FIG. 1A

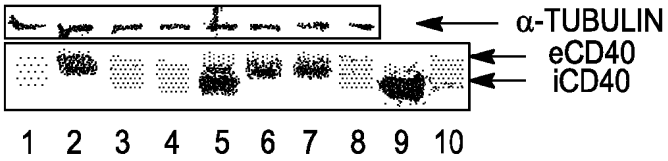


FIG. 1B

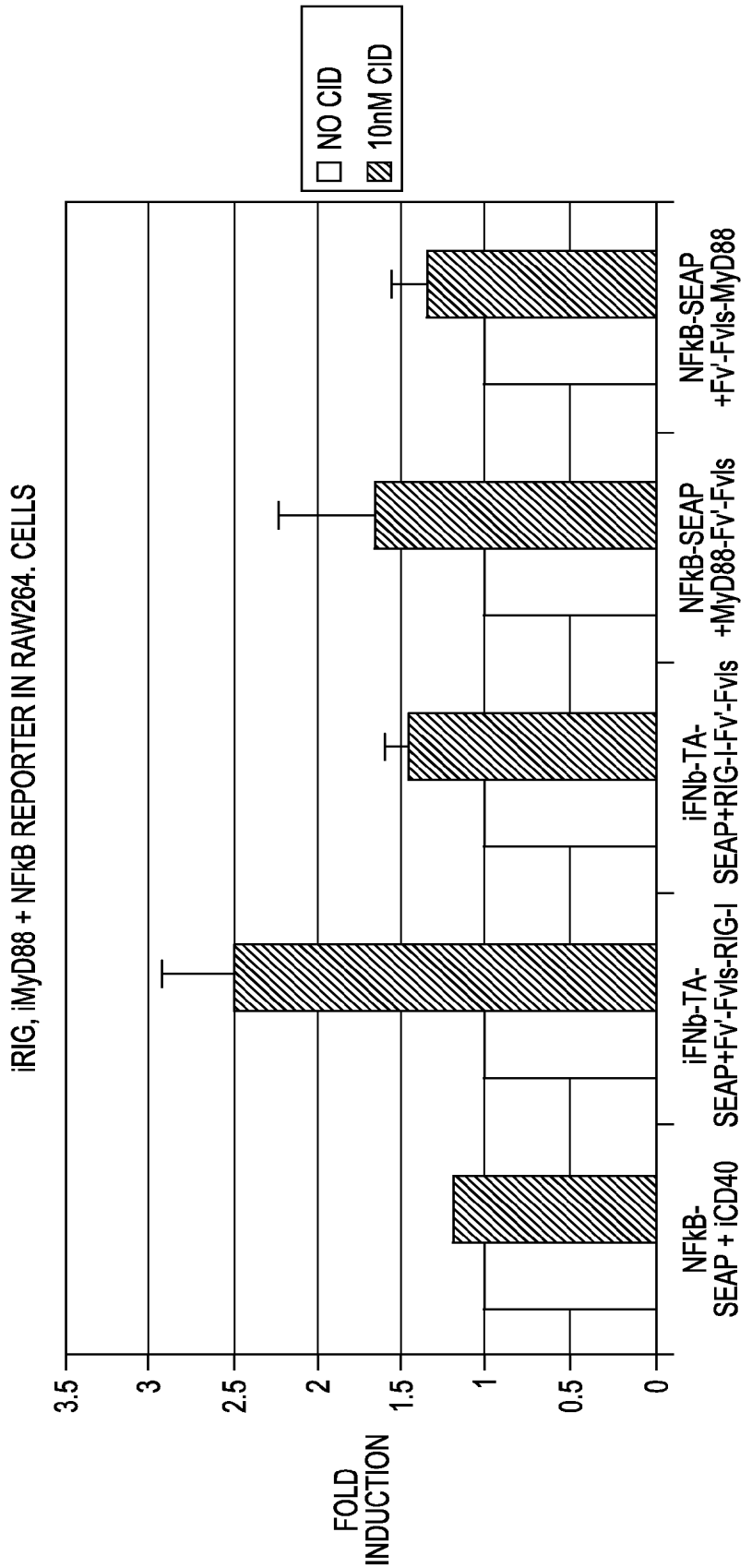

iRIG, iMyD88 + NFkB REPORTER IN RAW264. CELLS
NO CID
10nM CID
FOLD INDUCTION
3.5
3
2.5
2
1.5
1
0.5
0
NFkB-SEAP + iCD40
iFNb-TA-SEAP+Fv'-Fvls-RIG-I
iFNb-TA-SEAP+RIG-I-Fv'-Fvls
NFkB-SEAP +MyD88-Fv'-Fvls
NFkB-SEAP +Fv'-Fvls-MyD88

FIG. 2

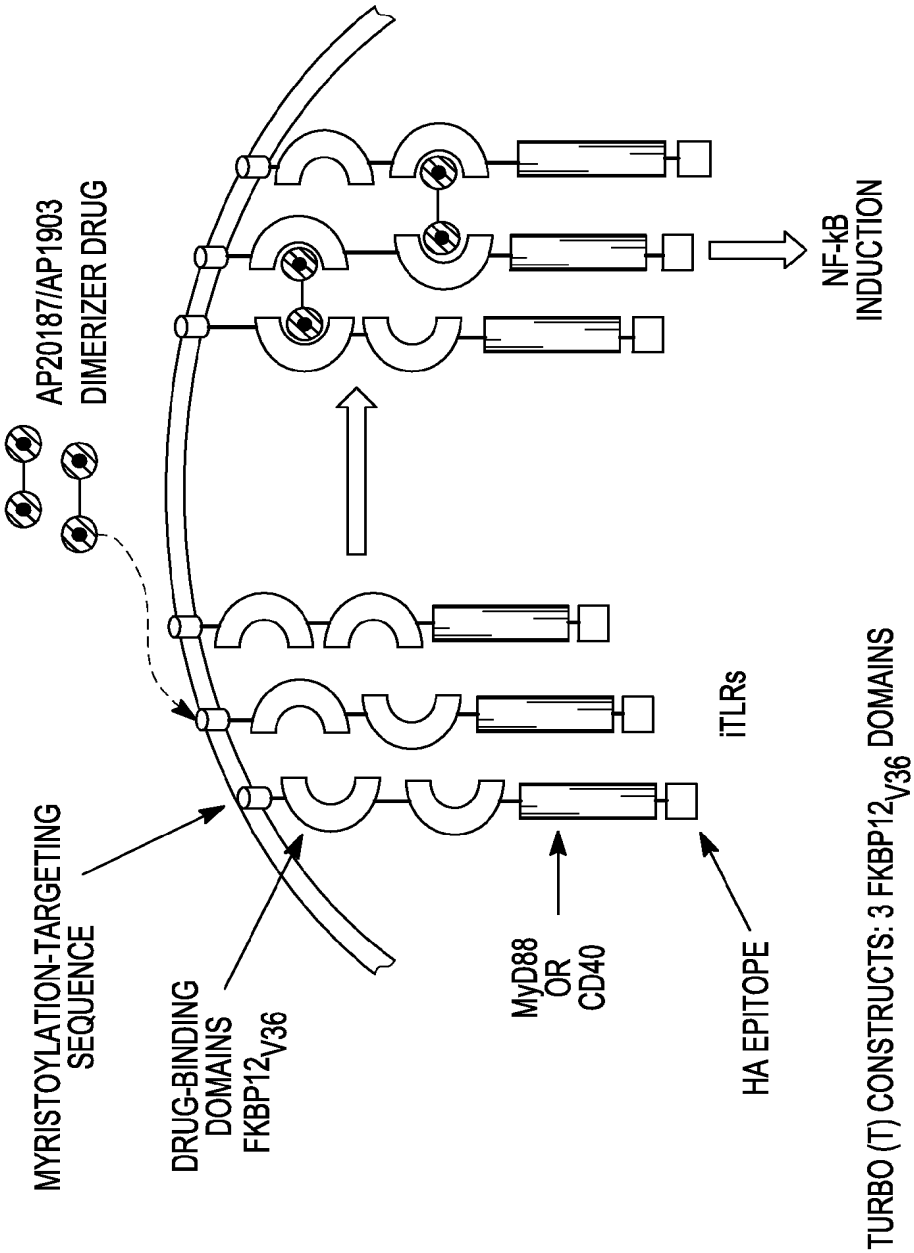

AP20187/AP1903
DIMERIZER DRUG
NF-kB
INDUCTION
MYRISTOYLATION-TARGETING
SEQUENCE
DRUG-BINDING
DOMAINS
FKBP12V36
MyD88
OR
CD40
iTLRs
HA EPITOPE
TURBO (T) CONSTRUCTS: 3 FKBP12V36 DOMAINS

FIG. 3

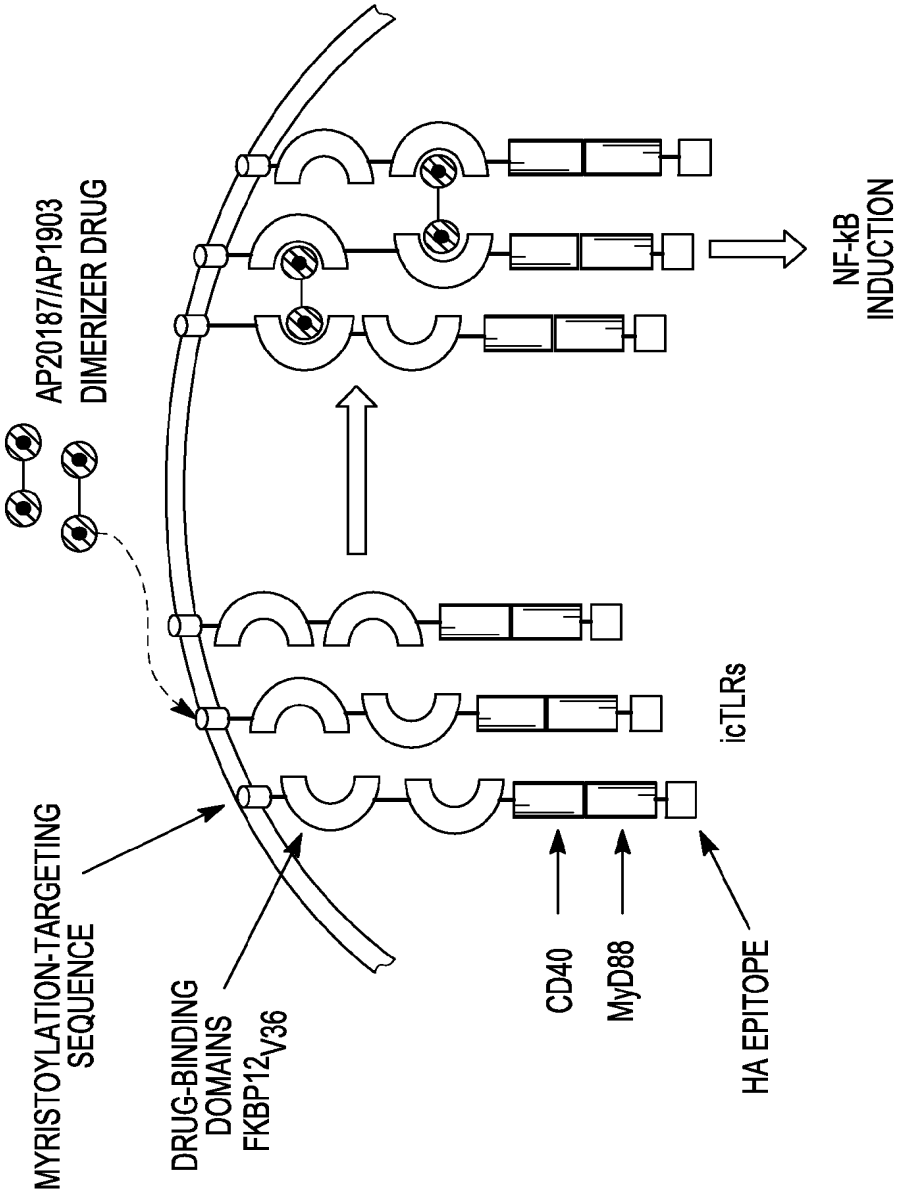

AP20187/AP1903
DIMERIZER DRUG
NF-kB
INDUCTION
icTLRs
MYRISTOYLATION-TARGETING
SEQUENCE
DRUG-BINDING
DOMAINS
FKBP12V36
CD40
MyD88
HA EPITOPE

