sucrose, cyclodextrin or a derivative of cyclodextrin (e.g. 2-hydroxypropyl-β-cyclodextrin)), salt, PEG, PVP or crown ether.

In an embodiment the amount of first and second agent in the particle that is not attached to the first or second polymer is less than about 5% (e.g., less than about 2% or less than about 1%, e.g., in terms of w/w or number/number) of the amount of first or second agent attached to the first polymer or second polymer.

In some embodiments, the first polymer is a biodegradable polymer (e.g., PLA, PGA, PLGA, PCL, PDO, polyanhydrides, polyorthoesters, or chitosan). In some embodiments, the first polymer is a hydrophobic polymer. In some embodiments, the percent by weight of the first polymer within the particle is from about 20% to about 90% (e.g., from about 20% to about 80%, from about 25% to about 75%, or from about 30% to about 70%). In some embodiments, the first polymer is PLA. In some embodiments, the first polymer is PGA.

In some embodiments, the first polymer is a copolymer of lactic and glycolic acid (e.g., PLGA). In some embodiments, the first polymer is a PLGA-ester. In some embodiments, the first polymer is a PLGA-lauryl ester. In some embodiments, the first polymer comprises a terminal free acid. In some embodiments, the first polymer comprises a terminal acyl group (e.g., an acetyl group). In some embodiments, the polymer comprises a terminal hydroxyl group. In some embodiments, the ratio of lactic acid monomers to glycolic acid monomers in PLGA is from about 0.1:99.9 to

about 99.9:0.1. In some embodiments, the ratio of lactic acid monomers to glycolic acid monomers in PLGA is from about 75:25 to about 25:75, e.g., about 60:40 to about 40:60 (e.g., about 50:50), about 60:40, or about 75:25.

In some embodiments, the weight average molecular weight of the first polymer is from about 1 kDa to about 20 kDa (e.g., from about 1 kDa to about 15 kDa, from about 2 kDa to about 12 kDa, from about 6 kDa to about 20 kDa, from about 5 kDa to about 15 kDa, from about 7 kDa to about 11 kDa, from about 5 kDa to about 10 kDa, from about 7 kDa to about 10 kDa, from about 5 kDa to about 7 kDa, from about 6 kDa to about 8 kDa, about 6 kDa, about 7 kDa, about 8 kDa, about 9 kDa, about 10 kDa, about 11 kDa, about 12 kDa, about 13 kDa, about 14 kDa, about 15 kDa, about 16 kDa or about 17 kDa). In some embodiments, the first polymer has a glass transition temperature of from about 20 °C to about 60 °C. In some embodiments, the first polymer has a polymer polydispersity index of less than or equal to about 2.5 (e.g., less than or equal to about 2.2, or less than or equal to about 2.0). In some embodiments, the first polymer has a polymer polydispersity index of about 1.0 to about 2.5, e.g., from about 1.0 to about 2.0, from about 1.0 to about 1.8, from about 1.0 to about 1.7, or from about 1.0 to about 1.6.

In some embodiments, the second polymer is a biodegradable polymer (e.g., PLA, PGA, PLGA, PCL, PDO, polyanhydrides, polyorthoesters, or chitosan). In some embodiments, the second polymer is a hydrophobic polymer. In some embodiments, the percent by weight of the second polymer within the particle is from about 20% to about 90% (e.g., from about 20% to about 80%, from about 25% to about 75%, or from about 30% to about 70%). In some embodiments, the second polymer is PLA. In some embodiments, the second polymer is PGA.

In some embodiments, the second polymer is a copolymer of lactic and glycolic acid (e.g., PLGA). In some embodiments, the second polymer is a PLGA-ester. In some embodiments, the second polymer is a PLGA-lauryl ester. In some embodiments, the second polymer comprises a terminal free acid. In some embodiments, the second polymer comprises a terminal acyl group (e.g., an acetyl group). In some embodiments, the polymer comprises a terminal hydroxyl group. In some embodiments, the ratio of lactic acid monomers to glycolic acid monomers in

PLGA is from about 0.1:99.9 to about 99.9:0.1. In some embodiments, the ratio of lactic acid monomers in PLGA to glycolic acid monomers is from about 75:25 to about 25:75, e.g., about 60:40 to about 40:60 (e.g., about 50:50), about 60:40, or about 75:25.

In some embodiments, the weight average molecular weight of the second polymer is from about 1 kDa to about 20 kDa (e.g., from about 1 kDa to about 15 kDa, from about 2 kDa to about 12 kDa, from about 6 kDa to about 20 kDa, from about 5 kDa to about 15 kDa, from about 7 kDa to about 11 kDa, from about 5 kDa to about 10 kDa, from about 7 kDa to about 10 kDa, from about 5 kDa to about 7 kDa, from about 6 kDa to about 8 kDa, about 6 kDa, about 7 kDa, about 8 kDa, about 9 kDa, about 10 kDa, about 11 kDa, about 12 kDa, about 13 kDa, about 14 kDa, about 15 kDa, about 16 kDa or about 17 kDa). In some embodiments, the second polymer has a glass transition temperature of from about 20 °C to about 60 °C. In some embodiments, the second polymer has a polymer polydispersity index of less than or equal to about 2.5 (e.g., less than or equal to about 2.2, or less than or equal to about 2.0). In some embodiments, the second polymer has a polymer polydispersity index of about 1.0 to about 2.5, e.g., from about 1.0 to about 2.0, from about 1.0 to about 1.8, from about 1.0 to about 1.7, or from about 1.0 to about 1.6.

In some embodiments, the percent by weight of the third polymer within the particle is up to about 50% by weight (e.g., from about 4 to any of about 50%, about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45% or about 50% by weight). In some embodiments, the third polymer has a hydrophilic portion and a hydrophobic portion. In some embodiments, the third polymer is a block copolymer. In some embodiments, the third polymer comprises two regions, the two regions together being at least about 70% by weight of the polymer (e.g., at least about 80%, at least about 90%, at least about 95%). In some embodiments, the third polymer is a block copolymer comprising a hydrophobic polymer and a hydrophilic polymer. In some embodiments, the third polymer, e.g., a diblock copolymer, comprises a hydrophobic polymer and a hydrophilic polymer. In some embodiments, the third polymer, e.g., a triblock copolymer, comprises a hydrophobic polymer, a hydrophilic polymer and a hydrophobic polymer, e.g., PLA-

PEG-PLA, PGA-PEG-PGA, PLGA-PEG-PLGA, PCL-PEG-PCL, PDO-PEG-PDO, PEG-PLGA-PEG, PLA-PEG-PGA, PGA-PEG-PLA, PLGA-PEG-PLA or PGA-PEG-PLGA.

In some embodiments, the hydrophobic portion of the third polymer is a biodegradable polymer (e.g., PLA, PGA, PLGA, PCL, PDO, polyanhydrides, polyorthoesters, or chitosan). In some embodiments, the hydrophobic portion of the third polymer is PLA. In some embodiments, the hydrophobic portion of the third polymer is PGA. In some embodiments, the hydrophobic portion of the third polymer is a copolymer of lactic and glycolic acid (e.g., PLGA). In some embodiments, the hydrophobic portion of the third polymer has a weight average molecular weight of from about 1 kDa to about 20 kDa (e.g., from about 1 kDa to about 18 kDa, 17 kDa, 16 kDa, 15 kDa, 14 kDa or 13 kDa, from about 2 kDa to about 12 kDa, from about 6 kDa to about 20 kDa, from about 5 kDa to about 18 kDa, from about 7 kDa to about 17 kDa, from about 8 kDa to about 13 kDa, from about 9 kDa to about 11 kDa, from about 10 kDa to about 14 kDa, from about 6 kDa to about 8 kDa, about 6 kDa, about 7 kDa, about 8 kDa, about 9 kDa, about 10 kDa, about 11 kDa, about 12 kDa, about 13 kDa, about 14 kDa, about 15 kDa, about 16 kDa or about 17 kDa).

In some embodiments, the hydrophilic polymer portion of the third polymer is PEG. In some embodiments, the hydrophilic portion of the third polymer has a weight average molecular weight of from about 1 kDa to about 21 kDa (e.g., from about 1 kDa to about 3 kDa, e.g., about 2 kDa, or from about 2 kDa to about 5 kDa, e.g., about 3.5 kDa, or from about 4 kDa to about 6 kDa, e.g., about 5 kDa). In some embodiments, the ratio of weight average molecular weight of the hydrophilic to hydrophobic polymer portions of the third polymer is from about 1:1 to about 1:20 (e.g., about 1:4 to about 1:10, about 1:4 to about 1:7, about 1:3 to about 1:7, about 1:3 to about 1:6, about 1:4 to about 1:6.5 (e.g., 1:4, 1:4.5, 1:5, 1:5.5, 1:6, 1:6.5) or about 1:1 to about 1:4 (e.g., about 1:1.4, 1:1.8, 1:2, 1:2.4, 1:2.8, 1:3, 1:3.2, 1:3.5 or 1:4). In one embodiment, the hydrophilic portion of the third polymer has a weight average molecular weight of from about 2 kDa to 3.5 kDa and the ratio of the weight average molecular weight of the hydrophilic to hydrophobic portions of the third polymer is from about 1:4 to about 1:6.5 (e.g., 1:4, 1:4.5, 1:5, 1:5.5, 1:6, 1:6.5). In one

embodiment, the hydrophilic portion of the third polymer has a weight average molecular weight of from about 4 kDa to 6 kDa (e.g., 5 kDa) and the ratio of the weight average molecular weight of the hydrophilic to hydrophobic portions of the third polymer is from about 1:1 to about 1:3.5 (e.g., about 1:1.4, 1:1.8, 1:2, 1:2.4, 1:2.8, 1:3, 1:3.2, or 1:3.5).

In some embodiments, the hydrophilic polymer portion of the third polymer has a terminal hydroxyl moiety. In some embodiments, the hydrophilic polymer portion of the third polymer has a terminal alkoxy moiety. In some embodiments, the hydrophilic polymer portion of the third polymer is a methoxy PEG (e.g., a terminal methoxy PEG). In some embodiments, the hydrophilic polymer portion of the third polymer does not have a terminal alkoxy moiety. In some embodiments, the terminus of the hydrophilic polymer portion of the third polymer is conjugated to hydrophobic polymer, e.g., to make a triblock copolymer.

In some embodiments, the hydrophilic polymer portion of the third polymer comprises a terminal conjugate. In some embodiments, the terminal conjugate is a targeting agent or a dye. In some embodiments, the terminal conjugate is a folate or a rhodamine. In some embodiments, the terminal conjugate is a targeting peptide (e.g., an RGD peptide).

In some embodiments, the hydrophilic polymer portion of the third polymer is attached to the hydrophobic polymer portion through a covalent bond. In some embodiments, the hydrophilic polymer is attached to the hydrophobic polymer through an amide, ester, ether, amino, carbamate, or carbonate bond (e.g., an ester or an amide).

In some embodiments, the ratio by weight of the combined first and second polymers to the third polymer is from about 1:1 to about 20:1, e.g., about 1:1 to about 10:1, e.g., about 1:1 to 9:1, or about 1.2: to 8:1. In some embodiments, the ratio of the first and second polymer is from about 85:15 to about 55:45 percent by weight or about 84:16 to about 60:40 percent by weight. In some embodiments, the ratio by weight of the combined first and second polymers to the compound comprising at least one acidic moiety is from about 1:3 to about 1000:1, e.g., about 1:1 to about 10:1, or about 1.5:1. In some embodiments, the ratio of the third polymer to the

compound comprising at least one acidic moiety is from about 1:10 to about 250:1, e.g., from about 1:5 to about 5:1, or from about 1:3.5 to about 1:1.

In some embodiments the particle is substantially free of a targeting agent (e.g., of a targeting agent covalently linked to a component of the particle, e.g., to the first or second polymer or agent), e.g., a targeting agent able to bind to or otherwise associate with a target biological entity, e.g., a membrane component, a cell surface receptor, prostate specific membrane antigen, or the like. In some embodiments the particle is substantially free of a targeting agent that causes the particle to become localized to a tumor, a disease site, a tissue, an organ, a type of cell, e.g., a cancer cell, within the body of a subject to whom a therapeutically effective amount of the particle is administered. In some embodiments, the particle is substantially free of a targeting agent selected from nucleic acid aptamers, growth factors, hormones, cytokines, interleukins, antibodies, integrins, fibronectin receptors, p-glycoprotein receptors, peptides and cell binding sequences. In some embodiments, no polymer is conjugated to a targeting moiety. In an embodiment substantially free of a targeting agent means substantially free of any moiety other than the first polymer, the second polymer, a third polymer, a surfactant (if present), and the agent, e.g., an anti-cancer agent or other therapeutic or diagnostic agent, that targets the particle. Thus, in such embodiments, any contribution to localization by the first polymer, the second polymer, a third polymer, a surfactant (if present), and the agent is not considered to be "targeting." In an embodiment the particle is free of moieties added for the purpose of selectively targeting the particle to a site in a subject, e.g., by the use of a moiety on the particle having a high and specific affinity for a target in the subject.

In some embodiments the third polymer is other than a lipid, e.g., other than a phospholipid. In some embodiments the particle is substantially free of an amphiphilic layer that reduces water penetration into the nanoparticle. In some embodiment the particle comprises less than 5 or 10% (e.g., as determined as w/w, v/v) of a lipid, e.g., a phospholipid. In some embodiments the particle is substantially free of a lipid layer, e.g., a phospholipid layer, e.g., that reduces water penetration into the nanoparticle. In some embodiments the particle is substantially free of lipid, e.g., is substantially free of phospholipid.

In some embodiments the particle is substantially free of a radiopharmaceutical agent, e.g., a radiotherapeutic agent, radiodiagnostic agent, prophylactic agent, or other radioisotope. In some embodiments the particle is substantially free of an immunomodulatory agent, e.g., an immunostimulatory agent or immunosuppressive agent. In some embodiments the particle is substantially free of a vaccine or immunogen, e.g., a peptide, sugar, lipid-based immunogen, B cell antigen or T cell antigen. In some embodiments, the particle is substantially free of water soluble PLGA (e.g., PLGA having a weight average molecular weight of less than about 1 kDa).

In some embodiments, the ratio of the combined first and second polymer to the third polymer is such that the particle comprises at least 5%, 8%, 10%, 12%, 15%, 18%, 20%, 23%, 25% or 30% by weight of a polymer having a hydrophobic portion and a hydrophilic portion.

In some embodiments, the zeta potential of the particle surface, when measured in water, is from about -80 mV to about 50 mV, e.g., about -50 mV to about 30 mV, about -20 mV to about 20 mV, or about -10 mV to about 10 mV. In some embodiments, the zeta potential of the particle surface, when measured in water, is neutral or slightly negative. In some embodiments, the zeta potential of the particle surface, when measured in water, is less than 0, e.g., about 0 mV to about -20 mV.

In some embodiments, the particle comprises less than 5000 ppm of a solvent (e.g., acetone, *tert*-butylmethyl ether, heptane, dichloromethane, dimethylformamide, ethyl acetate, acetonitrile, tetrahydrofuran, ethanol, methanol, isopropyl alcohol, methyl ethyl ketone, butyl acetate, or propyl acetate), (e.g., less than 4500 ppm, less than 4000 ppm, less than 3500 ppm, less than 3000 ppm, less than 2500 ppm, less than 2000 ppm, less than 1500 ppm, less than 1000 ppm, less than 500 ppm, less than 250 ppm, less than 100 ppm, less than 50 ppm, less than 25 ppm, less than 10 ppm, less than 5 ppm, less than 2 ppm, or less than 1 ppm). In some embodiments, the particle is substantially free of a solvent (e.g., acetone, *tert*-butylmethyl ether, heptane, dichloromethane, dimethylformamide, ethyl acetate, acetonitrile, tetrahydrofuran, ethanol, methanol, isopropyl alcohol, methyl ethyl ketone, butyl acetate, or propyl acetate).

In some embodiments, the particle is substantially free of a class II or class III solvent as defined by the United States Department of Health and Human Services Food and Drug Administration "Q3c -Tables and List." In some embodiments, the particle comprises less than 5000 ppm of acetone. In some embodiments, the particle comprises less than 5000 ppm of *tert*-butylmethyl ether. In some embodiments, the particle comprises less than 5000 ppm of heptane. In some embodiments, the particle comprises less than 600 ppm of dichloromethane. In some embodiments, the particle comprises less than 880 ppm of dimethylformamide. In some embodiments, the particle comprises less than 5000 ppm of ethyl acetate. In some embodiments, the particle comprises less than 410 ppm of acetonitrile. In some embodiments, the particle comprises less than 720 ppm of tetrahydrofuran. In some embodiments, the particle comprises less than 5000 ppm of ethanol. In some embodiments, the particle comprises less than 3000 ppm of methanol. In some embodiments, the particle comprises less than 5000 ppm of isopropyl alcohol. In some embodiments, the particle comprises less than 5000 ppm of methyl ethyl ketone. In some embodiments, the particle comprises less than 5000 ppm of butyl acetate. In some embodiments, the particle comprises less than 5000 ppm of propyl acetate.

In some embodiments, a composition comprising a plurality of particles is substantially free of solvent.

In some embodiments, in a composition of a plurality of particles, the particles have an average diameter of from about 50 nm to about 500 nm (e.g., from about 50 to about 200 nm). In some embodiments, in a composition of a plurality of particles, the particles have a Dv50 (median particle size) from about 50 nm to about 220 nm (e.g., from about 75 nm to about 200 nm). In some embodiments, in a composition of a plurality of particles, the particles have a Dv90 (particle size below which 90% of the volume of particles exists) of about 50 nm to about 500 nm (e.g., about 75 nm to about 220 nm).

In some embodiments, a single first agent is attached to a single first polymer, e.g., to a terminal end of the polymer. In some embodiments, a plurality of first agents are attached to a single first polymer (e.g., 2, 3, 4, 5, 6, or more). In some embodiments, the agents are the same agent. In some embodiments, the agents are

different agents. In some embodiments, a single second agent is attached to a single second polymer, e.g., to a terminal end of the polymer. In some embodiments, a plurality of second agents are attached to a single second polymer (e.g., 2, 3, 4, 5, 6, or more). In some embodiments, the agents are the same agent. In some embodiments, the agents are different agents.

In some embodiments, the first agent or the second agent is a diagnostic agent. In some embodiments, the first agent or the second agent is a therapeutic agent.

In some embodiments, the therapeutic agent is an anti-inflammatory agent. In some embodiments, the therapeutic agent is an anti-cancer agent. In some embodiments, the anti-cancer agent is an alkylating agent, a vascular disrupting agent, a microtubule targeting agent, a mitotic inhibitor, a topoisomerase inhibitor, an anti-angiogenic agent or an anti-metabolite. In some embodiments, the anti-cancer agent is a taxane (e.g., paclitaxel, docetaxel, larotaxel or cabazitaxel). In some embodiments, the anti-cancer agent is an anthracycline (e.g., doxorubicin). In some embodiments, the anti-cancer agent is a platinum-based agent (e.g., cisplatin). In some embodiments, the anti-cancer agent is a pyrimidine analog (e.g., gemcitabine).

In some embodiments, the anti-cancer agent is paclitaxel, attached to the polymer via the hydroxyl group at the 2' position, the hydroxyl group at the 1 position and/or the hydroxyl group at the 7 position. In some embodiments, the anti-cancer agent is paclitaxel, attached to the polymer via the hydroxyl group at the 2' position and/or the hydroxyl group at the 7 position.

In some embodiments, the anti-cancer agent is docetaxel, attached to the polymer via the hydroxyl group at the 2' position, the hydroxyl group at the 7 position, the hydroxyl group at the 10 position and/or the hydroxyl group at the 1 position. In some embodiments, the anti-cancer agent is docetaxel, attached to the polymer via the hydroxyl group at the 2' position, the hydroxyl group at the 7 position and/or the hydroxyl group at the 10 position.

In some embodiments, the anti-cancer agent is docetaxel-succinate.

In some embodiments, the anti-cancer agent is a taxane that is attached to the polymer via the hydroxyl group at the 7 position and has an acyl group or a hydroxy protecting group on the hydroxyl group at the 2' position (e.g., wherein the anti-

cancer agent is a taxane such as paclitaxel, docetaxel, larotaxel or cabazitaxel). In some embodiments, the anti-cancer agent is larotaxel. In some embodiments, the anti-cancer agent is cabazitaxel.

In some embodiments, the anti-cancer agent is doxorubicin.

In some embodiments, the therapeutic agent is an agent for the treatment or prevention of cardiovascular disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the treatment of cardiovascular disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the prevention of cardiovascular disease, for example as described herein.

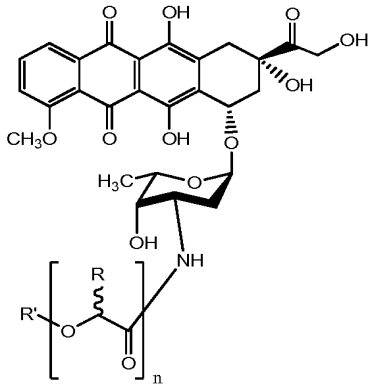
In some embodiments, the therapeutic agent is an agent for the treatment or prevention of an inflammatory or autoimmune disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the treatment of inflammatory or autoimmune disease, for example as described herein. In some embodiments, the therapeutic agent is an agent for the prevention of an inflammatory or autoimmune disease, for example as described herein.

In some embodiments, the first agent is attached directly to the first polymer, e.g., through a covalent bond. In some embodiments, the first agent is attached to a terminal end of the first polymer via an amide, ester, ether, amino, carbamate or carbonate bond. In some embodiments, the first agent is attached to a terminal end of the first polymer. In some embodiments, the first polymer comprises one or more side chains and the first agent is directly attached to the first polymer through one or more of the side chains.

In some embodiments, the second agent is attached directly to the second polymer, e.g., through a covalent bond. In some embodiments, the second agent is attached to a terminal end of the second polymer via an amide, ester, ether, amino, carbamate or carbonate bond. In some embodiments, the second agent is attached to a terminal end of the second polymer. In some embodiments, the second polymer comprises one or more side chains and the second agent is directly attached to the second polymer through one or more of the side chains.

In some embodiments, the agent is doxorubicin, and is covalently attached to the first polymer through an amide bond.

In some embodiments, the first or second polymer-agent conjugate in the particle, e.g., the nanoparticle, is:

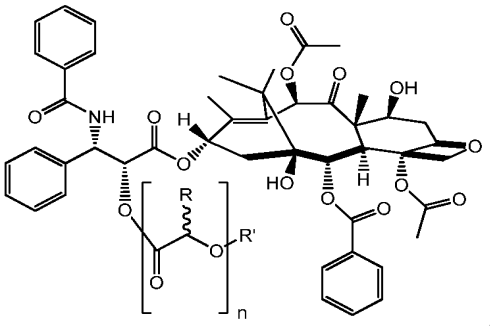


,

wherein about 30% to about 70%, 35% to about 65%, 40% to about 60%, 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, 35% to about 65%, 40% to about 60%, 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is paclitaxel, and is covalently attached to the polymer through an ester bond. In some embodiments, the agent is paclitaxel, and is attached to the polymer via the hydroxyl group at the 2' position.

In some embodiments, the first or second polymer-agent conjugate in the particle, e.g., the nanoparticle, is:

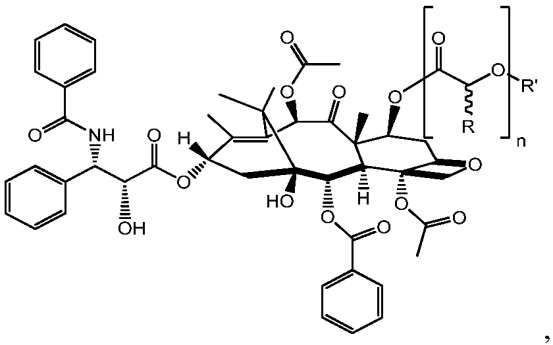


,

wherein about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, 40% to about 60%, 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is paclitaxel, and is attached to the polymer via the hydroxyl group at the 7 position.

In some embodiments, the first or second polymer-agent conjugate in the particle, e.g., the nanoparticle, is:



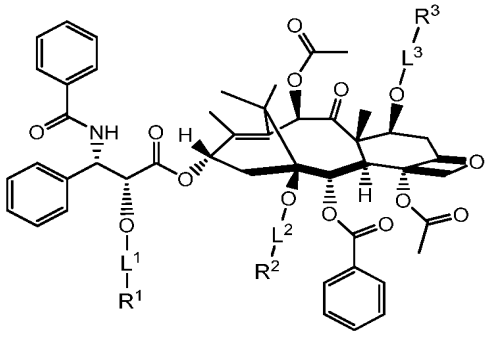
,

wherein about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen

and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the particle includes a combination of polymer-paclitaxel conjugates described herein, e.g., polymer-paclitaxel conjugates illustrated above.

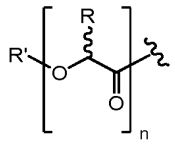
In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, has the following formula (I):



(I),

wherein L^1, L^2 and L^3 are each independently a bond or a linker, e.g., a linker described herein;

wherein R^1, R^2 and R^3 are each independently hydrogen, C_1-C_6 alkyl, acyl, or a polymer of formula (II):



(II),

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g.,

from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)); and

wherein at least one of R^1, R^2 and R^3 is a polymer of formula (II).

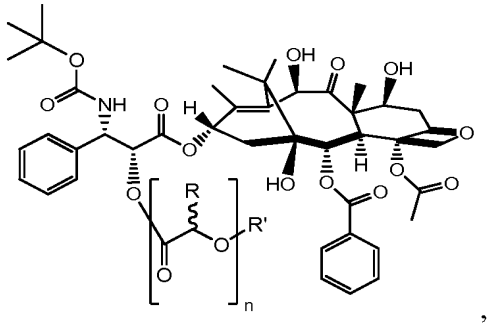
In some embodiments, L^2 is a bond and R^2 is hydrogen.

In some embodiments, the agent is paclitaxel, and is covalently attached to the polymer via a carbonate bond.

In some embodiments, the agent is docetaxel, and is covalently attached to the polymer through an ester bond.

In some embodiments, the agent is docetaxel, and is attached to the polymer via the hydroxyl group at the 2' position.

In some embodiments, the first or second polymer-agent conjugate in the particle, e.g., the nanoparticle, is:

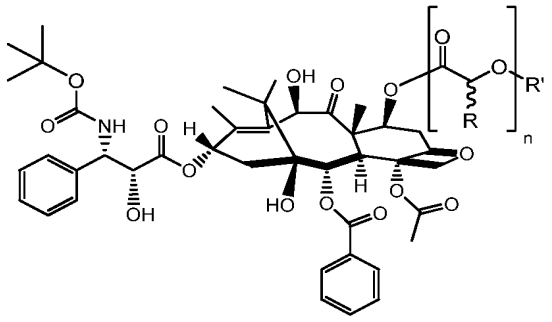


,

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is docetaxel, and is attached to the polymer via the hydroxyl group at the 7 position.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:

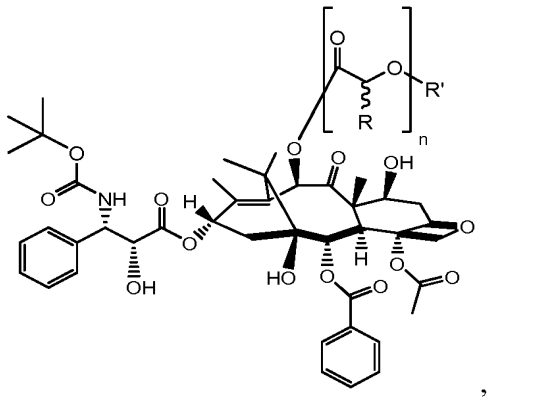


,

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is docetaxel, and is attached to the polymer via the hydroxyl group at the 10 position.

In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, is:



,

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

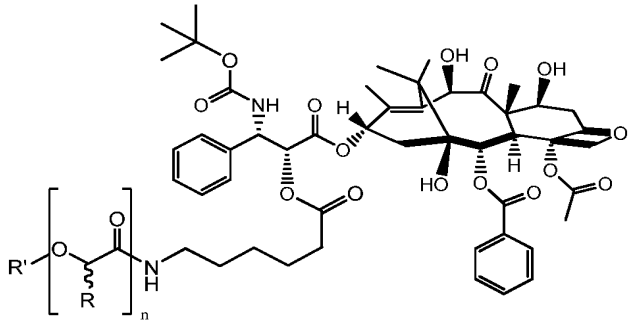
In some embodiments, the agent is docetaxel, and is covalently attached to the polymer through a carbonate bond.

In some embodiments, the particle includes a combination of polymer-docetaxel conjugates described herein, e.g., polymer-docetaxel conjugates illustrated above.