FIG. 4

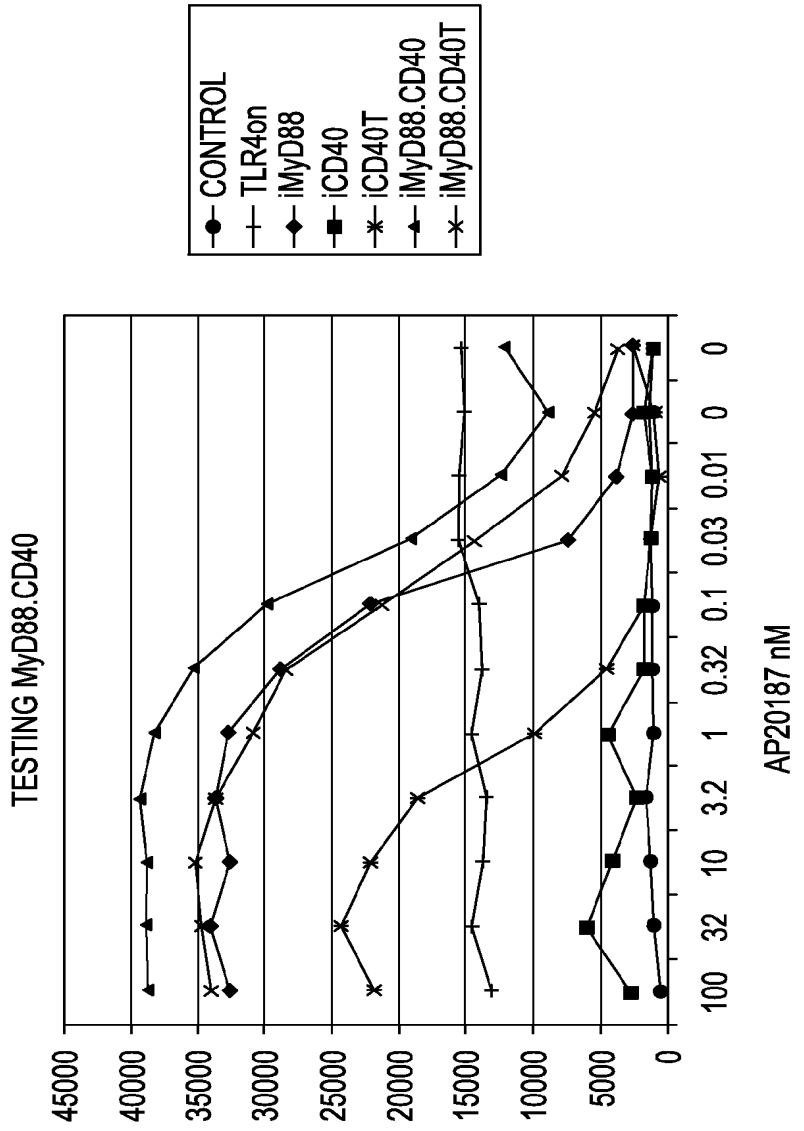

CONTROL
TLR4on
iMyD88
iCD40
iCD40T
iMyD88.CD40
iMyD88.CD40T
TESTING MyD88.CD40
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
100 32 10 3.2 1 0.32 0.1 0.03 0.01 0 0
AP20187 nM

FIG. 5

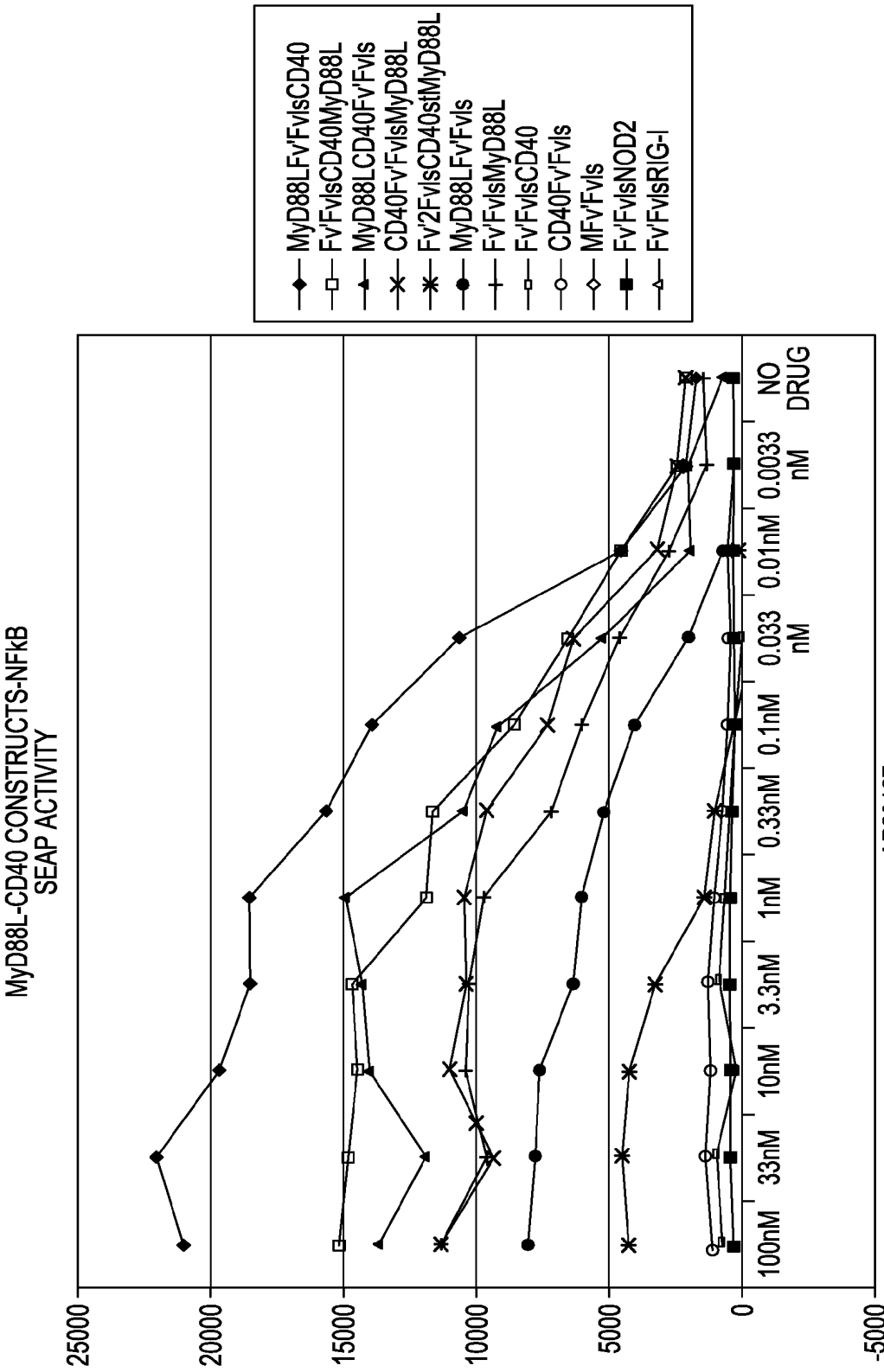

MyD88L-CD40 CONSTRUCTS-NFkB
SEAP ACTIVITY
MyD88LFv'FvlsCD40
Fv'FvlsCD40MyD88L
MyD88LCD40Fv'Fvls
CD40Fv'FvlsMyD88L
Fv'2FvlsCD40stMyD88L
MyD88LFv'Fvls
Fv'FvlsMyD88L
Fv'FvlsCD40
CD40Fv'Fvls
MFv'Fvls
Fv'FvlsNOD2
Fv'FvlsRIG-I
25000
20000
15000
10000
5000
0
-5000
100nM
33nM
10nM
3.3nM
1nM
0.33nM
0.1nM
0.033 nM
0.01nM
0.0033 nM
NO DRUG
AP20187
3 HOURS WITH SUBSTRATE (NO ASSAY SATURATION)

FIG. 6

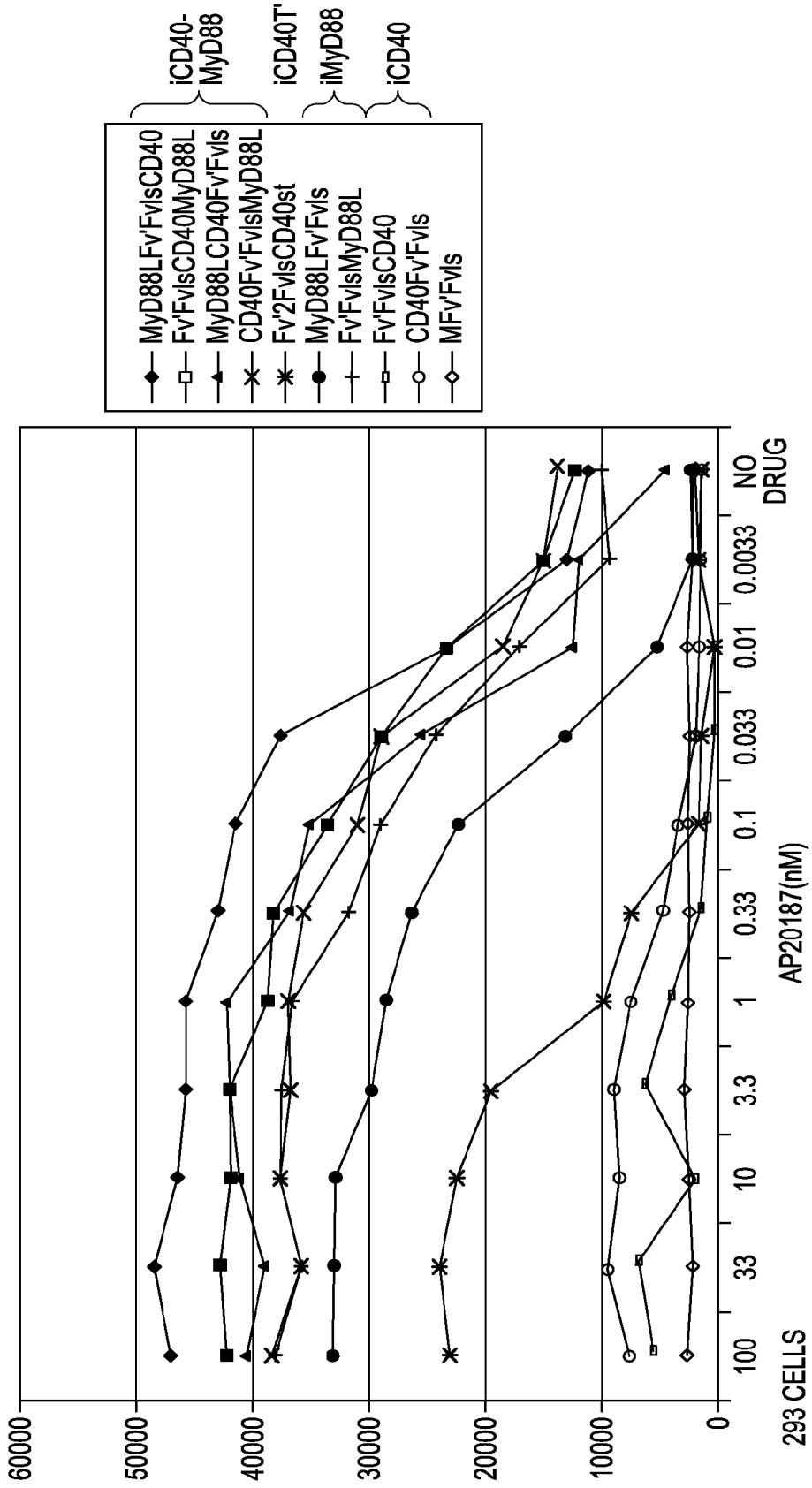

iCD40-MyD88 TESTING
293 CELLS
NF-κB REPORTER
AP20187(nM)
NO DRUG
0.0033
0.01
0.033
0.1
0.33
1
3.3
10
33
100
0
10000
20000
30000
40000
50000
60000
iCD40-MyD88
iCD40T'
iMyD88
iCD40
MyD88LFv'FvlsCD40
Fv'FvlsCD40MyD88L
MyD88LCD40Fv'Fvls
CD40Fv'FvlsMyD88L
Fv'2FvlsCD40st
MyD88LFv'Fvls
Fv'FvlsMyD88L
Fv'FvlsCD40
CD40Fv'Fvls
MFv'Fvls

FIG. 7

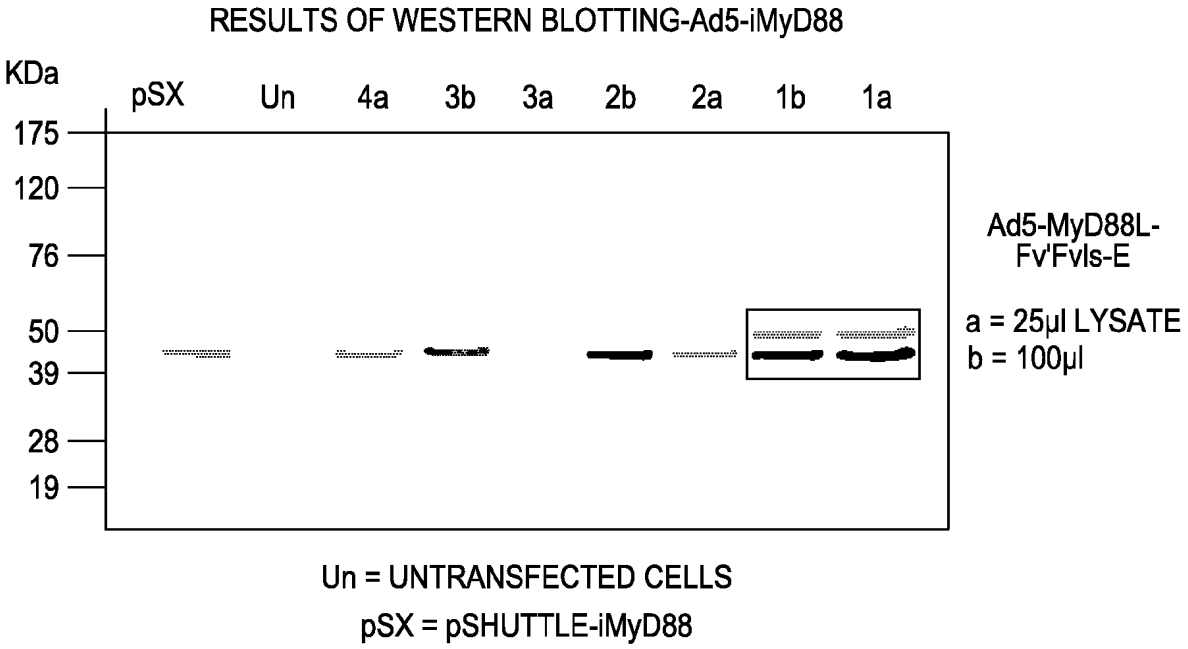
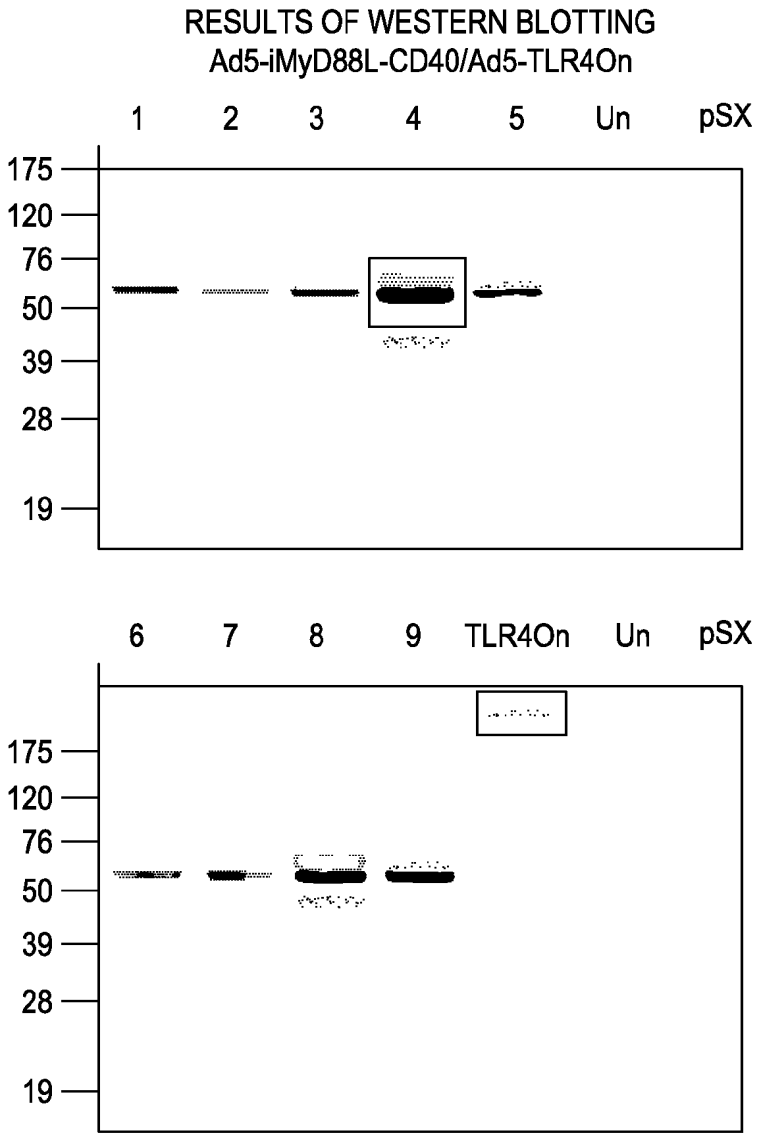

RESULTS OF WESTERN BLOTTING-Ad5-iMyD88
KDa
pSX
Un
4a
3b
3a
2b
2a
1b
1a
175
120
76
50
39
28
19
Ad5-MyD88L-Fv'FvIs-E
a = 25µl LYSATE
b = 100µl
Un = UNTRANSFECTED CELLS
pSX = pSHUTTLE-iMyD88

FIG. 8



Un = UNTRANSFECTED CELLS
pSX = pSHUTTLE-iMyD88-CD40

FIG. 9

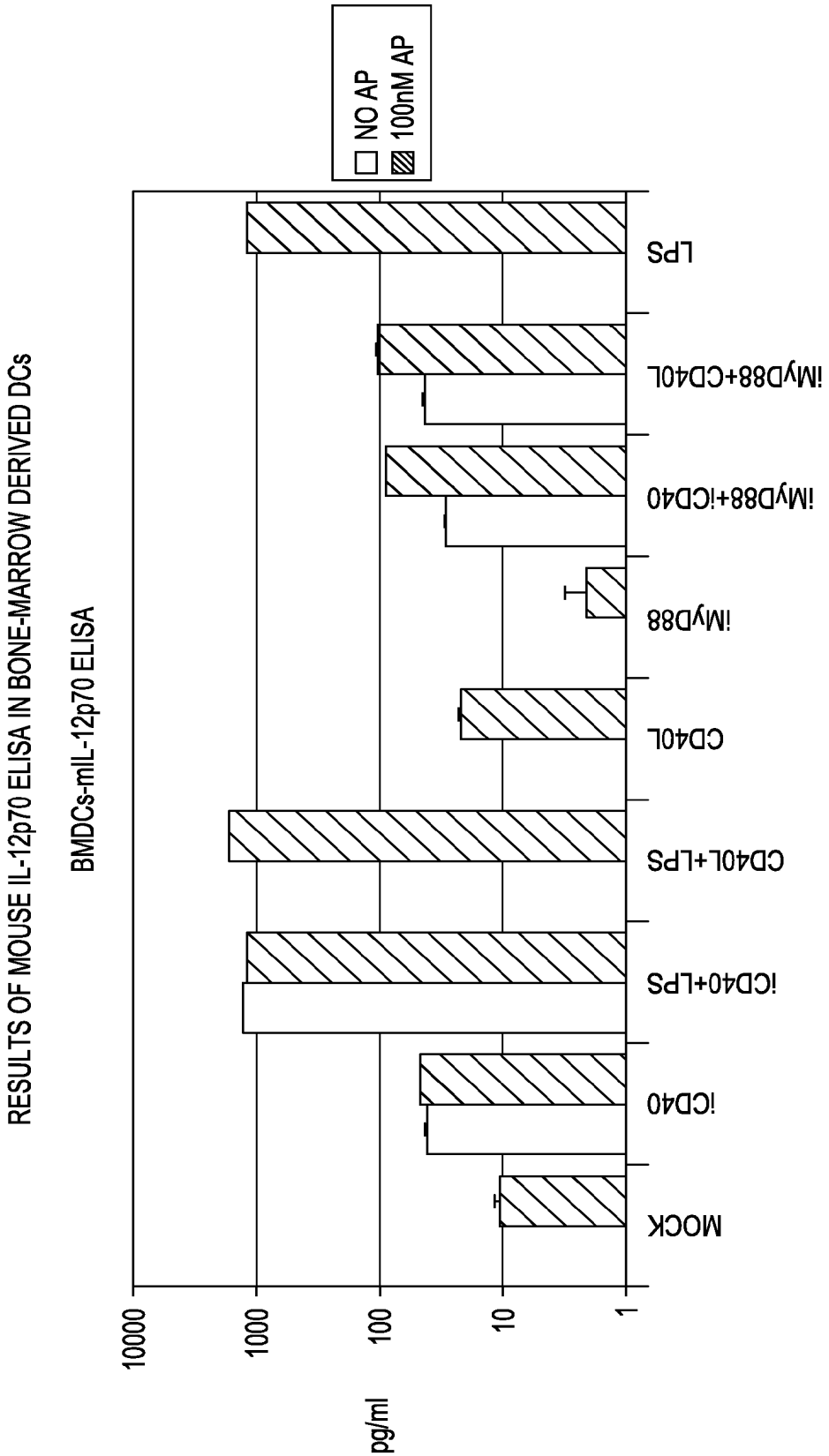

RESULTS OF MOUSE IL-12p70 ELISA IN BONE-MARROW DERIVED DCs
BMDCs-mIL-12p70 ELISA
NO AP
100nM AP
pg/ml
10000
1000
100
10
1
MOCK
iCD40
iCD40+LPS
CD40L+LPS
CD40L
iMyD88
iMyD88+iCD40
iMyD88+CD40L
LPS
TREATMENT