In some embodiments, the agent is attached to the polymer through a linker. In some embodiments, the linker is an alkanoate linker. In some embodiments, the linker is a PEG-based linker. In some embodiments, the linker comprises a disulfide bond. In some embodiments, the linker is a self-immolative linker. In some embodiments, the linker is an amino acid or a peptide (e.g., glutamic acid such as L-glutamic acid, D-glutamic acid, DL-glutamic acid or β-glutamic acid, branched glutamic acid or polyglutamic acid). In some embodiments, the linker is β-alanine glycolate.

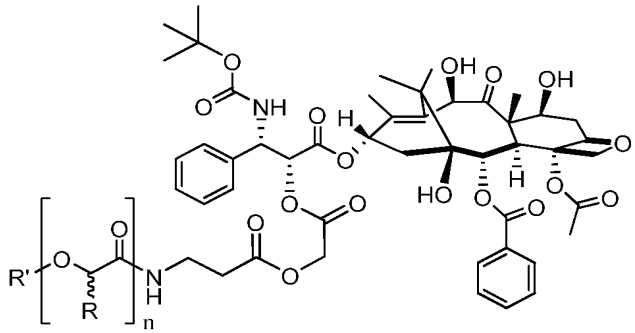
In some embodiments the linker is a multifunctional linker. In some embodiments, the multifunctional linker has 2, 3, 4, 5, 6 or more reactive moieties that may be functionalized with an agent. In some embodiments, all reactive moieties are functionalized with an agent. In some embodiments, not all of the reactive moieties are functionalized with an agent (e.g., the multifunctional linker has two reactive moieties, and only one reacts with an agent; or the multifunctional linker has four reactive moieties, and only one, two or three react with an agent.)

In some embodiments, the first or second polymer-agent conjugate in the particle, e.g., the nanoparticle, is:



wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

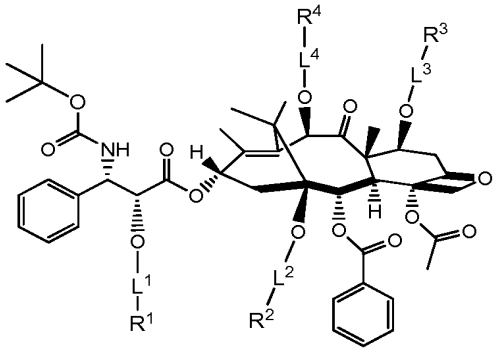
In some embodiments, the polymer-agent conjugate is:



wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g.,

from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

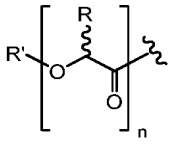
In some embodiments, the polymer-agent conjugate in the particle, e.g., the nanoparticle, has the following formula (III):



(III)

wherein L^1, L^2, L^3 and L^4 are each independently a bond or a linker, e.g., a linker described herein;

R^1, R^2, R^3 and R^4 are each independently hydrogen, C_1-C_6 alkyl, acyl, a hydroxy protecting group, or a polymer of formula (IV):



(IV)

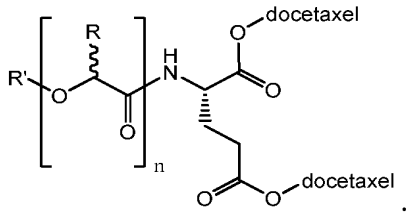
wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)); and

wherein at least one of R^1, R^2, R^3 and R^4 is a polymer of formula (IV).

In some embodiments, L^2 is a bond and R^2 is hydrogen.

In some embodiments, two agents are attached to a polymer via a multifunctional linker. In some embodiments, the two agents are the same agent. In some embodiments, the two agents are different agents. In some embodiments, the agent is docetaxel, and is covalently attached to the polymer via a glutamate linker.

In some embodiments, the first or second polymer-agent conjugate in the particle, e.g., the nanoparticle, is:



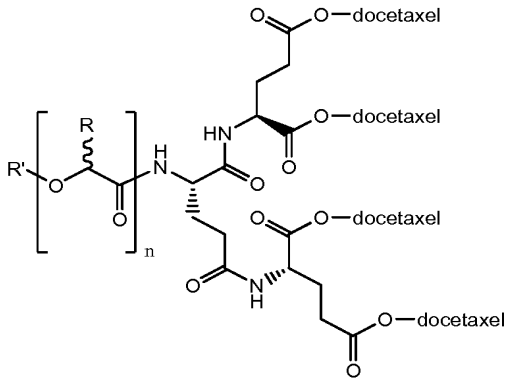
wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 2' position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 7 position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 10 position. In some embodiments, at least one docetaxel is attached to the polymer via the hydroxyl group at the 1 position. In some embodiments, each docetaxel is attached via the same hydroxyl group, e.g., the hydroxyl group at the 2' position, the hydroxyl group at the 7 position, the hydroxyl group at the 1 position or the hydroxyl group at the 10 position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 2' position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 7 position. In some embodiments,

each docetaxel is attached via the hydroxyl group at the 10 position. In some embodiments, each docetaxel is attached via a different hydroxyl group, e.g., one docetaxel is attached via the hydroxyl group at the 2' position and the other is attached via the hydroxyl group at the 7 position.

In some embodiments, four agents are attached to a polymer via a multifunctional linker. In some embodiments, the four agents are the same agent. In some embodiments, the four agents are different agents. In some embodiments, the agent is docetaxel, and is covalently attached to the polymer via a tri(glutamate) linker.

In some embodiments, the first or second polymer-agent conjugate in the particle, e.g., the nanoparticle, is:

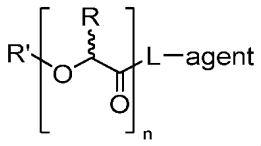


wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, each docetaxel is attached via the same hydroxyl group, e.g., the hydroxyl group at the 2' position, the hydroxyl group at the 7 position or the hydroxyl group at the 10 position. In some embodiments, each docetaxel is

attached via the hydroxyl group at the 2' position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 7 position. In some embodiments, each docetaxel is attached via the hydroxyl group at the 10 position. In some embodiments, each docetaxel is attached via a different hydroxyl group, e.g., three docetaxel molecules are attached via the hydroxyl group at the 2' position and the other is attached via the hydroxyl group at the 7 position.

In some embodiments, the polymer-agent conjugate has the following formula:



,

wherein L is a bond or linker, e.g., a linker described herein; and

wherein about 30% to about 70%, e.g., about 35% to about 65%, 40% to about 60%, about 45% to about 55% of R substituents are hydrogen (e.g., about 50%) and about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55% are methyl (e.g., about 50%); R' is selected from hydrogen and acyl (e.g., acetyl); and wherein n is an integer from about 15 to about 308, e.g., about 77 to about 232, e.g., about 105 to about 170 (e.g., n is an integer such that the weight average molecular weight of the polymer is from about 1 kDa to about 20 kDa (e.g., from about 5 to about 15 kDa, from about 6 to about 13 kDa, or from about 7 to about 11 kDa)).

In some embodiments, the agent is a taxane, e.g., docetaxel, paclitaxel, larotaxel or cabazitaxel.

In some embodiments, L is a bond.

In some embodiments, L is a linker, e.g., a linker described herein.

In some embodiments, the particle comprises a plurality of polymer-agent conjugates. In some embodiments, the plurality of polymer-agent conjugates have the same polymer and the same agent, and differ in the nature of the linkage between the agent and the polymer. For example, in some embodiments, the polymer is PLGA, the agent is paclitaxel, and the plurality of polymer-agent conjugates includes PLGA

polymers attached to paclitaxel via the hydroxyl group at the 2' position, and PLGA polymers attached to paclitaxel via the hydroxyl group at the 7 position. In some embodiments, the polymer is PLGA, the agent is paclitaxel, and the plurality of polymer-agent conjugates includes PLGA polymers attached to paclitaxel via the hydroxyl group at the 2' position, PLGA polymers attached to paclitaxel via the hydroxyl group at the 7 position, and/or PLGA polymers attached to paclitaxel via the hydroxyl group at the 1 position. In some embodiments, the polymer is PLGA, the agent is paclitaxel, and the plurality of polymer-agent conjugates includes paclitaxel molecules attached to more than one polymer chain, e.g., paclitaxel molecules with PLGA polymers attached to the hydroxyl group at the 2' position, the hydroxyl group at the 7 position and/or the hydroxyl group at the 1 position.

In some embodiments, the polymer is PLGA, the agent is docetaxel, and the plurality of polymer-agent conjugates includes PLGA attached to docetaxel via the hydroxyl group at the 2' position and PLGA attached to docetaxel via the hydroxyl group at the 7 position. In some embodiments, the polymer is PLGA, the agent is docetaxel, and the plurality of polymer-agent conjugates includes PLGA polymers attached to docetaxel via the hydroxyl group at the 2' position, PLGA polymers attached to docetaxel via the hydroxyl group at the 7 position, and/or PLGA polymers attached to docetaxel via the hydroxyl group at the 10 position. In some embodiments, the polymer is PLGA, the agent is docetaxel, and the plurality of polymer-agent conjugates includes PLGA polymers attached to docetaxel via the hydroxyl group at the 2' position, PLGA polymers attached to docetaxel via the hydroxyl group at the 7 position, PLGA polymers attached to docetaxel via the hydroxyl group at the 10 position and/or PLGA polymers attached to docetaxel via the hydroxyl group at the 1 position. In some embodiments, the polymer is PLGA, the agent is docetaxel, and the plurality of polymer-agent conjugates includes docetaxel molecules attached to more than one polymer chain, e.g., docetaxel molecules with PLGA polymers attached to the hydroxyl group at the 2' position, the hydroxyl group at the 7 position, the hydroxyl group at the 10 position and/or the hydroxyl group at the 1 position.

In some embodiments, the plurality of polymer-agent conjugates have the same polymer and the same agent, but the agent may be attached to the polymer via different linkers. In some embodiments, the plurality of polymer-agent conjugates includes a polymer directly attached to an agent and a polymer attached to an agent via a linker. In an embodiment, one agent is released from one polymer-agent conjugate in the plurality with a first release profile and a second agent is released from a second polymer-agent conjugate in the plurality with a second release profile. E.g., a bond between the first agent and the first polymer is more rapidly broken than a bond between the second agent and the second polymer. E.g., the first polymer-agent conjugate can comprise a first linker (e.g., a linker or a bond) linking the first agent to the first polymer and the second polymer-agent conjugate can comprise a second linker (e.g., a linker or a bond) linking the second agent to the second polymer, wherein the linkers provide for different profiles for release of the first and second agents from their respective agent-polymer conjugates.

In some embodiments, the plurality of polymer-agent conjugates includes different polymers. In some embodiments, the plurality of polymer-agent conjugates includes different agents.

In some embodiments, the first agent is present in the particle in an amount of from about 1 to about 30% by weight (e.g., from about 3 to about 30% by weight, from about 4 to about 25 % by weight, or from about 5 to about 13%, 14%, 15%, 16%, 17%, 18%, 19% or 20% by weight).

In some embodiments, the second agent is present in the particle in an amount of from about 1 to about 30% by weight (e.g., from about 3 to about 30% by weight, from about 4 to about 25 % by weight, or from about 5 to about 13%, 14%, 15%, 16%, 17%, 18%, 19% or 20% by weight).

In an embodiment the particle comprises the enumerated elements.

In an embodiment the particle consists of the enumerated elements.

In an embodiment the particle consists essentially of the enumerated elements.

In yet another aspect, the invention features a method of making a particle described herein, the method comprising:

providing a hydrophobic polymer having a weight average molecular weight range from about 5 kDa to about 15 kDa (e.g., about 6 to about 13 kDa, or about 7 kDa to about 11 kDa) with an agent attached thereto,

providing a polymer comprising a hydrophilic portion and a hydrophobic portion to form a mixture, and

subjecting the mixture to conditions sufficient to form a particle comprising the agent attached to the hydrophobic polymer and the polymer having a hydrophilic portion and a hydrophobic portion.

In some embodiments, the method further comprises attaching the agent to the hydrophobic polymer.

In some embodiments, the method further comprises providing a compound comprising at least one acidic moiety in the mixture.

In some embodiments, the method further comprises providing a surfactant in the mixture.

In some embodiments, the polymer polydispersity index of the hydrophobic polymer is less than about 2.5 (e.g., less than or equal to about 2.2, or less than or equal to about 2.0). In some embodiments, the polymer has a polymer polydispersity index of about 1.0 to about 2.5, e.g., from about 1.0 to about 2.0, from about 1.0 to about 1.8, from about 1.0 to about 1.7, or from about 1.0 to about 1.6. In some embodiments, the particle is precipitated from the mixture. In some embodiments, the particle is lyophilized from the mixture.

In another aspect, the invention features a method of making a particle described herein, the method comprising:

providing a hydrophobic polymer having a weight average molecular weight range from about 5 kDa to about 15 kDa (e.g., about 6 to about 13 kDa, or about 7 kDa to about 11 kDa) having a first agent attached thereto,

providing a polymer comprising a hydrophilic portion and a hydrophobic portion,

providing a second agent to form a mixture, and

subjecting the mixture to conditions sufficient to form a particle comprising the first agent attached to the hydrophobic polymer, the polymer comprising a hydrophilic portion and a hydrophobic portion, and a second agent.

In some embodiments, the method further comprises attaching the first agent to the hydrophobic polymer.

In some embodiments, the method further comprises providing a compound comprising at least one acidic moiety in the mixture.

In some embodiments, the method further comprises providing a surfactant in the mixture.

In some embodiments, the polymer polydispersity index of the hydrophobic polymer is less than about 2.5 (e.g., less than or equal to about 2.2, or less than or equal to about 2.0). In some embodiments, the polymer has a polymer polydispersity index of about 1.0 to about 2.5, e.g., from about 1.0 to about 2.0, from about 1.0 to about 1.8, from about 1.0 to about 1.7, or from about 1.0 to about 1.6. In some embodiments, the particle is precipitated from the mixture. In some embodiments, the particle is lyophilized from the mixture.

In another aspect, the invention features a method of making a particle described herein, the method comprising:

providing a hydrophobic polymer having a weight average molecular weight range from about 5 kDa to about 15 kDa (e.g., about 6 to about 13 kDa, or about 7 kDa to about 11 kDa),

providing a polymer comprising a hydrophilic portion and a hydrophobic portion,

providing an agent to form a mixture, and

subjecting the mixture to conditions sufficient to form a particle comprising the hydrophobic polymer, the polymer comprising a hydrophilic portion and a hydrophobic portion, and the agent.

In some embodiments, the method further comprises providing a surfactant in the mixture.

In some embodiments, the polymer polydispersity index of the hydrophobic polymer is less than about 2.5 (e.g., less than or equal to about 2.2, or less than or equal to about 2.0). In some embodiments, the polymer has a polymer polydispersity index of about 1.0 to about 2.5, e.g., from about 1.0 to about 2.0, from about 1.0 to about 1.8, from about 1.0 to about 1.7, or from about 1.0 to about 1.6. In some embodiments, the particle is precipitated from the mixture. In some embodiments, the particle is lyophilized from of the mixture.