FIG. 10

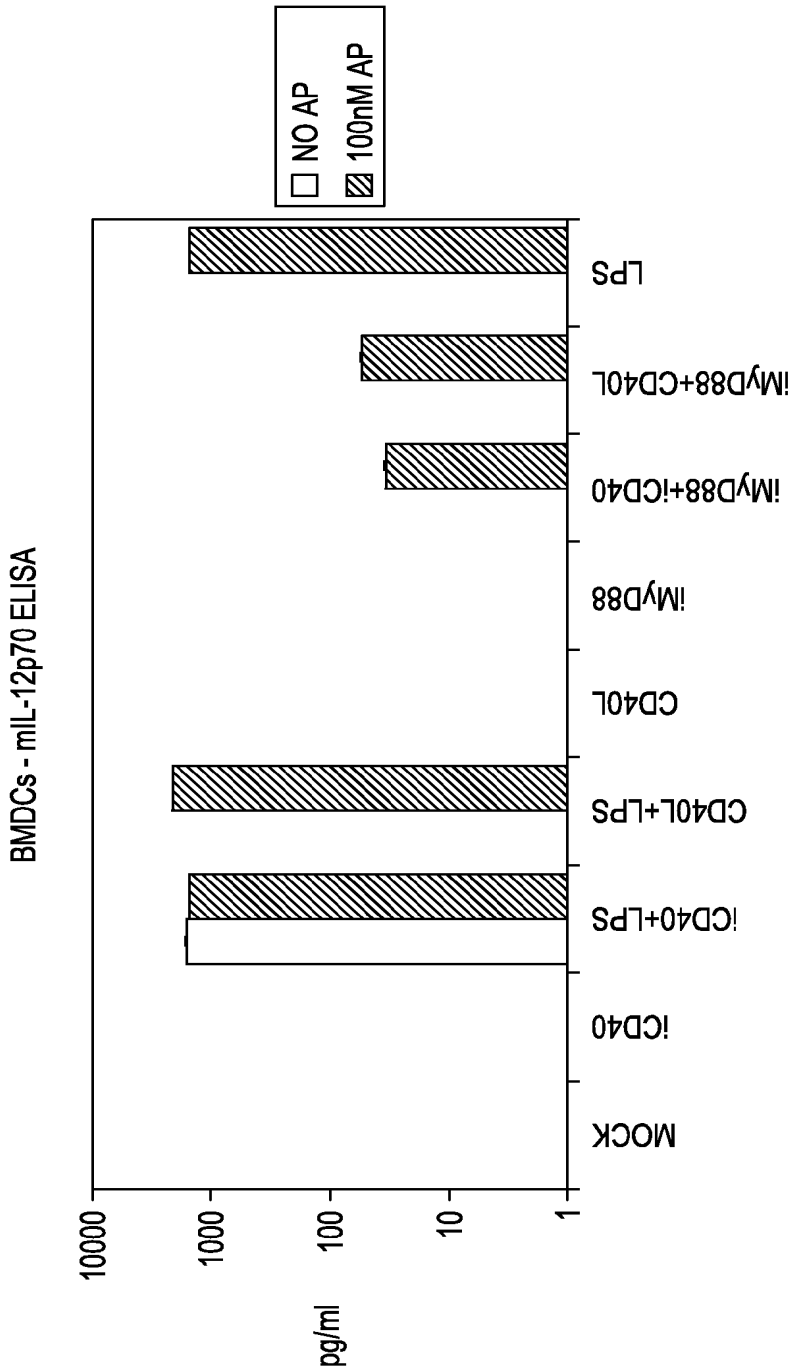

NO AP
100nM AP
BMDCs - mIL-12p70 ELISA
pg/ml
10000
1000
100
10
1
MOCK
iCD40
iCD40+LPS
CD40L+LPS
CD40L
iMyD88
iMyD88+iCD40
iMyD88+CD40L
LPS
TREATMENT

FIG. 11

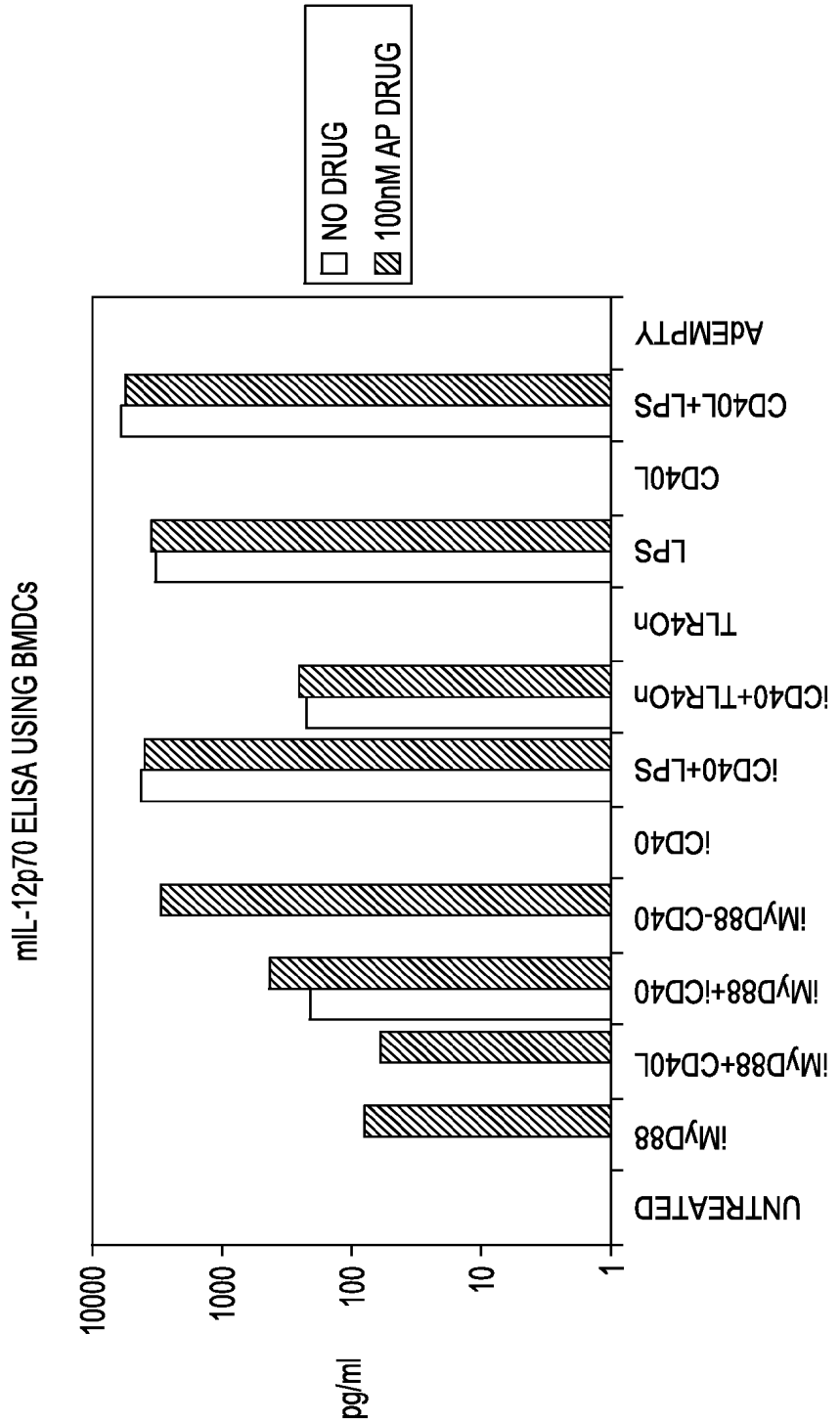

NO DRUG
100nM AP DRUG
mIL-12p70 ELISA USING BMDCs
pg/ml
10000
1000
100
10
1
UNTREATED
iMyD88
iMyD88+iCD40L
iMyD88+iCD40
iMyD88-CD40
iCD40
iCD40+LPS
iCD40+TLR4On
TLR4On
LPS
CD40L
CD40L+LPS
AdEMPTY
TREATMENT GROUPS