In another aspect, the invention features a method of making a particle described herein, the method comprising:

dissolving a hydrophobic polymer-agent conjugate and polymer comprising a hydrophilic portion and a hydrophobic portion in an organic solvent to provide an organic solution;

combining the organic solution with an aqueous solution, the aqueous solution comprising a surfactant; and

mixing the resulting combination to provide a mixture comprising a particle described herein.

In some embodiments, the method further comprises providing a compound comprising at least one acidic moiety in the organic solution.

In some embodiments, the organic solution is filtered (e.g., through a 0.22 micron filter) prior to mixing. In some embodiments, the aqueous solution is filtered (e.g., through a 0.22 micron filter) prior to mixing.

In some embodiments, the organic solvent is miscible with water. In some embodiments, the solvent is acetone, ethanol, methanol, isopropyl alcohol, dichloromethane, acetonitrile, methyl ethyl ketone, tetrahydrofuran, butyl acetate, ethyl acetate, propyl acetate or dimethylformamide. In some embodiments, the organic solvent is immiscible with water.

In some embodiments, the ratio of the hydrophobic polymer-agent conjugate and polymer comprising a hydrophilic portion and a hydrophobic portion in the organic solution is from about 90:10 to about 55:45 weight% (e.g., from about 85:15 to about 60:40 weight%).

In some embodiments, the concentration of the surfactant in the aqueous solution is from about 0.1 to about 3.0 weight/volume. In one embodiment, the surfactant is a polymer (e.g., PVA).

In some embodiments, the mixture is purified. In some embodiments, the mixture is concentrated. In some embodiments, the mixture is subjected to tangential flow filtration or dialysis.

In some embodiments, the resulting particle is lyophilized. In one embodiment, the resulting particle is lyophilized in the presence of a lyoprotectant (e.g., a carbohydrate (e.g., a carbohydrate described herein, such as, e.g., sucrose, cyclodextrin or a derivative of cyclodextrin (e.g. 2-hydroxypropyl-β-cyclodextrin)), salt, PEG, PVP or crown ether).

In some embodiments, the method provides a plurality of particles. In one embodiment, the particles are filtered (e.g., though a 0.22 micron filter). In some embodiments, subsequent to filtering a composition of a plurality of particles, the particles have a Dv90 of less than about 200 nm.

In another aspect, the invention features a mixture, the mixture comprising:

a hydrophobic polymer-agent conjugate;

a polymer comprising a hydrophilic portion and a hydrophobic portion; and

a liquid, wherein the polymer-agent conjugate and polymer comprising a hydrophilic portion and a hydrophobic portion are each independently suspended or dissolved in the liquid.

In some embodiments, the liquid is water. In some embodiments, the liquid is an organic solvent. In some embodiments, the organic solvent is miscible with water. In some embodiments, the organic solvent is acetone, ethanol, methanol, isopropyl alcohol, dichloromethane, acetonitrile, methyl ethyl ketone, tetrahydrofuran, butyl acetate, ethyl acetate, propyl acetate or dimethylformamide. In some embodiments, the liquid is a mixture of water and an organic solvent.

In some embodiments, the mixture further comprises a surfactant (e.g., PVA). In some embodiments, the mixture further comprises a compound comprising at least one acidic moiety.

In some embodiments, the hydrophobic polymer-agent conjugate and polymer comprising a hydrophilic portion and a hydrophobic portion are in the mixture as a particle (e.g., a particle described herein).

In another aspect, the invention features a mixture, the mixture comprising:

a first hydrophobic polymer;

a second polymer comprising a hydrophilic portion and a hydrophobic portion;

a first agent attached to the first or second polymer;

a second agent; and

a liquid, wherein the first polymer, the second polymer, the first agent, and the second agent are each independently suspended or dissolved in the liquid.

In some embodiments, the first hydrophilic polymer, second polymer comprising a hydrophilic portion and a hydrophobic portion, first agent attached to the first or second polymer, and second agent are in the mixture as a particle (e.g., a particle described herein).

In some embodiments, the liquid is water. In some embodiments, the liquid is an organic solvent. In some embodiments, the organic solvent is acetone, ethanol, methanol, isopropyl alcohol, dichloromethane, acetonitrile, methyl ethyl ketone, tetrahydrofuran, butyl acetate, ethyl acetate, propyl acetate or dimethylformamide. In some embodiments, the liquid is a mixture of water and an organic solvent.

In yet another aspect, the invention features a composition (e.g., a pharmaceutical composition) comprising a plurality of particles described herein. In some embodiments, the composition further comprises an additional component. In some embodiments, the additional component is a pharmaceutically acceptable carrier. In some embodiments, the additional component is a surfactant or a polymer, e.g., a surfactant or a polymer not associated with a particle. In some embodiments, the surfactant is PEG, PVA, PVP, poloxamer, a polysorbate, a polyoxyethylene ester, a PEG-lipid (e.g., PEG-ceramide, d-alpha-tocopheryl polyethylene glycol 1000 succinate), 1,2-Distearoyl-*sn*-Glycero-3-[Phospho-*rac*-(1-glycerol)] or lecithin. In some embodiments, the surfactant is PVA and the PVA is from about 3 kDa to about

50 kDa (e.g., from about 5 kDa to about 45 kDa, about 7 kDa to about 42 kDa, from about 9 kDa to about 30 kDa, or from about 11 to about 28 kDa) and up to about 98% hydrolyzed (e.g., about 75-95%, about 80-90% hydrolyzed, or about 85% hydrolyzed). In some embodiments, the surfactant is polysorbate 80. In some embodiments, the surfactant is Solutol® HS 15. In some embodiments, the surfactant is present in an amount of up to about 35% by weight of the particle (e.g., up to about 20% by weight or up to about 25% by weight, from about 15 % to about 35% by weight, from about 20% to about 30% by weight, or from about 23% to about 26% by weight).

In some embodiments, the composition further comprises a stabilizer or lyoprotectant, e.g., a stabilizer or lyoprotectant described herein. In some embodiments, the stabilizer or lyoprotectant is a carbohydrate (e.g., a carbohydrate described herein, such as, e.g., sucrose, cyclodextrin or a derivative of cyclodextrin (e.g. 2-hydroxypropyl-β-cyclodextrin)), salt, PEG, PVP or crown ether.

In some embodiments, the composition further comprises a solvent or suspending liquid (e.g., dextrose). In some embodiments, the composition further comprises one or more of the following: antioxidant, antibacterial, buffer, bulking agent, chelating agent, inert gas, tonicity agent or viscosity agent.

In yet another aspect, the invention features, a composition, e.g., a pharmaceutical composition, that comprises at least two structurally distinct types of particles described herein. The first and second type of particle can differ, e.g., by: the agent, the first polymer, the second polymer, or an additional component, e.g., a surfactant.

E.g., the composition can comprise a first particle comprising a first polymer-agent conjugate, and a second, structurally distinct polymer-agent conjugate. In an embodiment the first polymer-agent conjugate comprises a first agent, e.g., a first anti-cancer drug, and the second polymer-agent conjugate comprises a second agent, e.g., a second anti-cancer drug.

In an embodiment the first or second polymer of the first type of particle and the corresponding polymer of the second type of particle can differ. E.g., they can

differ by molecular weight, subunit composition (e.g., the first and second polymers are PLGA polymers having different ratios of ratio of lactic acid monomers to glycolic acid monomers), or subunit identity, e.g. a chitosan polymer and a PLGA polymer.

In an embodiment the first type of particle provides for a different profile for release of its agent as compared with the second type of particle, e.g., agent is released from the first type of particle with a first release profile and agent is released from the second type of particle with a second (different) release profile (the agent can be the same or different, e.g., two different anti-cancer agents). E.g., a bond between the agent and polymer in the first type of particle is more rapidly broken than a bond between the agent and polymer in the second type of particle. Thus, the release profile of one or more agents can be optimized.

In yet another aspect, the invention features a kit comprising a polymer-agent conjugate, particle or composition described herein and a device for delivery of the polymer-agent conjugate, particle or composition to a subject. In some embodiments, the device for delivery is an IV admixture bag, an IV infusion set, or a piggy back set.

In another aspect, the invention features a kit comprising a polymer-agent conjugate, particle or composition described herein and a container. In some embodiments, the container is a vial. In some embodiments, the vial is a sealed vial (e.g., under inert atmosphere). In some embodiments, the vial is sealed with a flexible seal, e.g., a rubber or silicone closure (e.g., polybutadiene or polyisoprene). In some embodiments, the vial is a light blocking vial. In some embodiments, the vial is substantially free of moisture.

In another aspect, the invention features a kit comprising a polymer-agent conjugate, particle or composition described herein and instructions for reconstituting the polymer-agent conjugate, particle or composition into a pharmaceutically acceptable composition. In embodiments the kit comprises a liquid for reconstitution, e.g., in a single or multi dose formant.

In another aspect, the invention features a kit comprising a polymer-agent conjugate, particle or composition described herein and pharmaceutically acceptable carrier.

In some embodiments, the kit comprises a single dosage unit of a polymer-agent conjugate, particle or composition described herein.

In another aspect, the invention features a method of storing a polymer-agent conjugate, particle or composition described herein, the method comprising providing a polymer-agent conjugate, article or composition described herein in a container, and storing the container for at least about 24 hours. In some embodiments, the container is stored at ambient conditions. In some embodiments, the container is stored at a temperature of less than or equal to about 4 °C. In some embodiments, the container is a light blocking container. In some embodiments, the container is maintained under inert atmosphere. In some embodiments, the container is substantially free of moisture. In some embodiments, the container is a vial. In some embodiments, the vial is a sealed vial (e.g., under inert atmosphere). In some embodiments, vial is sealed with a rubber or silicone closure (e.g., polybutadiene or polyisoprene). In some embodiments, the vial is a light blocking vial. In some embodiments, the vial is substantially free of moisture.

In some embodiments, the invention features a dosage form comprising a polymer-agent conjugate, particle or composition described herein. In some embodiments, the dosage form is an oral dosage form. In some embodiments, the dosage form is a parenteral dosage form.

In some embodiments, the dosage form further comprises one or more of the following: antioxidant, antibacterial, buffer, bulking agent, chelating agent, inert gas, tonicity agent or viscosity agent.

In some embodiments, the dosage form is a parenteral dosage form (e.g., an intravenous dosage form). In some embodiments, the dosage form is an oral dosage form. In some embodiments, the dosage form is an inhaled dosage form. In some embodiments, the inhaled dosage form is delivered via nebulzation, propellant or a dry powder device). In some embodiments, the dosage form is a topical dosage form. In some embodiments, the dosage form is a mucosal dosage form (e.g., a rectal

dosage form or a vaginal dosage form). In some embodiments, the dosage form is an ophthalmic dosage form.

In some embodiments, the dosage form is a solid dosage form. In some embodiments, the dosage form is a liquid dosage form.

In yet another aspect, the invention features a single dosage unit comprising a polymer-agent conjugate, particle or composition described herein. In some embodiments, the single dosage unit is an intravenous dosage unit.

In another aspect, the invention features a method of preparing a liquid dosage form, the method comprising:

providing a polymer-agent conjugate, particle or composition described herein; and

dissolving or suspending the polymer-agent conjugate, particle or composition in a pharmaceutically acceptable carrier.

In one aspect, the invention features a method of instructing a user to prepare a liquid dosage form, the method comprising:

providing a polymer-agent conjugate, particle or composition described herein; and

instructing a user to dissolve or suspend the polymer-agent conjugate, particle or composition in a pharmaceutically acceptable carrier.

In one aspect, the invention features a method of evaluating a polymer-agent conjugate, particle or composition described herein, the method comprising:

subjecting a polymer-agent conjugate, particle or composition described herein to an analytical measurement and evaluating the particle or composition based on that measurement.

In some embodiments, the analytical measurement is evaluation of the presence or amount of an impurity or residual solvent. In some embodiments, the analytical measurement is a measurement of the polymer polydispersity index. In some embodiments, the analytical measurement is a measurement of the average particle size. In some embodiments, the analytical measurement is a measurement of the median particle size (Dv50). In some embodiments, the analytical measurement is a measurement of the particle size below which 90% of the volume of particles exists

(Dv90). In some embodiments, the analytical measurement is a measurement of the particle polydispersity index.

In another aspect, the invention features a method of treating a disorder or disease described herein, the method comprising administering to a subject a polymer-agent conjugate, particle or composition described herein.

In an embodiment, the method further comprises administering agent not disposed in a particle, e.g., a particle described herein and/or not conjugated to a polymer, referred to herein as a "free" agent. In an embodiment, the agent disposed in a particle and the free agent are both anti-cancer agents, both agents for treating or preventing a cardiovascular disease, or both anti-inflammatory agents.

In an embodiment, the agent disposed in a particle and the free agent are the same anti-cancer agent. E.g., the agent is a taxane (e.g., paclitaxel, docetaxel, larotaxel or cabazitaxel). In an embodiment, the agent is an anthracycline (e.g., doxorubicin).

In an embodiment, the agent disposed in a particle and the free agent are different anti-cancer agents.

In an embodiment, the agent disposed in a particle and the free agent are the same agent for treating or preventing a cardiovascular disease.

In an embodiment, the agent disposed in a particle and the free agent are different agents for treating or preventing a cardiovascular disease.

In an embodiment, the agent disposed in a particle and the free agent are different anti-inflammatory agents.

In yet another aspect, the invention features a method of treating a proliferative disorder, e.g., a cancer, in a subject, e.g., a human, the method comprises: administering a composition that comprises a polymer-agent conjugate, particle or composition, e.g., a polymer-agent conjugate, particle or composition described herein, to a subject in an amount effective to treat the disorder, to thereby treat the proliferative disorder. In some embodiments, the polymer-agent conjugate, particle or composition is a polymer-anticancer agent conjugate, particle or composition. In an embodiment, the polymer-anticancer agent conjugate comprises an anticancer agent such as docetaxel, paclitaxel, larotaxel, cabazitaxel or

doxorubicin, coupled, e.g., via a linker, to a polymer described herein. In an embodiment, the polymer-anticancer agent conjugate comprises an anticancer agent, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer. In an embodiment, the polymer-anticancer agent conjugate is a polymer-anticancer agent conjugate shown in Fig. 1 or Fig. 2.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with one or more additional chemotherapeutic agent, e.g., a chemotherapeutic agent or combination of chemotherapeutic agents described herein.

In an embodiment, the method further comprises administering an anti-cancer agent as a free agent.