FIG. 12

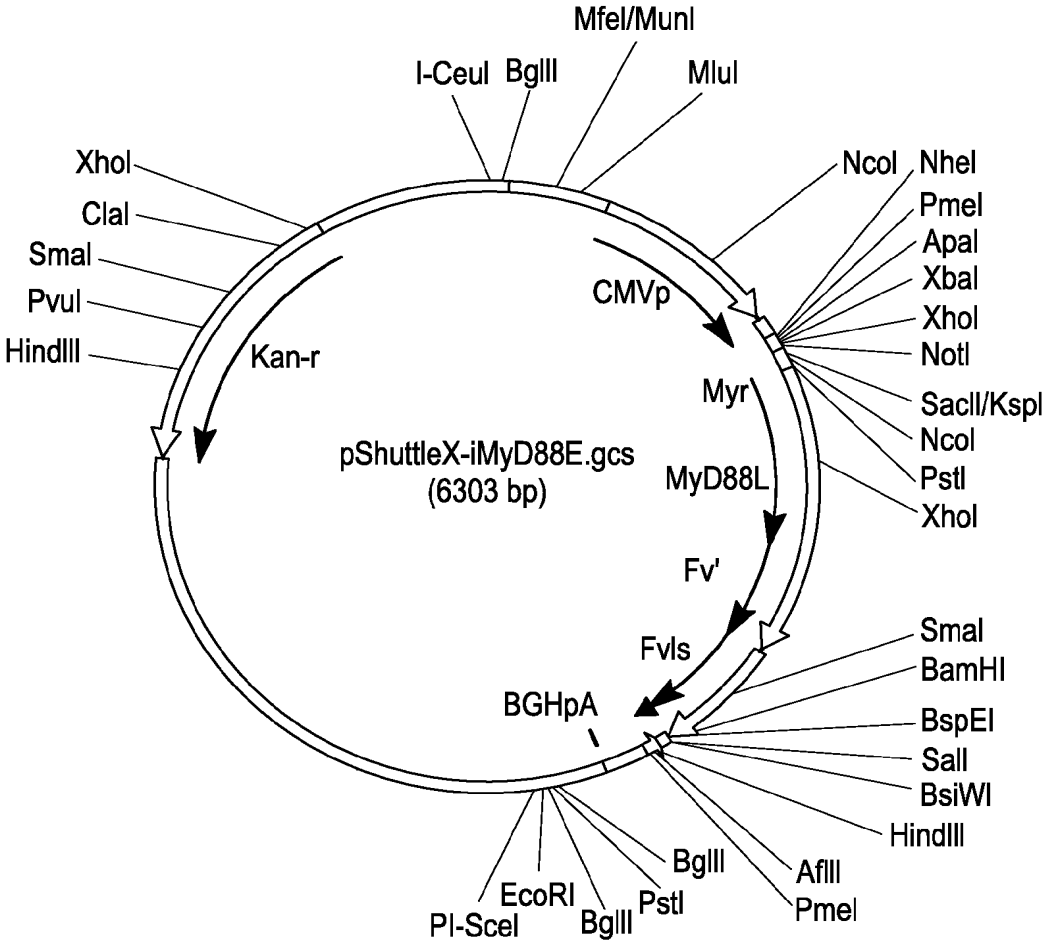

MfeI/MunI
I-CeuI
BglII
MluI
XhoI
ClaI
SmaI
PvuI
HindIII
NcoI
NheI
PmeI
ApaI
XbaI
XhoI
NotI
SacII/KspI
NcoI
PstI
XhoI
CMVp
Kan-r
Myr
pShuttleX-iMyD88E.gcs
(6303 bp)
MyD88L
Fv'
FvIs
SmaI
BamHI
BGHpA
BspEI
SalI
BsiWI
HindIII
BglII
AflII
EcoRI
PstI
PmeI
PI-SceI
BglII

FIG. 13

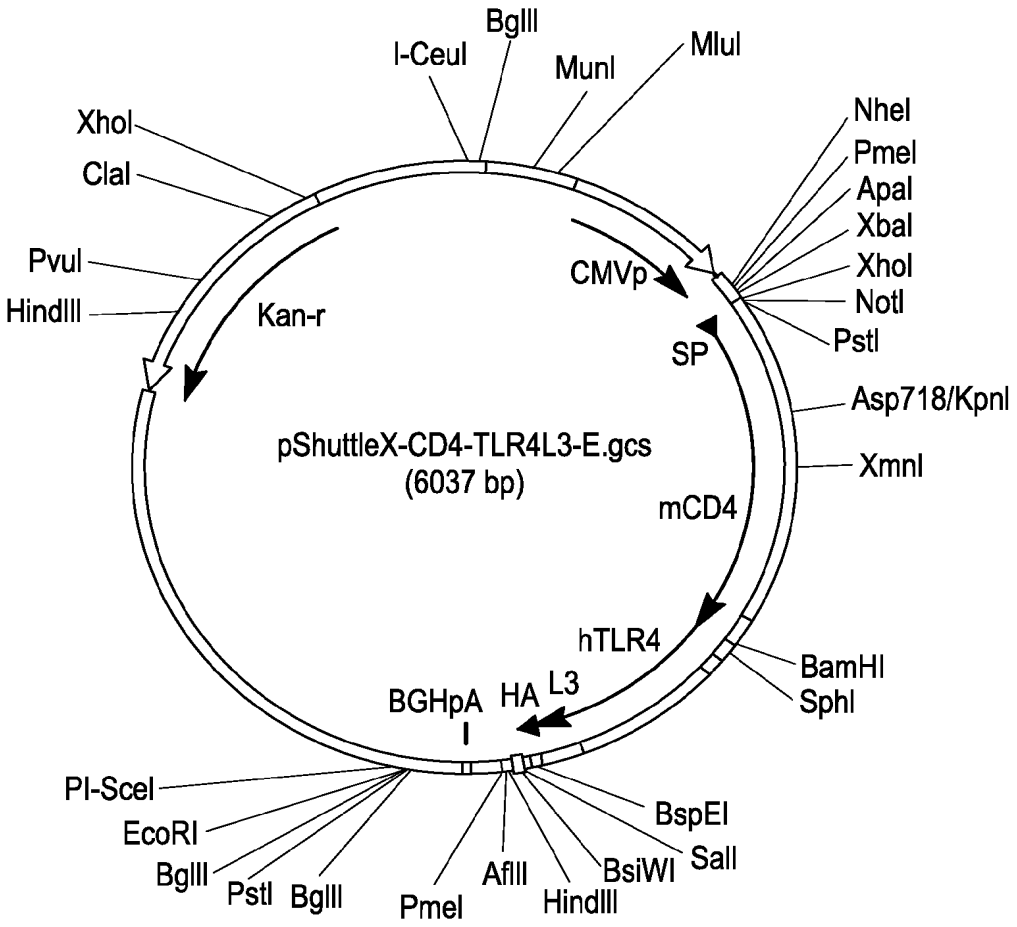

BglII
I-CeuI
MunI
MluI
NheI
PmeI
ApaI
XbaI
XhoI
NotI
PstI
Asp718/KpnI
XmnI
BamHI
SphI
BspEI
SalI
BsiWI
HindIII
AflII
PmeI
BglII
PstI
BglII
EcoRI
PI-SceI
XhoI
ClaI
PvuI
HindIII
Kan-r
CMVp
SP
pShuttleX-CD4-TLR4L3-E.gcs
(6037 bp)
mCD4
hTLR4
HA
L3
BGHpA

FIG. 14

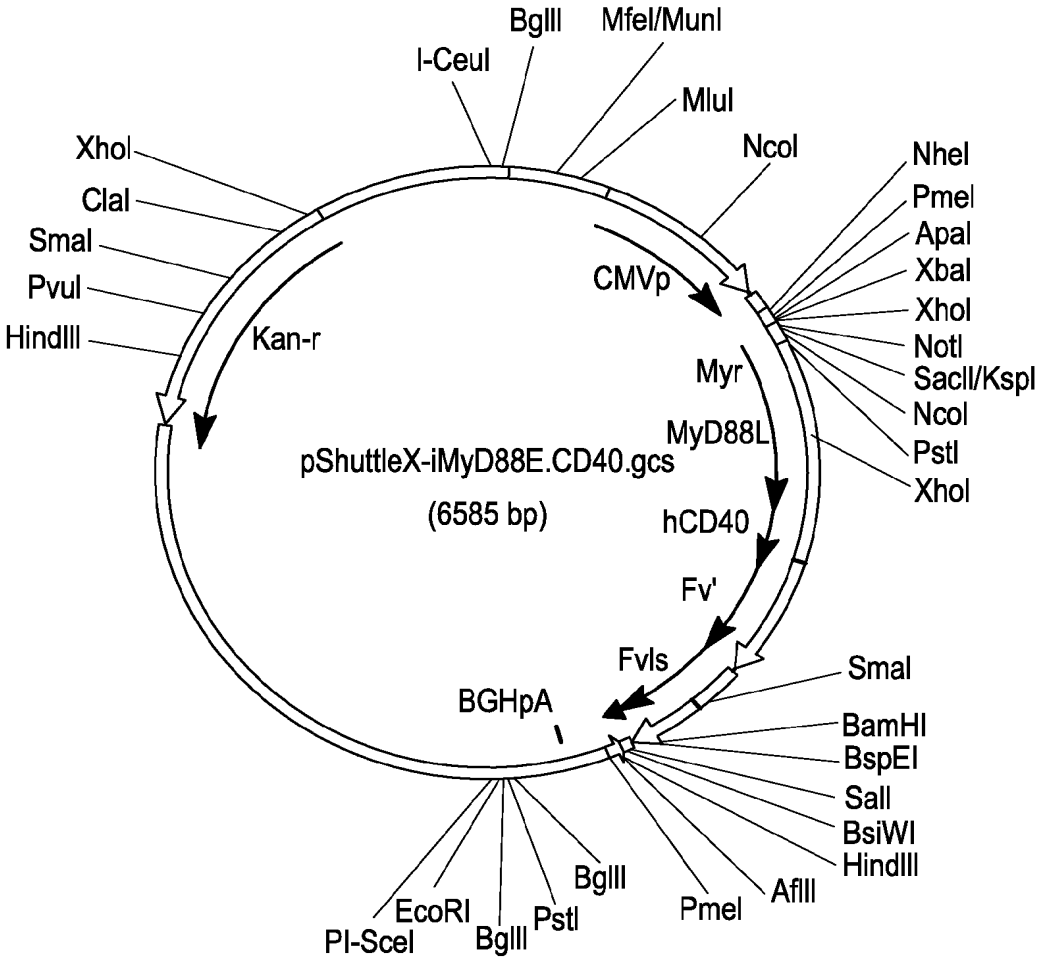

BglII
MfeI/MunI
I-CeuI
MluI
NcoI
NheI
PmeI
ApaI
XbaI
XhoI
NotI
SacII/KspI
NcoI
PstI
XhoI
XhoI
ClaI
SmaI
PvuI
HindIII
Kan-r
CMVp
Myr
MyD88L
pShuttleX-iMyD88E.CD40.gcs
(6585 bp)
hCD40
Fv'
Fvls
SmaI
BGHpA
BamHI
BspEI
SalI
BsiWI
HindIII
AflII
PmeI
BglII
PstI
EcoRI
BglII
PI-SceI

FIG. 15

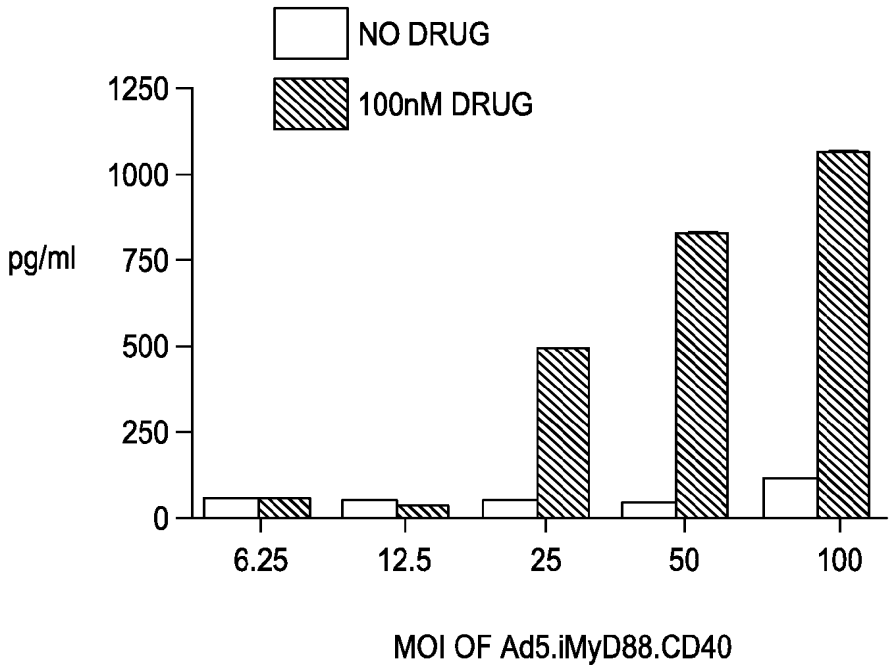

NO DRUG
100nM DRUG
1250
1000
750
500
250
0
pg/ml
6.25
12.5
25
50
100
MOI OF Ad5.iMyD88.CD40