In an embodiment, the agent disposed in a particle and the free agent are the same anti-cancer agent. E.g., the agent is a taxane (e.g., paclitaxel, docetaxel, larotaxel or cabazitaxel). In an embodiment, the agent is an anthracycline (e.g., doxorubicin).

In an embodiment, the agent disposed in a particle and the free agent are different anti-cancer agents.

In one embodiment, the cancer is a cancer described herein. For example, the cancer can be a cancer of the bladder (including accelerated, locally advanced and metastatic bladder cancer), breast (e.g., estrogen receptor positive breast cancer; estrogen receptor negative breast cancer; HER-2 positive breast cancer; HER-2 negative breast cancer; progesterone receptor positive breast cancer; progesterone receptor negative breast cancer; estrogen receptor negative, HER-2 negative and progesterone receptor negative breast cancer (i.e., triple negative breast cancer); inflammatory breast cancer), colon (including colorectal cancer), kidney (e.g., transitional cell carcinoma), liver, lung (including small and non-small cell lung cancer (including lung adenocarcinoma, bronchoalveolar cancer and squamous cell cancer)), genitourinary tract, e.g., ovary (including fallopian tube and peritoneal cancers), cervix, prostate, testes, kidney, and ureter, lymphatic system, rectum, larynx, pancreas (including exocrine pancreatic carcinoma), esophagus, stomach, gall bladder, thyroid, skin (including squamous cell carcinoma), brain (including

glioblastoma multiforme), head and neck (e.g., occult primary), and soft tissue (e.g., Kaposi's sarcoma (e.g., AIDS related Kaposi's sarcoma), leiomyosarcoma, angiosarcoma, and histiocytoma). Preferred cancers include breast cancer (e.g., metastatic or locally advanced breast cancer), prostate cancer (e.g., hormone refractory prostate cancer), renal cell carcinoma, lung cancer (e.g., non-small cell lung cancer and small cell lung cancer (including lung adenocarcinoma, bronchoalveolar cancer and squamous cell cancer) e.g., unresectable, locally advanced or metastatic non-small cell lung cancer and small cell lung cancer), pancreatic cancer, gastric cancer (e.g., metastatic gastric adenocarcinoma), colorectal cancer, rectal cancer, squamous cell cancer of the head and neck, lymphoma (Hodgkin's lymphoma or non-Hodgkin's lymphoma), renal cell carcinoma, carcinoma of the urothelium, soft tissue sarcoma (e.g., Kaposi's sarcoma (e.g., AIDS related Kaposi's sarcoma), leiomyosarcoma, angiosarcoma, and histiocytoma), gliomas, myeloma (e.g., multiple myeloma), melanoma (e.g., advanced or metastatic melanoma), germ cell tumors, ovarian cancer (e.g., advanced ovarian cancer, e.g., advanced fallopian tube or peritoneal cancer), and gastrointestinal cancer.

In one embodiment, the conjugate, particle or composition is administered by intravenous administration, e.g., an intravenous administration that is completed in a period equal to or less than 2 hours, 1.5 hours, 1 hour, 45 minutes or 30 minutes. In one embodiment, the composition is administered as a bolus infusion or intravenous push, e.g., over a period of 15 minutes, 10 minutes, 5 minutes or less.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-docetaxel conjugate, particle or composition, e.g., a polymer-docetaxel conjugate, particle or composition described herein, e.g., a polymer-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a polymer described herein, and e.g., the polymer-docetaxel conjugate, particle or composition is administered to the subject in an amount that includes 60 mg/m^2 or greater (e.g., 65 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 85 mg/m^2, 90 mg/m^2, 95 mg/m^2, 100 mg/m^2, 105 mg/m^2, 110 mg/m^2, 115 mg/m^2, 120 mg/m^2, 125 mg/m^2, 130 mg/m^2, 135 mg/m^2, 140 mg/m^2, 145 mg/m^2, or 150 mg/m^2) of docetaxel, to thereby treat the disorder. In one embodiment, the conjugate, particle or composition is

administered by intravenous administration over a period of about 30 minutes, 45 minutes, 60 minutes, 90 minutes, 120 minutes, 150 minutes or 180 minutes. In one embodiment, the subject is administered at least one additional dose of the conjugate, particle or composition, e.g., the subject is administered at least two, three, four, five, six, seven, eight, nine, ten or eleven additional doses of the conjugate, particle or composition. In one embodiment, the conjugate, particle or composition is administered once every one, two, three, four, five, six weeks. In another embodiment, the polymer-docetaxel conjugate, particle or composition, e.g., a polymer-docetaxel conjugate, particle or composition described herein, e.g., a polymer-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a polymer described herein, and e.g., the polymer-docetaxel conjugate, particle or composition is administered to the subject in an amount that includes 30 mg/m^2 or greater (e.g., 31 mg/m^2, 33 mg/m^2, 35 mg/m^2, 37 mg/m^2, 40 mg/m^2, 43 mg/m^2, 45 mg/m^2, 47 mg/m^2, 50 mg/m^2, 55 mg/m^2, 60 mg/m^2) of docetaxel, to thereby treat the disorder. In one embodiment, the conjugate, particle or composition is administered by intravenous administration over a period of about 30 minutes, 45 minutes, 60 minutes, 90 minutes, 120 minutes, 150 minutes or 180 minutes. In one embodiment, the subject is administered at least one additional dose of the conjugate, particle or composition, e.g., the subject is administered at least two, three, four, five, six, seven, eight, nine, ten or eleven additional doses of the conjugate, particle or composition. In one embodiment, the conjugate, particle or composition is administered once a week for three, four, five six, seven weeks, e.g., followed by one, two or three weeks without administration of the polymer-docetaxel conjugate, particle or composition. In one embodiment, the dosing schedule is not changed between doses. For example, when the dosing schedule is once every three weeks, an additional dose (or doses) is administered in three weeks. In one embodiment, when at least one additional dose is administered, the additional dose (or additional doses) is administered in an amount such that the conjugate, particle or composition includes 60 mg/m^2 or greater (e.g., 65 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 85 mg/m^2, 90 mg/m^2, 95 mg/m^2, 100 mg/m^2, 105 mg/m^2, 110 mg/m^2, 115 mg/m^2, 120 mg/m^2, 125 mg/m^2, 130 mg/m^2, 135 mg/m^2, 140 mg/m^2, 145 mg/m^2, or 150 mg/m^2) of docetaxel. In one embodiment, when at

least one additional dose is administered, the additional dose (or additional doses) is administered by intravenous administration over a period equal to or less than about 30 minutes, 45 minutes, 60 minutes, 90 minutes, 120 minutes, 150 minutes or 180 minutes. In an embodiment, the polymer-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-docetaxel conjugate is a polymer-docetaxel conjugate shown in Fig. 1.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-docetaxel conjugate, particle or composition, e.g., a polymer-docetaxel conjugate, particle or composition described herein, e.g., a polymer-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a polymer described herein, and the conjugate, particle or composition is administered to the subject in an amount of the composition that includes 60 mg/m^2 or greater (e.g., 65 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 85 mg/m^2, 90 mg/m^2, 95 mg/m^2, 100 mg/m^2, 105 mg/m^2, 110 mg/m^2, 115 mg/m^2, 120 mg/m^2, 125 mg/m^2, 130 mg/m^2, 135 mg/m^2, 140 mg/m^2, 145 mg/m^2, or 150 mg/m^2) of docetaxel, administered by intravenous administration over a period equal to or less than about 30 minutes, 45 minutes, 60 minutes, 90 minutes, 120 minutes, 150 minutes or 180 minutes, for at least one, two, three, fours, five or six doses, wherein the subject is administered a dose of the conjugate, particle or composition once every two, three, four, five or six weeks.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-docetaxel conjugate, particle or composition, e.g., a polymer-docetaxel conjugate, particle or composition described herein, e.g., a polymer-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a polymer described herein, and the conjugate, particle or composition is administered to the subject in an amount of the composition that includes 30 mg/m^2 or greater (e.g., 31 mg/m^2, 33 mg/m^2, 35 mg/m^2, 37 mg/m^2, 40 mg/m^2, 43 mg/m^2, 45 mg/m^2, 47 mg/m^2, 50 mg/m^2, 55 mg/m^2, 60 mg/m^2) of docetaxel, administered by intravenous administration over a period equal to or less than about 30 minutes, 45 minutes, 60 minutes, 90 minutes, 120 minutes, 150 minutes or 180 minutes, for at least two, three,

fours, five or six doses, wherein the subject is administered a dose of the conjugate, particle or composition once a week for two, three four, five, six doses, e.g., followed by one, two or three weeks without administration of the polymer-docetaxel conjugate, particle or composition.

In one embodiment, the composition includes a polymer-docetaxel conjugate, particle or composition e.g., a polymer-docetaxel conjugate, particle or composition described herein, e.g., a polymer-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a polymer described herein, and at least two, three, four, five, six, seven, eight, nine, ten or eleven doses are administered to the subject and each dose is an amount of the composition that includes 60 mg/m^2 or greater (e.g., 65 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 85 mg/m^2, 90 mg/m^2, 95 mg/m^2, 100 mg/m^2, 105 mg/m^2, 110 mg/m^2, 115 mg/m^2, 120 mg/m^2, 125 mg/m^2, 130 mg/m^2, 135 mg/m^2, 140 mg/m^2, 145 mg/m^2, or 150 mg/m^2) of docetaxel, to thereby treat the disorder. In one embodiment, the dose is administered once every one, two, three, four, five, six, seven or eight weeks. In one embodiment, a dose is administered once every three weeks. In one embodiment, the composition includes a polymer-docetaxel conjugate, particle or composition e.g., a polymer-docetaxel conjugate, particle or composition described herein, e.g., a polymer-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a polymer described herein, and at least two, three, four, five, six, seven, eight, nine, ten or eleven doses are administered to the subject and each dose is an amount of the composition that includes 30 mg/m^2 or greater (e.g., 31 mg/m^2, 33 mg/m^2, 35 mg/m^2, 37 mg/m^2, 40 mg/m^2, 43 mg/m^2, 45 mg/m^2, 47 mg/m^2, 50 mg/m^2, 55 mg/m^2, 60 mg/m^2) of docetaxel, to thereby treat the disorder. In one embodiment, the dose is administered once a week for two, three, four, five, six, seven weeks, e.g., followed by one, two, three weeks without administration of the polymer-docetaxel conjugate, particle or composition. In one embodiment, each dose is administered by intravenous administration over a period of about 30 minutes, 45 minutes, 60 minutes, 90 minutes, 120 minutes, 150 minutes or 180 minutes. In one embodiment, the dosing schedule is not changed between doses. For example, when the dosing schedule is once every three weeks, an additional dose (or doses) is administered in three weeks.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-paclitaxel conjugate, particle or composition, e.g., a polymer-paclitaxel conjugate, particle or composition described herein and, e.g., a polymer-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a polymer described herein, and, e.g., the conjugate, particle or composition is administered in an amount that includes 135 mg/m^2 or greater (e.g., 140 mg/m^2, 145 mg/m^2, 150 mg/m^2, 155 mg/m^2, 160 mg/m^2, 165 mg/m^2, 170 mg/m^2, 175 mg/m^2, 180 mg/m^2, 185 mg/m^2, 190 mg/m^2, 195 mg/m^2, 200 mg/m^2, 210 mg/m^2, 220 mg/m^2, 225 mg/m^2, 230 mg/m^2, 240 mg/m^2, 250 mg/m^2, 260 mg/m^2, 270 mg/m^2, 280 mg/m^2, 290 mg/m^2, 300 mg/m^2) of paclitaxel, to thereby treat the disorder. In one embodiment, the polymer-paclitaxel conjugate, particle or composition is administered by intravenous administration over a period equal to or less than about 30 minutes, 45 minutes, 60 minutes, 90 minutes, 120 minutes, 150 minutes or 180 minutes. In one embodiment, the subject is administered at least one additional dose of the conjugate, particle or composition, e.g., the subject is administered at least two, three, four, five, six, seven, eight, nine or ten additional doses of the conjugate, particle or composition. In one embodiment, the polymer-paclitaxel conjugate, particle or composition is administered once every one, two, three, four, five or six weeks. In one embodiment, the dosing schedule is not changed between doses. For example, when the dosing schedule is once every three weeks, an additional dose (or doses) is administered in three weeks. In one embodiment, when at least one additional dose is administered, the additional dose (or additional doses) is administered in an amount that includes 135 mg/m^2 or greater (e.g., 140 mg/m^2, 145 mg/m^2, 150 mg/m^2, 155 mg/m^2, 160 mg/m^2, 165 mg/m^2, 170 mg/m^2, 175 mg/m^2, 180 mg/m^2, 185 mg/m^2, 190 mg/m^2, 195 mg/m^2, 200 mg/m^2, 210 mg/m^2, 220 mg/m^2, 230 mg/m^2, 240 mg/m^2, 250 mg/m^2, 260 mg/m^2, 270 mg/m^2, 280 mg/m^2, 290 mg/m^2, 300 mg/m^2) of paclitaxel. In one embodiment, when at least one additional dose is administered, the additional dose (or additional doses) is administered by intravenous administration over a period equal to or less than about 30 minutes, 45 minutes, 60 minutes, 90 minutes, 120 minutes, 150 minutes or 180 minutes. In an embodiment, the polymer-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 1 or Fig. 2 to a