FIG. 16

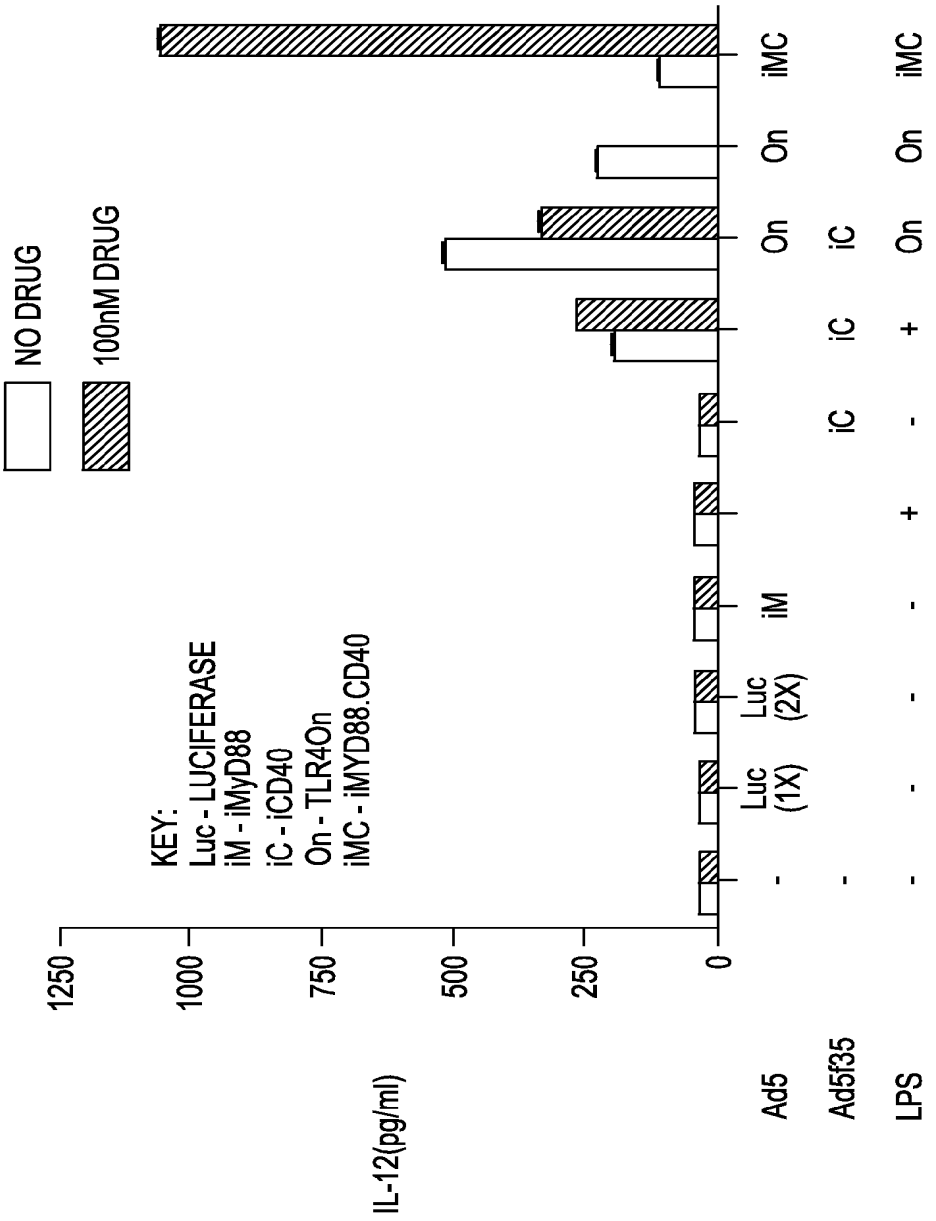

NO DRUG
100nM DRUG
KEY:
Luc - LUCIFERASE
iM - iMyD88
iC - iCD40
On - TLR4On
iMC - iMYD88.CD40
IL-12(pg/ml)
1250
1000
750
500
250
0
Ad5
Ad5f35
LPS
- Luc (1X) Luc (2X) iM
- - - - + -
- - - - - +
iC iC On iC On On
On On iMC
iMC

FIG. 17

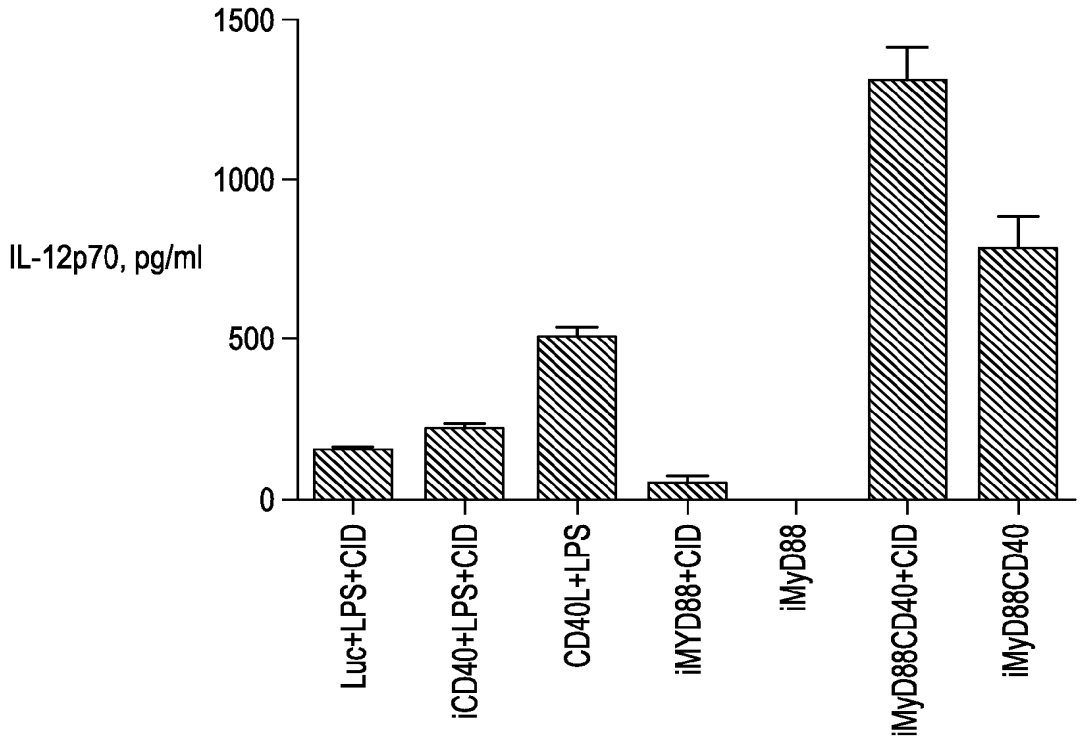

1500
1000
500
0
IL-12p70, pg/ml
Luc+LPS+CID
iCD40+LPS+CID
CD40L+LPS
iMYD88+CID
iMyD88
iMyD88CD40+CID
iMyD88CD40