polymer described herein. In an embodiment, the polymer-paclitaxel conjugate is a polymer-paclitaxel conjugate shown in Fig. 1 or Fig. 2.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition includes a polymer-paclitaxel conjugate, particle or composition, e.g., a polymer-paclitaxel conjugate, particle or composition described herein, e.g., a polymer-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a polymer described herein, and the conjugate, particle or composition is administered to the subject in an amount that includes 135 mg/m^2 or greater (e.g., 140 mg/m^2, 145 mg/m^2, 150 mg/m^2, 155 mg/m^2, 160 mg/m^2, 165 mg/m^2, 170 mg/m^2, 175 mg/m^2, 180 mg/m^2, 185 mg/m^2, 190 mg/m^2, 195 mg/m^2, 200 mg/m^2, 210 mg/m^2, 220 mg/m^2, 230 mg/m^2, 240 mg/m^2, 250 mg/m^2, 260 mg/m^2, 270 mg/m^2, 280 mg/m^2, 290 mg/m^2, 300 mg/m^2) of paclitaxel, administered by intravenous administration over a period equal to or less than about 30 minutes, 45 minutes, 60 minutes, 90 minutes, 120 minutes, 150 minutes or 180 minutes, for at least two, three, fours, five, six, seven or eight doses, wherein the subject is administered a dose of the composition once every one, two, three, four, five or six weeks.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-paclitaxel conjugate, particle or composition, e.g., a polymer-paclitaxel conjugate, particle or composition described herein, e.g., a polymer-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a polymer described herein, and at least two, three, four, five, six, seven, eight, nine or ten doses are administered to the subject and each dose is an amount that includes 135 mg/m^2 or greater (e.g., 140 mg/m^2, 145 mg/m^2, 150 mg/m^2, 155 mg/m^2, 160 mg/m^2, 165 mg/m^2, 170 mg/m^2, 175 mg/m^2, 180 mg/m^2, 185 mg/m^2, 190 mg/m^2, 195 mg/m^2, 200 mg/m^2, 210 mg/m^2, 220 mg/m^2, 230 mg/m^2, 240 mg/m^2, 250 mg/m^2, 260 mg/m^2 , 270 mg/m^2, 280 mg/m^2, 290 mg/m^2, 300 mg/m^2) of paclitaxel, to thereby treat the disorder. In one embodiment, the dose is administered once every one, two, three, four, five, six, seven or eight weeks. In one embodiment, a dose is administered once every three weeks. In one embodiment, each dose is administered by intravenous administration over a period equal to or less than about 30 minutes, 45 minutes, 60 minutes, 90 minutes, 120 minutes, 150 minutes or 180 minutes. In one embodiment,

the dosing schedule is not changed between doses. For example, when the dosing schedule is once every three weeks, an additional dose (or doses) is administered in three weeks.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-doxorubicin conjugate, particle or composition, e.g., a polymer-doxorubicin conjugate, particle or composition described herein, e.g., a polymer-doxorubicin conjugate comprising doxorubicin, coupled, e.g., via linkers, to a polymer described herein, and, e.g., the conjugate, particle or composition is administered in an amount that includes 60 mg/m^2 or greater (e.g., 65 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 85 mg/m^2, 90 mg/m^2, 95 mg/m^2, 100 mg/m^2 , 105 mg/m^2, 110 mg/m^2, 115 mg/m^2, 120 mg/m^2) of the doxorubicin, to thereby treat the disorder. In another embodiment, the polymer-doxorubicin conjugate, particle or composition is administered with one or more additional chemotherapeutic agent and the conjugate, particle or composition is administered in an amount that includes 40 mg/m^2 or greater (e.g., 45 mg/m^2, 50 mg/m^2, 55 mg/m^2, 60 mg/m^2, 65 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2) of the doxorubicin, to thereby treat the disorder. In one embodiment, the conjugate, particle or composition is administered by intravenous administration over a period equal to or less than about 30 minutes, 45 minutes, 60 minutes, 90 minutes, 120 minutes, 150 minutes or 180 minutes. In one embodiment, the subject is administered at least one additional dose of the composition, e.g., the subject is administered at least two, three, four, five, six, seven or eight additional doses of the composition. In one embodiment, the conjugate, particle or composition is administered once every one, two, three, four, five or six weeks. In one embodiment, the dosing schedule is not changed between doses. For example, when the dosing schedule is once every three weeks, an additional dose (or doses) is administered in three weeks. In one embodiment, when at least one additional dose is administered, an additional dose (or additional doses) is administered in an amount of the conjugate, particle or composition that includes 60 mg/m^2 or greater (e.g., 65 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 85 mg/m^2, 90 mg/m^2, 95 mg/m^2, 100 mg/m^2, 105 mg/m^2, 110 mg/m^2, 115 mg/m^2, 120 mg/m^2) of the doxorubicin, or 40 mg/m^2 or greater (e.g., 45 mg/m^2, 50 mg/m^2, 55 mg/m^2, 60 mg/m^2, 65 mg/m^2, 70 mg/m^2, 75

mg/m^2, 80 mg/m^2) of the doxorubicin when administered in combination with an additional chemotherapeutic agent. In one embodiment, when at least one additional dose is administered, the additional dose (or additional doses) is administered by intravenous administration over a period equal to or less than about 30 minutes, 45 minutes, 60 minutes, 90 minutes, 120 minutes, 150 minutes or 180 minutes. In an embodiment, the polymer-doxorubicin conjugate comprises doxorubicin, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-doxorubicin conjugate is a polymer-doxorubicin conjugate shown in Fig. 1.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-doxorubicin conjugate, particle or composition, e.g., a polymer-doxorubicin conjugate, particle or composition described herein, e.g., a polymer-doxorubicin conjugate comprising doxorubicin, coupled, e.g., via linkers, to a polymer described herein, and the conjugate, particle or composition is administered to the subject in an amount that includes 60 mg/m^2 or greater (e.g., 65 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 85 mg/m^2, 90 mg/m^2, 95 mg/m^2, 100 mg/m^2, 105 mg/m^2, 110 mg/m^2, 115 mg/m^2, 120 mg/m^2) of the doxorubicin, administered by intravenous administration over a period equal to or less than about 30 minutes, 45 minutes, 60 minutes, 90 minutes, 120 minutes, 150 minutes or 180 minutes, for at least two, three, fours, five or six doses, wherein the subject is administered a dose of the composition once every one, two, three, four, five or six weeks. In another embodiment, the conjugate, particle or composition is administered in combination with an additional chemotherapeutic agent and the conjugate, particle or composition is administered to the subject in an amount that includes 40 mg/m^2 or greater (e.g., 45 mg/m^2, 50 mg/m^2, 55 mg/m^2, 60 mg/m^2, 65 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2) of the doxorubicin, administered by intravenous administration over a period equal to or less than about 30 minutes, 45 minutes, 60 minutes, 90 minutes, 120 minutes, 150 minutes or 180 minutes, for at least two, three, fours, five or six doses, wherein the subject is administered a dose of the composition once every one, two, three, four, five or six weeks.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-doxorubicin conjugate, particle or composition, e.g., a polymer-doxorubicin conjugate, particle or composition described herein, e.g., a polymer-doxorubicin conjugate, particle or composition comprising doxorubicin, coupled, e.g., via linkers, to a polymer described herein, and at least two, three, four, five, six, seven or eight doses are administered to the subject and each dose is an amount of the composition that includes 60 mg/m^2 or greater (e.g., 65 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 85 mg/m^2, 90 mg/m^2, 95 mg/m^2, 100 mg/m^2, 105 mg/m^2, 110 mg/m^2, 115 mg/m^2, 120 mg/m^2) of the doxorubicin, to thereby treat the disorder. In one embodiment, at least two, three, four, five, six, seven or eight doses of the polymer-doxorubicin conjugate, particle or composition are administered to the subject in combination with an additional chemotherapeutic agent and each dose of the conjugate, particle or composition is an amount that includes 40 mg/m^2 or greater (e.g., 45 mg/m^2, 50 mg/m^2, 55 mg/m^2, 60 mg/m^2, 65 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2) of the doxorubicin, to thereby treat the disorder. In one embodiment, the dose is administered once every one, two, three, four, five, six, seven or eight weeks. In one embodiment, a dose is administered once every three weeks. In one embodiment, each dose is administered by intravenous administration over a period equal to or less than about 30 minutes, 45 minutes, 60 minutes, 90 minutes, 120 minutes, 150 minutes or 180 minutes. In one embodiment, the dosing schedule is not changed between doses. For example, when the dosing schedule is once every three weeks, an additional dose (or doses) is administered in three weeks.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition, e.g., a polymer-anticancer agent conjugate, particle or composition comprising an anticancer agent coupled, e.g., via linkers, to a polymer described herein, is administered once every three weeks in combination with one or more additional chemotherapeutic agent that is also administered once every three weeks. In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered once every three weeks in combination with one or more of the following chemotherapeutic agents: a vinca alkaloid (e.g., vinblastine, vincristine, vindesine and vinorelbine); an alkylating agent (e.g., cyclophosphamide, dacarbazine,

melphalan, ifosfamide, temozolomide); a topoisomerase inhibitor (e.g., topotecan, irinotecan, etoposide, teniposide, lamellarin D, SN-38, camptothecin (e.g., IT-101)); a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin); an antibiotic (e.g., mitomycin, actinomycin, bleomycin), an antimetabolite (e.g., an antifolate (e.g., pemetrexed, floxuridine, raltitrexed) and a pyrimidine analogue (e.g., capecitabine, cytarabine, gemcitabine, 5FU)); an anthracycline (e.g., doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone, valrubicin); and a taxane (e.g., paclitaxel, docetaxel, larotaxel or cabazitaxel).

In one embodiment, the polymer-anticancer agent conjugate, e.g., a polymer-anticancer agent conjugate, particle or composition comprising an anticancer agent coupled, e.g., via linkers, to a polymer described herein, is administered once every two weeks in combination with one or more additional chemotherapeutic agent that is administered orally. In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered once every two weeks in combination with one or more of the following chemotherapeutic agents: capecitabine, estramustine, erlotinib, rapamycin, SDZ-RAD, CP-547632; AZD2171, sunitinib, sorafenib and everolimus.

In another aspect, the invention features a method of treating an unresectable cancer, a chemotherapeutic sensitive cancer, a chemotherapeutic refractory cancer, a chemotherapeutic resistant cancer, and/or a relapsed cancer. The method comprises: administering a polymer-anticancer agent conjugate, particle or composition, e.g., a polymer-anticancer agent conjugate, particle or composition described herein, to a subject, e.g., a human, in an amount effective to treat the cancer, to thereby treat the cancer.

In an embodiment, the polymer-anticancer agent conjugate comprises an anticancer agent such as docetaxel, paclitaxel, larotaxel, cabazitaxel or doxorubicin, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-anticancer agent conjugate comprises an anticancer agent, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-anticancer agent conjugate is a polymer-anticancer agent conjugate shown in Fig. 1 or Fig. 2.

In one embodiment, the cancer is refractory to, resistant to and/or relapsed during or after, treatment with, one or more of: an anthracycline (e.g., doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone, valrubicin), an alkylating agent (e.g., cyclophosphamide, dacarbazine, melphalan, ifosfamide, temozolomide), an antimetabolite (e.g., an antifolate (e.g., pemetrexed, floxuridine, raltitrexed) and a pyrimidine analogue (e.g., capecitabine, cytarabine, gemcitabine, 5FU)), a vinca alkaloid (e.g., vinblastine, vincristine, vindesine, vinorelbine), a topoisomerase inhibitor (e.g., topotecan, irinotecan, etoposide, teniposide, lamellarin D, SN-38, camptothecin (e.g., IT-101)) and a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin). In one embodiment, the cancer is resistant to more than one chemotherapeutic agent, e.g., the cancer is a multidrug resistant cancer. In one embodiment, the cancer is resistant to one or more of a platinum based agent, an alkylating agent, an anthracycline and a vinca alkaloid. In one embodiment, the cancer is resistant to one or more of a platinum based agent, an alkylating agent, a taxane and a vinca alkaloid.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with a second chemotherapeutic agent, e.g., a chemotherapeutic agent described herein. For example, the polymer-anticancer agent conjugate, particle or composition can be administered in combination with a vinca alkaloid (e.g., vinblastine, vincristine, vindesine, vinorelbine) and/or a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin).

In one embodiment, the cancer is a cancer described herein. For example, the cancer can be a cancer of the bladder (including accelerated and metastatic bladder cancer), breast (e.g., estrogen receptor positive breast cancer; estrogen receptor negative breast cancer; HER-2 positive breast cancer; HER-2 negative breast cancer; progesterone receptor positive breast cancer; progesterone receptor negative breast cancer; estrogen receptor negative, HER-2 negative and progesterone receptor negative breast cancer (i.e., triple negative breast cancer); inflammatory breast cancer), colon (including colorectal cancer), kidney (e.g., transitional cell carcinoma), liver, lung (including small and non-small cell lung cancer (including lung adenocarcinoma, bronchoalveolar cancer and squamous cell cancer)), genitourinary

tract, e.g., ovary (including fallopian tube and peritoneal cancers), cervix, prostate, testes, kidney, and ureter, lymphatic system, rectum, larynx, pancreas (including exocrine pancreatic carcinoma), esophagus, stomach, gall bladder, thyroid, skin (including squamous cell carcinoma), brain (including glioblastoma multiforme), head and neck (e.g., occult primary), and soft tissue (e.g., Kaposi's sarcoma (e.g., AIDS related Kaposi's sarcoma), leiomyosarcoma, angiosarcoma, and histiocytoma). Preferred cancers include breast cancer (e.g., metastatic or locally advanced breast cancer), prostate cancer (e.g., hormone refractory prostate cancer), renal cell carcinoma, lung cancer (e.g., non-small cell lung cancer and small cell lung cancer (including lung adenocarcinoma, bronchoalveolar cancer and squamous cell cancer) e.g., unresectable, locally advanced or metastatic non-small cell lung cancer and small cell lung cancer), pancreatic cancer, gastric cancer (e.g., metastatic gastric adenocarcinoma), colorectal cancer, rectal cancer, squamous cell cancer of the head and neck, lymphoma (Hodgkin's lymphoma or non-Hodgkin's lymphoma), renal cell carcinoma, carcinoma of the urothelium, soft tissue sarcoma (e.g., Kaposi's sarcoma (e.g., AIDS related Kaposi's sarcoma), leiomyosarcoma, angiosarcoma, and histiocytoma), gliomas, myeloma (e.g., multiple myeloma), melanoma (e.g., advanced or metastatic melanoma), germ cell tumors, ovarian cancer (e.g., advanced ovarian cancer, e.g., advanced fallopian tube or peritoneal cancer), and gastrointestinal cancer.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-docetaxel conjugate, particle or composition, e.g., a polymer-docetaxel conjugate, particle or composition described herein, e.g., a polymer-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-docetaxel conjugate is a polymer-docetaxel conjugate shown in Fig. 1.

In one embodiment, the polymer-docetaxel conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-paclitaxel conjugate, particle or composition, e.g., a

polymer-paclitaxel conjugate, particle or composition described herein, e.g., a polymer-paclitaxel conjugate comprising paclitaxel coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-paclitaxel conjugate is a polymer-paclitaxel conjugate shown in Fig. 1 or Fig. 2.

In one embodiment, the polymer-paclitaxel conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-doxorubicin conjugate, particle or composition, e.g., a polymer-doxorubicin conjugate, particle or composition described herein, e.g., a polymer-doxorubicin conjugate comprising doxorubicin, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-doxorubicin conjugate comprises doxorubicin, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-doxorubicin conjugate is a polymer-doxorubicin conjugate shown in Fig. 1.