FIG. 18

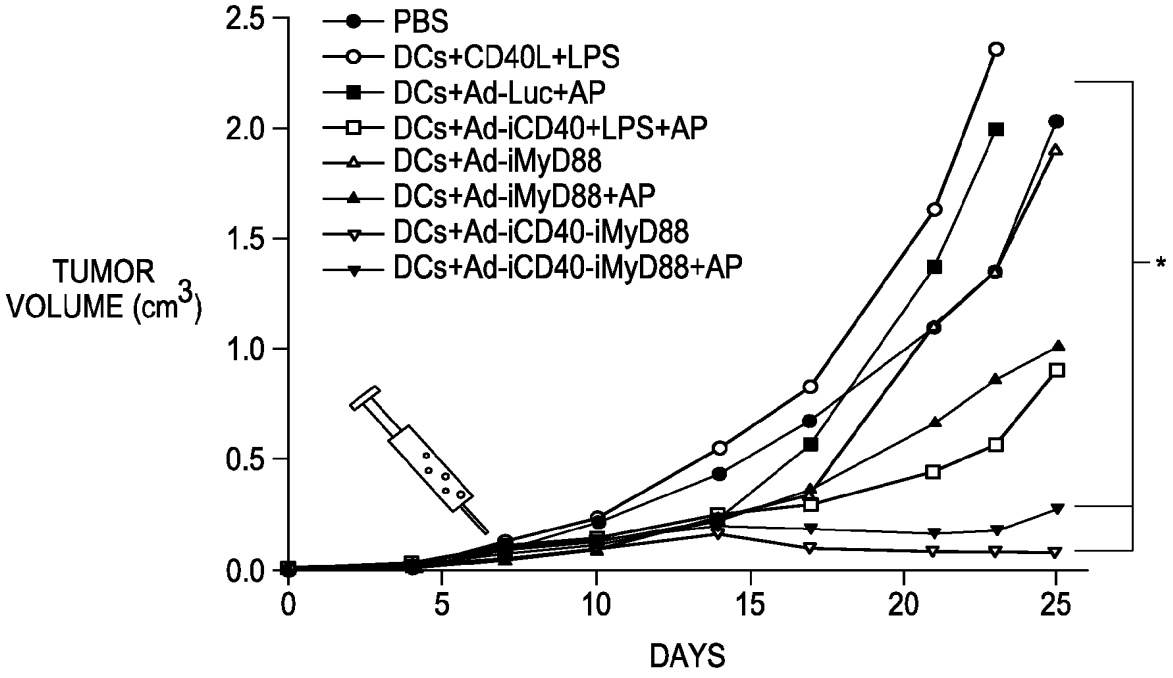


FIG.19A

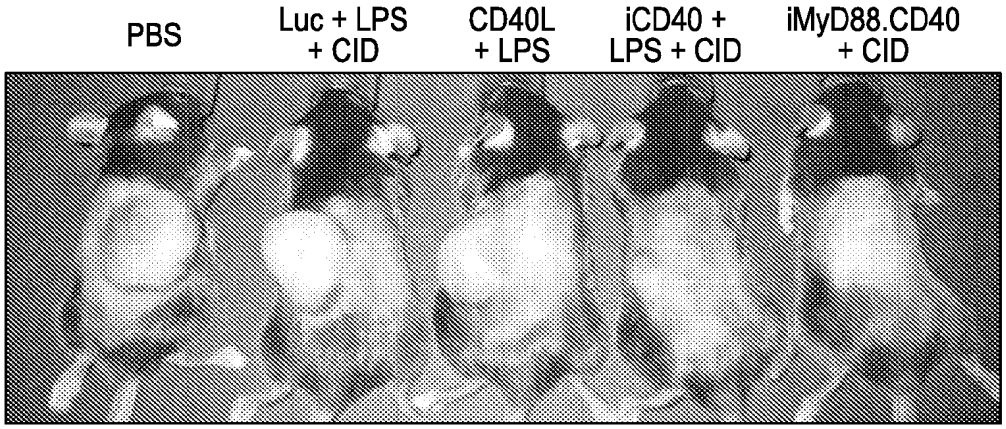


FIG. 19B

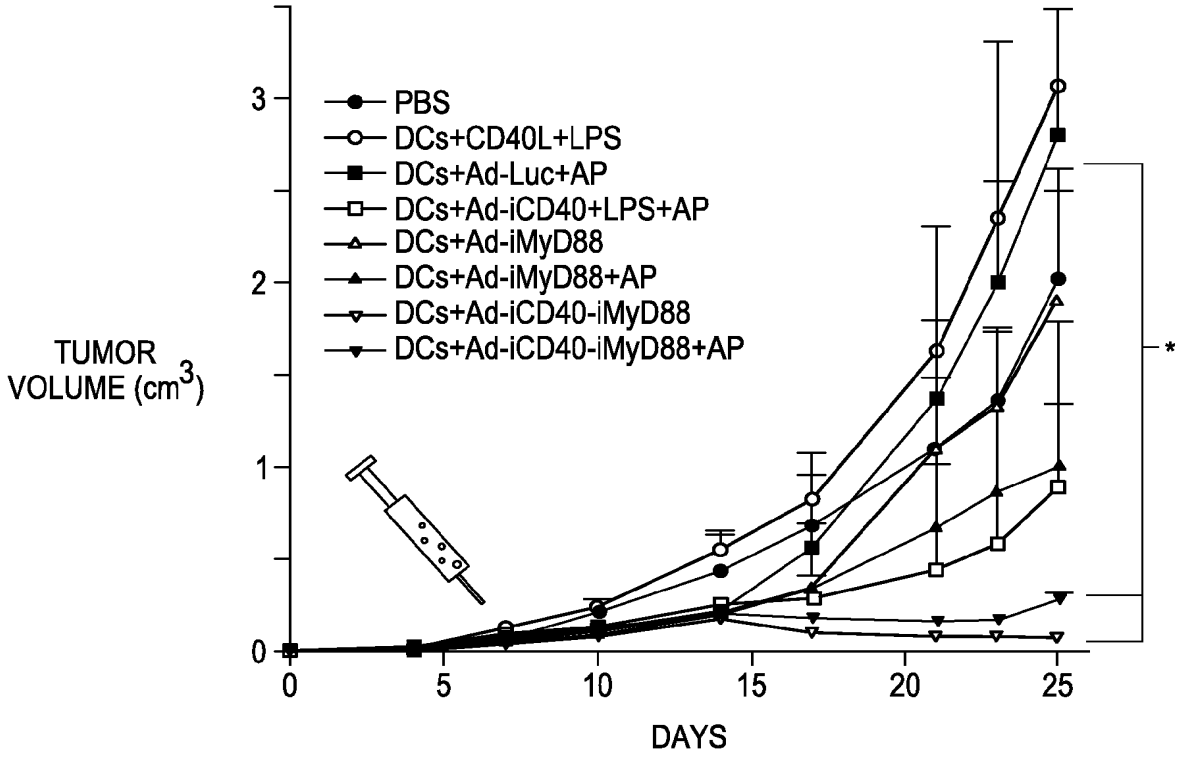
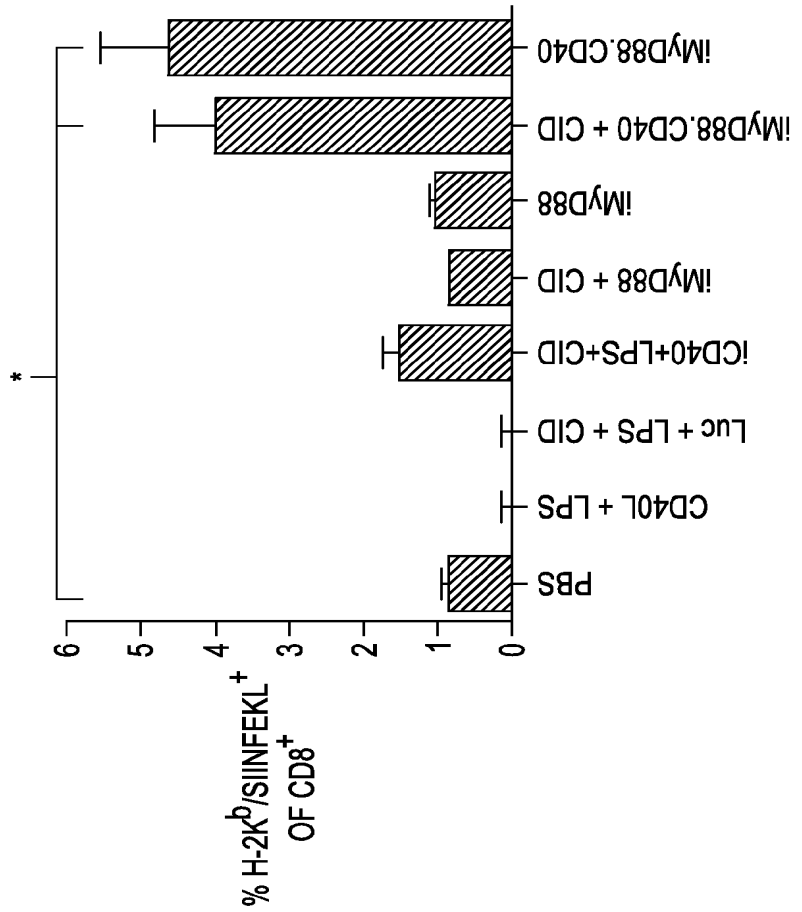

TUMOR VOLUME (cm^3)
PBS
DCs+CD40L+LPS
DCs+Ad-Luc+AP
DCs+Ad-iCD40+LPS+AP
DCs+Ad-iMyD88
DCs+Ad-iMyD88+AP
DCs+Ad-iCD40-iMyD88
DCs+Ad-iCD40-iMyD88+AP
*
0
1
2
3
0
5
10
15
20
25
DAYS

FIG. 19C


% H-2K^b/SIINFEKL$^+$ OF CD8$^+$
0
1
2
3
4
5
6
*
PBS
CD40L + LPS
Luc + LPS + CID
iCD40+LPS+CID
iMyD88 + CID
iMyD88
iMyD88.CD40 + CID
iMyD88.CD40

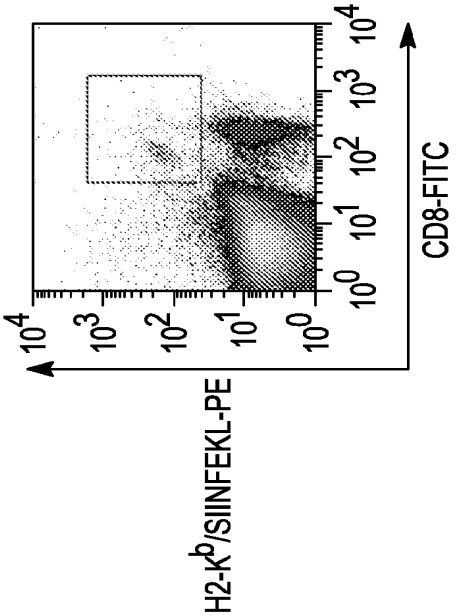

H2-K^b/SIINFEKL-PE
CD8-FITC
10^0
10^1
10^2
10^3
10^4

FIG. 20

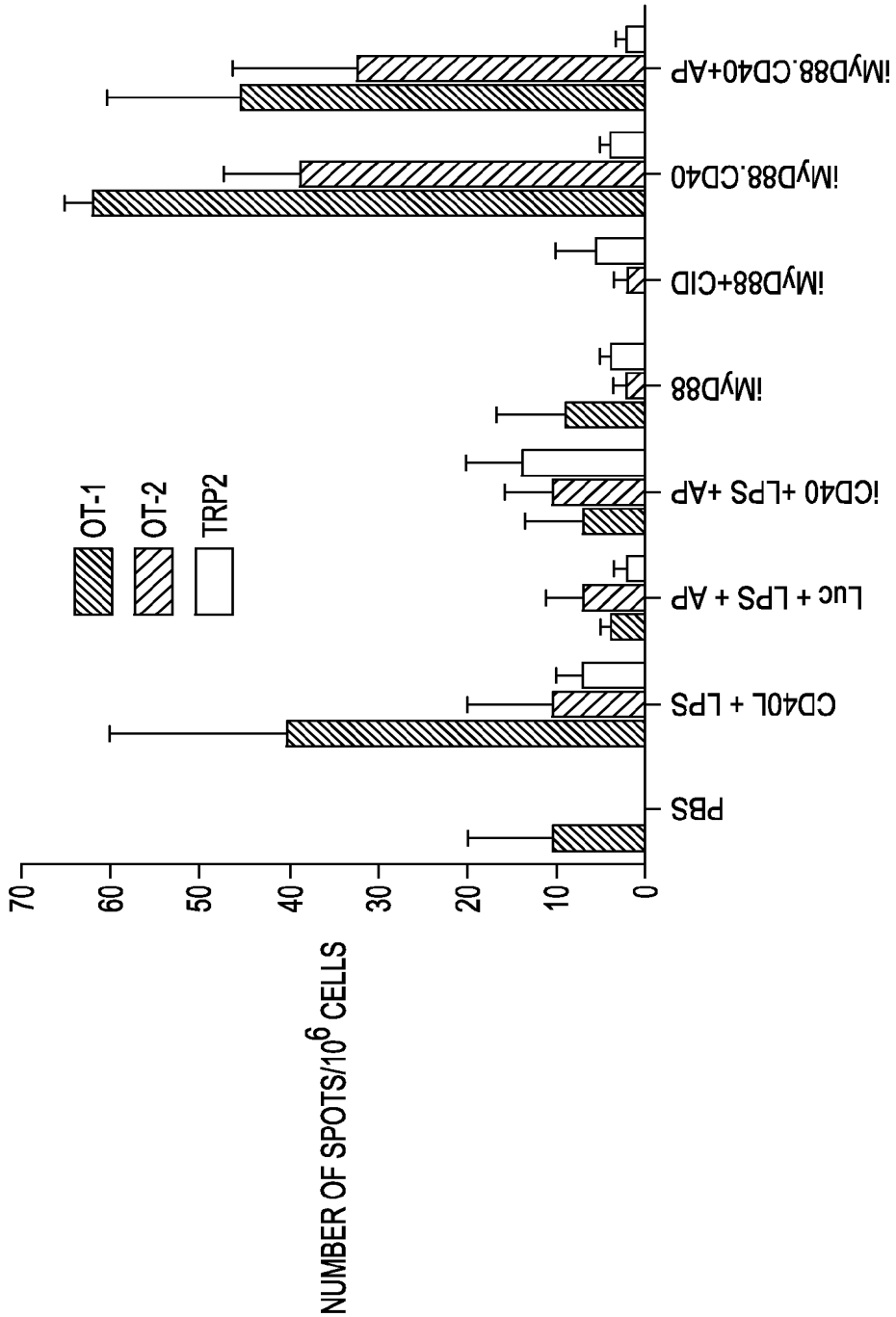

NUMBER OF SPOTS/10^6 CELLS
70
60
50
40
30
20
10
0
OT-1
OT-2
TRP2
PBS
CD40L + LPS
Luc + LPS + AP
iCD40 +LPS +AP
iMyD88
iMyD88+CID
iMyD88.CD40
iMyD88.CD40+AP