In one embodiment, the polymer-doxorubicin conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In yet another aspect, the invention features a method of treating metastatic or locally advanced breast cancer in a subject, e.g., a human. The method comprises: administering a polymer-anticancer agent conjugate, particle or composition, e.g., a polymer-anticancer agent conjugate, particle or composition described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer. In an embodiment, the polymer-anticancer agent conjugate comprises an anticancer agent such as docetaxel, paclitaxel, larotaxel, cabazitaxel or doxorubicin, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-anticancer agent conjugate comprises an anticancer agent, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-anticancer agent conjugate is a polymer-anticancer conjugate shown in Fig. 1 or Fig. 2.

In one embodiment, the breast cancer is estrogen receptor positive breast cancer; estrogen receptor negative breast cancer; HER-2 positive breast cancer; HER-

2 negative breast cancer; progesterone receptor positive breast cancer; progesterone receptor negative breast cancer; estrogen receptor negative, HER-2 negative and progesterone receptor negative breast cancer (i.e., triple negative breast cancer) or inflammatory breast cancer.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with a HER-2 pathway inhibitor, e.g., a HER-2 inhibitor or a HER-2 receptor inhibitor. For example, the polymer-anticancer agent conjugate, particle or composition is administered with trastuzumab.

In some embodiments, the polymer-anticancer agent conjugate, particle or composition is administered in combination with a second chemotherapeutic agent. For example, the polymer-anticancer agent conjugate, particle or composition is administered in combination with a vascular endothelial growth factor (VEGF) pathway inhibitor, e.g., a VEGF inhibitor (e.g., bevacizumab) or VEGF receptor inhibitor (e.g., CP-547632, AZD2171, sorafenib and sunitinib). In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with bevacizumab.

In some embodiments, the polymer-anticancer agent conjugate, particle or composition is administered in combination with an anthracycline (e.g., daunorubicin, doxorubicin, epirubicin, valrubicin and idarubicin). In some embodiments, the polymer-anticancer agent conjugate, particle or composition is a polymer-taxane conjugate, particle or composition that is administered in combination with an anthracycline (e.g., daunorubicin, doxorubicin, epirubicin, valrubicin and idarubicin).

In some embodiments, the polymer-anticancer agent conjugate, particle or composition is administered in combination with an anti-metabolite, e.g., an antifolate (e.g., floxuridine, pemetrexed) or pyrimidine analogue (e.g., 5FU)).

In some embodiments, the polymer-anticancer agent conjugate, particle or composition is administered in combination with an anthracycline (e.g., daunorubicin, doxorubicin, epirubicin, valrubicin and idarubicin) and an anti-metabolite (e.g., floxuridine, pemetrexed, 5FU). In some embodiments, the polymer-anticancer agent conjugate, particle or composition is a polymer-taxane conjugate, particle or composition that is administered in combination with an anthracycline (e.g.,

daunorubicin, doxorubicin, epirubicin, valrubicin and idarubicin) and an anti-metabolite (e.g., floxuridine, pemetrexed, 5FU).

In some embodiments, the polymer-anticancer agent conjugate, particle or composition is administered in combination with a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin).

In some embodiments, the polymer-anticancer agent conjugate, particle or composition is administered in combination with an mTOR inhibitor. Non-limiting examples of mTOR inhibitors include rapamycin, everolimus, AP23573, CCI-779 and SDZ-RAD.

In some embodiments, the polymer-anticancer agent conjugate, particle or composition is administered in combination with a poly ADP-ribose polymerase (PARP) inhibitor (e.g., BSI 201, Olaparib (AZD-2281), ABT-888, AG014699, CEP 9722, MK 4827, KU-0059436 (AZD2281), LT-673, 3-aminobenzamide).

In some embodiments, the polymer-anticancer agent conjugate, particle or composition is administered in combination with a vinca alkaloid (e.g., vinblastine, vincristine, vindesine, vinorelbine).

In some embodiments, the polymer-anticancer agent conjugate, particle or composition is administered in combination with an antibiotic (e.g., mitomycin, actinomycin, bleomycin).

In some embodiments, the polymer-anticancer agent conjugate, particle or composition is administered in combination with an alkylating agent (e.g., cyclophosphamide, dacarbazine, melphalan, ifosfamide, temozolomide).

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-docetaxel conjugate, particle or composition, e.g., a polymer-docetaxel conjugate, particle or composition described herein, e.g., a polymer-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-docetaxel conjugate is a polymer-docetaxel conjugate shown in Fig. 1.

In one embodiment, the polymer-docetaxel conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-paclitaxel conjugate, particle or composition, e.g., a polymer-paclitaxel conjugate, particle or composition described herein, e.g., a polymer-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-paclitaxel conjugate is a polymer-paclitaxel conjugate shown in Fig. 1 or Fig. 2.

In one embodiment, the polymer-paclitaxel conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-doxorubicin conjugate, particle or composition, e.g., a polymer-doxorubicin conjugate, particle or composition described herein, e.g., a polymer-doxorubicin conjugate comprising doxorubicin, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-doxorubicin conjugate comprises doxorubicin, coupled via a linker shown in Fig. 1 to a polymer described herein. In an embodiment, the polymer-doxorubicin conjugate is a polymer-doxorubicin conjugate shown in Fig. 1.

In one embodiment, the polymer-doxorubicin conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In yet another aspect, the invention features a method of treating metastatic or locally advanced breast cancer, e.g. a breast cancer described herein, in a subject, e.g., a human. The method comprises:

providing a subject who has metastatic or locally advanced breast cancer and has been treated with a chemotherapeutic agent which did not effectively treat the cancer (e.g., the subject has a chemotherapeutic refractory, a chemotherapeutic resistant and/or a relapsed cancer) or which had an unacceptable side effect (e.g., the subject has a chemotherapeutic sensitive cancer), and

administering a polymer-anticancer agent conjugate, particle or composition, e.g., a polymer-anticancer agent conjugate, particle or composition described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer. In an embodiment, the polymer-anticancer agent conjugate comprises an anticancer agent such as docetaxel, paclitaxel, larotaxel, cabazitaxel or doxorubicin, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-anticancer agent conjugate comprises an anticancer agent, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-anticancer agent conjugate is a polymer-anticancer agent conjugate shown in Fig. 1 or Fig. 2.

In one embodiment, the cancer is refractory to, resistant to, and/or relapsed with treatment with one or more of: a taxane, an anthracycline, a vinca alkaloid (e.g., vinblastine, vincristine, vindesine and vinorelbine), an alkylating agent (e.g., cyclophosphamide, dacarbazine, melphalan, ifosfamide, temozolomide) and a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin). In one embodiment, the cancer is refractory to, resistant to, and/or relapsed with treatment with one or more of: an anthracycline and an alkylating agent, and a polymer-taxane conjugate, particle or composition is administered to the subject.

In one embodiment, the cancer is a multidrug resistant cancer.

In one embodiment, the composition is administered in combination with a pyrimidine analogue, e.g., a pyrimidine analogue described herein (e.g., capecitabine).

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-docetaxel conjugate, particle or composition, e.g., a polymer-docetaxel conjugate, particle or composition described herein, e.g., a polymer-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-docetaxel conjugate is a polymer-docetaxel conjugate shown in Fig. 1.

In one embodiment, the polymer-docetaxel conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-paclitaxel conjugate, particle or composition, e.g., a polymer-paclitaxel conjugate, particle or composition described herein, e.g., a polymer-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-paclitaxel conjugate is a polymer-paclitaxel conjugate shown in Fig. 1 or Fig. 2.

In one embodiment, the polymer-paclitaxel conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-doxorubicin conjugate, particle or composition, e.g., a polymer-doxorubicin conjugate, particle or composition described herein, e.g., a polymer-doxorubicin conjugate comprising doxorubicin, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-doxorubicin conjugate comprises doxorubicin, coupled via a linker shown in Fig. 1 to a polymer described herein. In an embodiment, the polymer-doxorubicin conjugate is a polymer-doxorubicin conjugate shown in Fig. 1.

In one embodiment, the polymer-doxorubicin conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In yet another aspect, the invention features a method of treating hormone refractory prostate cancer in a subject, e.g., a human. The method comprises: administering a polymer-anticancer agent conjugate, particle or composition, e.g., a polymer-anticancer agent conjugate, particle or composition described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer. In an embodiment, the polymer-anticancer agent conjugate comprises an anticancer agent such as docetaxel, paclitaxel, larotaxel, cabazitaxel or doxorubicin, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-anticancer agent conjugate comprises an anticancer agent, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-anticancer agent conjugate is a polymer-anticancer agent conjugate shown in Fig. 1 or Fig. 2.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with prednisone.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with estramustine.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with an anthracenedione (e.g., mitoxantrone) and prednisone.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with a vascular endothelial growth factor (VEGF) pathway inhibitor, e.g., a VEGF inhibitor (e.g., bevacizumab) or VEGF receptor inhibitor (e.g., CP-547632; AZD2171, AV-951, sunitinib and sorafenib). .

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with an mTOR inhibitor. Non-limiting examples of mTOR inhibitors include rapamycin, everolimus, AP23573, CCI-779, and SDZ-RAD.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with abiraterone.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin).

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-docetaxel conjugate, particle or composition, e.g., a polymer-docetaxel conjugate, particle or composition described herein, e.g., a polymer-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-docetaxel conjugate is a polymer-docetaxel conjugate shown in Fig. 1.

In one embodiment, the polymer-docetaxel conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-paclitaxel conjugate, particle or composition, e.g., a polymer-paclitaxel conjugate, particle or composition described herein, e.g., a polymer-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-paclitaxel conjugate is a polymer-paclitaxel conjugate shown in Fig. 1 or Fig. 2.

In one embodiment, the polymer-paclitaxel conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-doxorubicin conjugate, particle or composition, e.g., a polymer-doxorubicin conjugate, particle or composition described herein, e.g., a polymer-doxorubicin conjugate comprising doxorubicin, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-doxorubicin conjugate comprises doxorubicin, coupled via a linker shown in Fig. 1 to a polymer described herein. In an embodiment, the polymer-doxorubicin conjugate is a polymer-doxorubicin conjugate shown in Fig. 1.

In one embodiment, the polymer-doxorubicin conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In yet another aspect, the invention features a method of treating hormone refractory prostate cancer in a subject, e.g., a human. The method comprises:

providing a subject who has hormone refractory prostate cancer and has been treated with a chemotherapeutic agent that did not effectively treat the cancer (e.g., the subject has a chemotherapeutic refractory, chemotherapeutic resistant and/or relapsed cancer) or who had unacceptable side effect (e.g., the subject has a chemotherapeutic sensitive cancer), and

administering a polymer-anticancer agent conjugate, particle or composition, e.g., a polymer-anticancer agent conjugate, particle or composition described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

In an embodiment, the polymer-anticancer agent conjugate, particle or composition comprises an anticancer agent such as docetaxel, paclitaxel, larotaxel, cabazitaxel or doxorubicin, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-anticancer agent conjugate comprises an anticancer agent, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-anticancer agent conjugate is a polymer-anticancer agent conjugate shown in Fig. 1 or Fig. 2.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-docetaxel conjugate, particle or composition, e.g., a polymer-docetaxel conjugate, particle or composition described herein, e.g., a polymer-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-docetaxel conjugate is a polymer-docetaxel conjugate shown in Fig. 1.

In one embodiment, the polymer-docetaxel conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-paclitaxel conjugate, particle or composition, e.g., a polymer-paclitaxel conjugate, particle or composition described herein, e.g., a polymer-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-paclitaxel conjugate is a polymer-paclitaxel conjugate shown in Fig. 1 or Fig. 2.

In one embodiment, the polymer-paclitaxel conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-doxorubicin conjugate, particle or composition, e.g., a polymer-doxorubicin conjugate, particle or composition described herein, e.g., a polymer-doxorubicin conjugate comprising doxorubicin, coupled, e.g., via linkers, to

a polymer described herein. In an embodiment, the polymer-doxorubicin conjugate comprises doxorubicin, coupled via a linker shown in Fig. 1 to a polymer described herein. In an embodiment, the polymer-doxorubicin conjugate is a polymer-doxorubicin conjugate shown in Fig. 1.

In one embodiment, the polymer-doxorubicin conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In yet another aspect, the invention features a method of treating metastatic or advanced ovarian cancer (e.g., peritoneal or fallopian tube cancer) in a subject, e.g., a human. The method comprises: administering a polymer-anticancer agent conjugate, particle or composition, e.g., a polymer-anticancer agent conjugate, particle or composition described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

In an embodiment, the polymer-anticancer agent conjugate comprises an anticancer agent such as docetaxel, paclitaxel, larotaxel, cabazitaxel or doxorubicin, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-anticancer agent conjugate comprises an anticancer agent coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-anticancer agent conjugate is a polymer-anticancer agent conjugate shown in Fig. 1 or Fig. 2.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin).

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with an alkylating agent (e.g., cyclophosphamide, dacarbazine, melphalan, ifosfamide, temozolomide).

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin) and an alkylating agent (e.g., cyclophosphamide, dacarbazine, melphalan, ifosfamide, temozolomide).

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with one or more of: an anti-metabolite,

e.g., an antifolate (e.g., pemetrexed, floxuridine, raltitrexed) or pyrimidine analog (e.g., capecitabine, cytarabine, gemcitabine, 5-fluorouracil); an alkylating agent (e.g., cyclophosphamide, dacarbazine, melphalan, ifosfamide, temozolomide); a topoisomerase inhibitor (e.g., etoposide, topotecan, irinotecan, teniposide, lamellarin D, SN-38); a platinum based agent (carboplatin, cisplatin, oxaliplatin); a vinca alkaloid (e.g., vinblastine, vincristine, vindesine, vinorelbine). In one embodiment, the composition is administered in combination with one or more of: capecitabine, cyclophosphamide, etoposide, gemcitabine, ifosfamide, irinotecan, melphalan, oxaliplatin, vinorelbine, vincristine and pemetrexed.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with a vascular endothelial growth factor (VEGF) pathway inhibitor, e.g., a VEGF inhibitor or VEGF receptor inhibitor. In one embodiment, the VEGF inhibitor is bevacizumab. In another embodiment, the VEGF receptor inhibitor is selected from CP-547632, AZD2171, sorafenib and sunitinib.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with an mTOR inhibitor, e.g., rapamycin, everolimus, AP23573, CCI-779 or SDZ-RAD.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-docetaxel conjugate, particle or composition, e.g., a polymer-docetaxel conjugate, particle or composition described herein, e.g., a polymer-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-docetaxel conjugate is a polymer-docetaxel conjugate shown in Fig. 1.

In one embodiment, the polymer-docetaxel conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-paclitaxel conjugate, particle or composition, e.g., a polymer-paclitaxel conjugate, particle or composition described herein, e.g., a polymer-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a

polymer described herein. In an embodiment, the polymer-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-paclitaxel conjugate is a polymer-paclitaxel conjugate shown in Fig. 1 or Fig. 2.

In one embodiment, the polymer-paclitaxel conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-doxorubicin conjugate, particle or composition, e.g., a polymer-doxorubicin conjugate, particle or composition described herein, e.g., a polymer-doxorubicin conjugate comprising doxorubicin, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-doxorubicin conjugate comprises doxorubicin, coupled via a linker shown in Fig. 1 to a polymer described herein. In an embodiment, the polymer-doxorubicin conjugate is a polymer-doxorubicin conjugate shown in Fig. 1.

In one embodiment, the polymer-doxorubicin conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In yet another aspect, the invention features a method of treating metastatic or advanced ovarian cancer (e.g., peritoneal or fallopian tube cancer) in a subject, e.g., a human. The method comprises:

providing a subject who has advanced ovarian cancer and has been treated with a chemotherapeutic agent that did not effectively treat the cancer (e.g., the subject has a chemotherapeutic refractory, a chemotherapeutic resistant and/or a relapsed cancer) or who had an unacceptable side effect (e.g., the subject has a chemotherapeutic sensitive cancer), and

administering a composition comprising a polymer-anticancer agent conjugate, particle or composition, e.g., a polymer-anticancer agent conjugate, particle or composition described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

In an embodiment, the polymer-anticancer agent conjugate comprises an anticancer agent such as docetaxel, paclitaxel, larotaxel, cabazitaxel or doxorubicin, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the

polymer-anticancer agent conjugate comprises an anticancer agent, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-anticancer agent conjugate is a polymer-anticancer agent conjugate shown in Fig. 1 or Fig. 2.

In one embodiment, the subject has been treated with a platinum-based agent that did not effectively treat the cancer (e.g., the subject has been treated with cisplatin, carboplatin or oxaliplatin which did not effectively treat the cancer). In one embodiment, the subject has been treated with cisplatin or carboplatin which did not effectively treat the cancer.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with a pyrimidine analog, e.g., capecitabine or gemcitabine.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with capecitabine and gemcitabine.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with an anthracycline, e.g., daunorubicin, doxorubicin, epirubicin, valrubicin and idarubicin. In one embodiment, the anthracycline is doxorubicin, e.g., liposomal doxorubicin.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with a topoisomerase I inhibitor, e.g., irinotecan, topotecan, teniposide, lamellarin D, SN-38, camptothecin (e.g., IT-101). In one embodiment the topoisomerase I inhibitor is topotecan. In another embodiment, the topoisomerase I inhibitor is irinotecan or etoposide.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with one or more of: an anti-metabolite, e.g., an antifolate (e.g., pemetrexed, floxuridine, raltitrexed) or pyrimidine analog (e.g., capecitabine, cytarabine, gemcitabine, 5FU); an alkylating agent (e.g., cyclophosphamide, dacarbazine, melphalan, ifosfamide, temozolomide); a platinum based agent (carboplatin, cisplatin, oxaliplatin); and a vinca alkaloid (e.g., vinblastine, vincristine, vindesine, vinorelbine). In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with one or more

of: capecitabine, cyclophosphamide, etoposide, gemcitabine, ifosfamide, irinotecan, melphalan, oxaliplatin, vinorelbine, vincristine and pemetrexed.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-docetaxel conjugate, particle or composition, e.g., a polymer-docetaxel conjugate, particle or composition described herein, e.g., a polymer-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-docetaxel conjugate is a polymer-docetaxel conjugate shown in Fig. 1.

In one embodiment, the polymer-docetaxel conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-paclitaxel conjugate, particle or composition, e.g., a polymer-paclitaxel conjugate, particle or composition described herein, e.g., a polymer-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-paclitaxel conjugate is a polymer-paclitaxel conjugate shown in Fig. 1 or Fig. 2.

In one embodiment, the polymer-paclitaxel conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-doxorubicin conjugate, particle or composition, e.g., a polymer-doxorubicin conjugate, particle or composition described herein, e.g., a polymer-doxorubicin conjugate comprising doxorubicin, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-doxorubicin conjugate comprises doxorubicin, coupled via a linker shown in Fig. 1 to a polymer described herein. In an embodiment, the polymer-doxorubicin conjugate is a polymer-doxorubicin conjugate shown in Fig. 1.

In one embodiment, the polymer-doxorubicin conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In yet another aspect, the invention features a method of treating non small cell lung cancer or small cell lung cancer (e.g., unresectable, locally advanced or metastatic non small cell lung cancer or small cell lung cancer) in a subject, e.g., a human. The method comprises: administering a polymer-anticancer agent conjugate, particle or composition, e.g., a polymer-anticancer agent conjugate, particle or composition described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer. The lung cancer can be a lung adenocarcinoma, a bronchoalveolar cancer, or a squamous cell cancer. In one embodiment, the subject has increased KRAS and/or ST expression levels, e.g., as compared to a reference standard, and/or has a mutation in a KRAS and/or ST gene. In one embodiment, the subject has a mutation at one or more of: codon 12 of the KRAS gene (e.g., a G to T transversion), codon 13 of the KRAS gene, codon 61 of the KRAS gene.

In an embodiment, the polymer-anticancer agent conjugate comprises an anticancer agent such as docetaxel, paclitaxel, larotaxel, cabazitaxel or doxorubicin, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-anticancer agent conjugate comprises an anticancer agent coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-anticancer agent conjugate is a polymer-anticancer agent conjugate shown in Fig. 1 or Fig. 2.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with a vascular endothelial (VEGF) pathway inhibitor, e.g., a VEGF inhibitor or VEGF receptor inhibitor. In one embodiment, the VEGF inhibitor is bevacizumab. In another embodiment, the VEGF receptor inhibitor is selected from CP-547632, AZD2171, sorafenib and sunitinib.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with an epidermal growth factor (EGF) pathway inhibitor, e.g., an EGF inhibitor or EGF receptor inhibitor. In one embodiment, the EGF receptor inhibitor is cetuximab, erlotinib, or gefitinib.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin). In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin) and a nucleoside analog (e.g., gemcitabine). In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin) and an anti-metabolite, e.g., an antifolate (e.g., floxuridine, pemetrexed) or pyrimidine analogue (e.g., 5FU). In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin) and a vinca alkaloid (e.g., vinblastine, vincristine, vindesine, vinorelbine).

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with a vinca alkaloid (e.g., vinblastine, vincristine, vindesine, vinorelbine).

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with an alkylating agent (e.g., cyclophosphamide, dacarbazine, melphalan, ifosfamide, temozolomide).

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with an mTOR inhibitor, e.g., rapamycin, everolimus, AP23573, CCI-779 or SDZ-RAD.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition, either alone or with any of the combinations described herein, is administered in combination with radiation.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-docetaxel conjugate, particle or composition, e.g., a polymer-docetaxel conjugate, particle or composition described herein, e.g., a polymer-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer

described herein. In an embodiment, the polymer-docetaxel conjugate is a polymer-docetaxel conjugate shown in Fig. 1.

In one embodiment, the polymer-docetaxel conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-paclitaxel conjugate, particle or composition, e.g., a polymer-paclitaxel conjugate, particle or composition described herein, e.g., a polymer-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-paclitaxel conjugate is a polymer-paclitaxel conjugate shown in Fig. 1 or Fig. 2.

In one embodiment, the polymer-paclitaxel conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-doxorubicin conjugate, particle or composition, e.g., a polymer-doxorubicin conjugate, particle or composition described herein, e.g., a polymer-doxorubicin conjugate comprising doxorubicin, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-doxorubicin conjugate comprises doxorubicin, coupled via a linker shown in Fig. 1 to a polymer described herein. In an embodiment, the polymer-doxorubicin conjugate is a polymer-doxorubicin conjugate shown in Fig. 1.

In one embodiment, the polymer-doxorubicin conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In yet another aspect, the invention features a method of treating unresectable, advanced or metastatic non small cell lung cancer in a subject, e.g., a human. The method comprises:

providing a subject who has unresectable, advanced or metastatic non small cell lung cancer and has been treated with a chemotherapeutic agent that did not effectively treat the cancer (e.g., the subject has a chemotherapeutic refractory, a

chemotherapeutic resistant and/or a relapsed cancer) or who had an unacceptable side effect (e.g., the subject has a chemotherapeutic sensitive cancer), and

administering a polymer-anticancer agent conjugate, particle or composition, e.g., a polymer-anticancer agent conjugate, particle or composition described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

In an embodiment, the polymer-anticancer agent conjugate comprises an anticancer agent such as docetaxel, paclitaxel, larotaxel, cabazitaxel or doxorubicin, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-anticancer agent conjugate comprises an anticancer agent, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-anticancer agent conjugate is a polymer-anticancer agent conjugate shown in Fig. 1 or Fig. 2.

In one embodiment, the subject has been treated with a vascular endothelial growth factor (VEGF) pathway inhibitor (e.g., a VEGF inhibitor or VEGF receptor inhibitor) which did not effectively treat the cancer (e.g., the subject has been treated with bevacizumab CP-547632, AZD2171, sorafenib and sunitinib which did not effectively treat the cancer).

In one embodiment, the subject has been treated with an endothelial growth factor (EGF) pathway inhibitor (e.g., an EGF inhibitor or an EGF receptor inhibitor) which did not effectively treat the cancer (e.g., the subject has been treated with cetuximab, erlotinib, gefitinib which did not effectively treat the cancer).

In one embodiment, the subject has been treated with a platinum-based agent which did not effectively treat the cancer (e.g., the subject has been treated with cisplatin, carboplatin or oxaliplatin which did not effectively treat the cancer).

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with an anti-metabolite, e.g., an antifolate, e.g., floxuridine, pemetrexed or pyrimidine analogue (e.g., 5FU).

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with an EGF pathway inhibitor, e.g., an EGF inhibitor or EGF receptor inhibitor. The EGF receptor inhibitor can be, e.g., cetuximab, erlotinib or gefitinib.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-docetaxel conjugate, particle or composition, e.g., a polymer-docetaxel conjugate, particle or composition described herein, e.g., a polymer-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-docetaxel conjugate is a polymer-docetaxel conjugate shown in Fig. 1.

In one embodiment, the polymer-docetaxel conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-paclitaxel conjugate, particle or composition, e.g., a polymer-paclitaxel conjugate, particle or composition described herein, e.g., a polymer-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-paclitaxel conjugate is a polymer-paclitaxel conjugate shown in Fig. 1 or Fig. 2.

In one embodiment, the polymer-paclitaxel conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-doxorubicin conjugate, particle or composition, e.g., a polymer-doxorubicin conjugate, particle or composition described herein, e.g., a polymer-doxorubicin conjugate comprising doxorubicin, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-doxorubicin conjugate comprises doxorubicin, coupled via a linker shown in Fig. 1 to a polymer described herein. In an embodiment, the polymer-doxorubicin conjugate is a polymer-doxorubicin conjugate shown in Fig. 1.

In one embodiment, the polymer-doxorubicin conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In yet another aspect, the invention features a method of treating multiple myeloma in a subject, e.g., a human. The method comprises: administering a composition comprising a polymer-anticancer agent conjugate, particle or composition, e.g., a polymer-anticancer agent conjugate, particle or composition described herein, to a subject in an amount effective to treat the myeloma, to thereby treat the myeloma.

In an embodiment, the polymer-anticancer agent conjugate comprises an anticancer agent such as docetaxel, paclitaxel or doxorubicin, coupled, e.g., via linkers, to a polymer described herein. In an embodiment, the polymer-anticancer agent conjugate comprises an anticancer agent, coupled via a linker shown in Fig. 1 or Fig. 2 to a polymer described herein. In an embodiment, the polymer-anticancer agent conjugate is a polymer-anticancer agent conjugate shown in Fig. 1 or Fig. 2.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered as a primary treatment for multiple myeloma.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with dexamethasone. In one embodiment, the polymer-anticancer agent conjugate, particle or composition is further administered in combination with an anthracycline (e.g., daunorubicin, doxorubicin (e.g., liposomal doxorubicin or a polymer-doxorubicin conjugate, particle or composition described herein), epirubicin, valrubicin and idarubicin), thalidomide or thalidomide derivative (e.g., lenalidomide). For example, in one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-docetaxel conjugate, particle or composition and/or a polymer-paclitaxel conjugate, particle or composition and the polymer-anticancer agent conjugate, particle or composition is further administered in combination with an anthracycline (e.g., daunorubicin, doxorubicin (e.g., liposomal doxorubicin or a polymer-doxorubicin conjugate, particle or composition described herein), epirubicin, valrubicin and idarubicin), thalidomide or thalidomide derivative (e.g., lenalidomide). In another embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-doxorubicin conjugate, particle or composition that is further administered in combination with thalidomide or thalidomide derivative (e.g., lenalidomide).

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with a proteasome inhibitor (e.g., bortezomib) and dexamethasone. In one embodiment, the polymer-anticancer agent conjugate, particle or composition is further administered in combination with an anthracycline (e.g., daunorubicin, doxorubicin (e.g., liposomal doxorubicin or a polymer-doxorubicin conjugate, particle or composition described herein), epirubicin, valrubicin and idarubicin), thalidomide or thalidomide derivative (e.g., lenalidomide). For example, in one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-docetaxel conjugate, particle or composition and/or a polymer-paclitaxel conjugate, particle or composition and the polymer-anticancer agent conjugate, particle or composition is further administered in combination with an anthracycline (e.g., daunorubicin, doxorubicin (e.g., liposomal doxorubicin or a polymer-doxorubicin conjugate, particle or composition described herein), epirubicin, valrubicin and idarubicin), thalidomide or thalidomide derivative (e.g., lenalidomide). In another embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-doxorubicin conjugate, particle or composition that is further administered in combination with thalidomide or thalidomide derivative (e.g., lenalidomide).

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is administered in combination with a vinca alkaloid (e.g., vinblastine, vincristine, vindesine and vinorelbine) and dexamethasone. In one embodiment, the polymer-anticancer agent conjugate, particle or composition is further administered in combination with an anthracycline (e.g., daunorubicin, doxorubicin (e.g., liposomal doxorubicin or a polymer-doxorubicin conjugate, particle or composition described herein), epirubicin, valrubicin and idarubicin). For example, in one embodiment, the polymer-anticancer agent conjugate, particle or composition is a polymer-docetaxel conjugate, particle or composition and/or a polymer-paclitaxel conjugate, particle or composition and the polymer-anticancer agent conjugate, particle or composition is further administered in combination with an anthracycline (e.g., daunorubicin, doxorubicin (e.g., liposomal doxorubicin or a polymer-doxorubicin conjugate, particle