FIG. 21

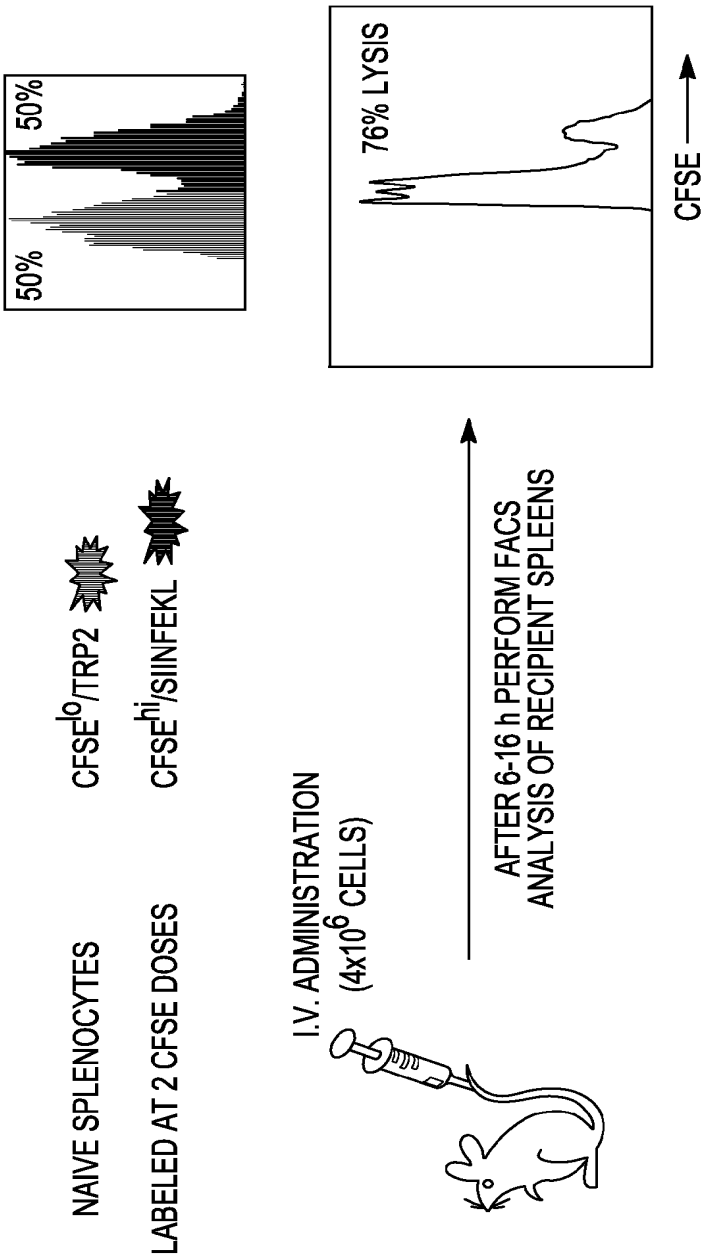

NAIVE SPLENOCYTES
LABELED AT 2 CFSE DOSES
CFSE^{lo}/TRP2
CFSE^{hi}/SIINFEKL
I.V. ADMINISTRATION
(4x10^6 CELLS)
AFTER 6-16 h PERFORM FACS
ANALYSIS OF RECIPIENT SPLEENS
50%
50%
76% LYSIS
CFSE

FIG. 22

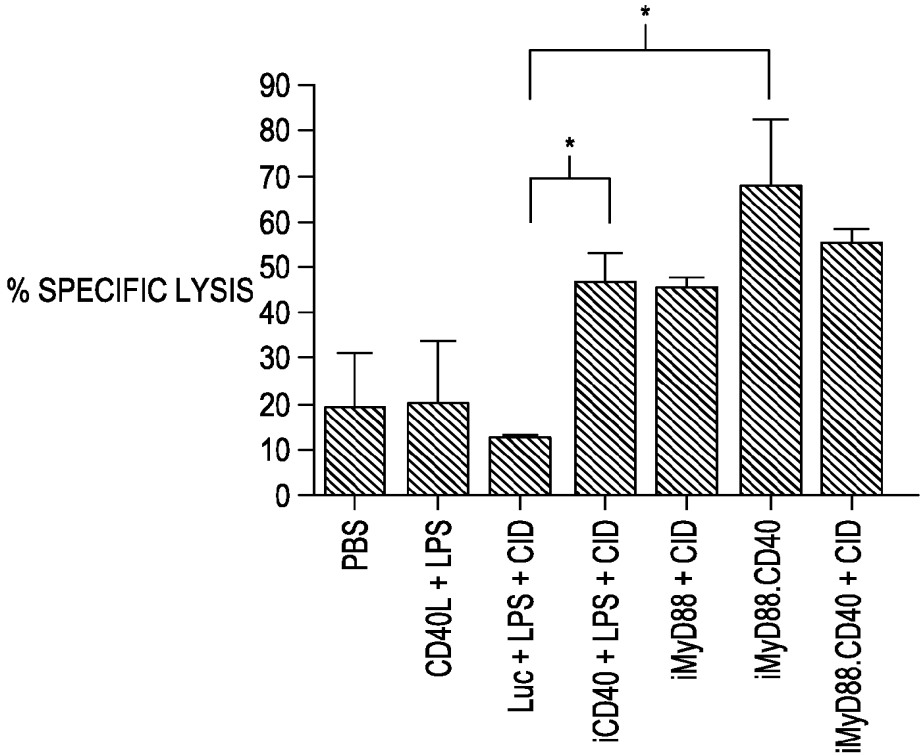

% SPECIFIC LYSIS
90
80
70
60
50
40
30
20
10
0
*
*
PBS
CD40L + LPS
Luc + LPS + CID
iCD40 + LPS + CID
iMyD88 + CID
iMyD88.CD40
iMyD88.CD40 + CID

FIG. 23

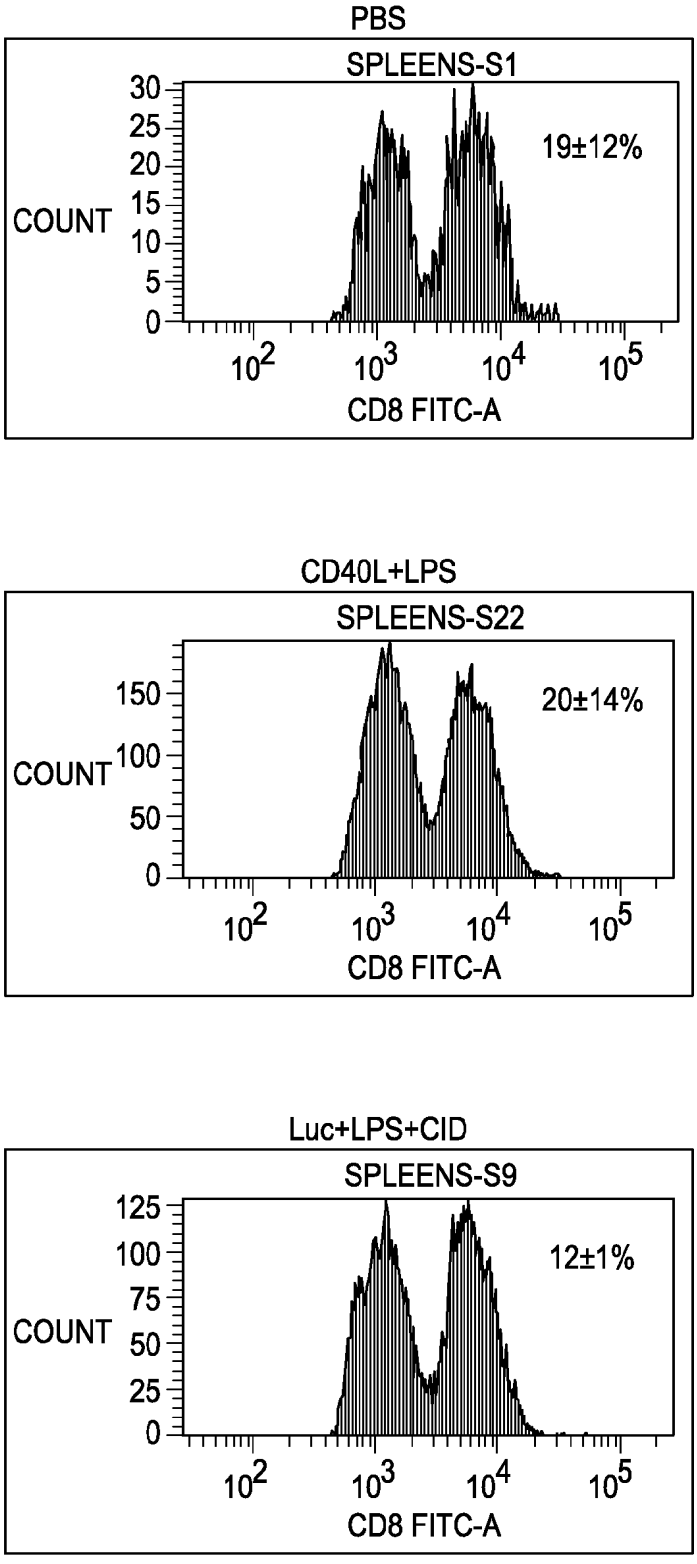
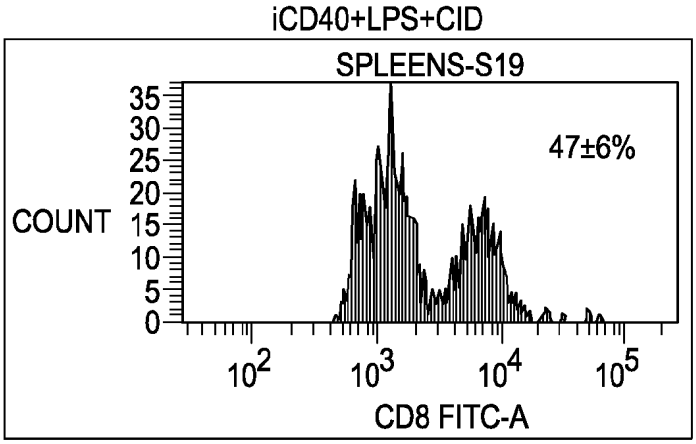

PBS
SPLEENS-S1
19±12%
COUNT
CD8 FITC-A
CD40L+LPS
SPLEENS-S22
20±14%
COUNT
CD8 FITC-A
Luc+LPS+CID
SPLEENS-S9
12±1%
COUNT
CD8 FITC-A

FIG. 24



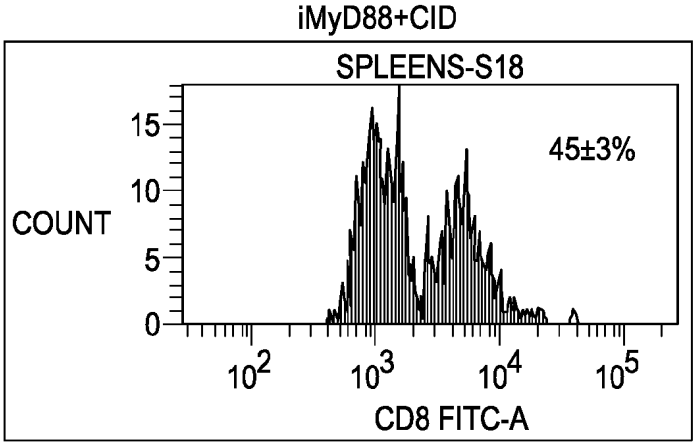
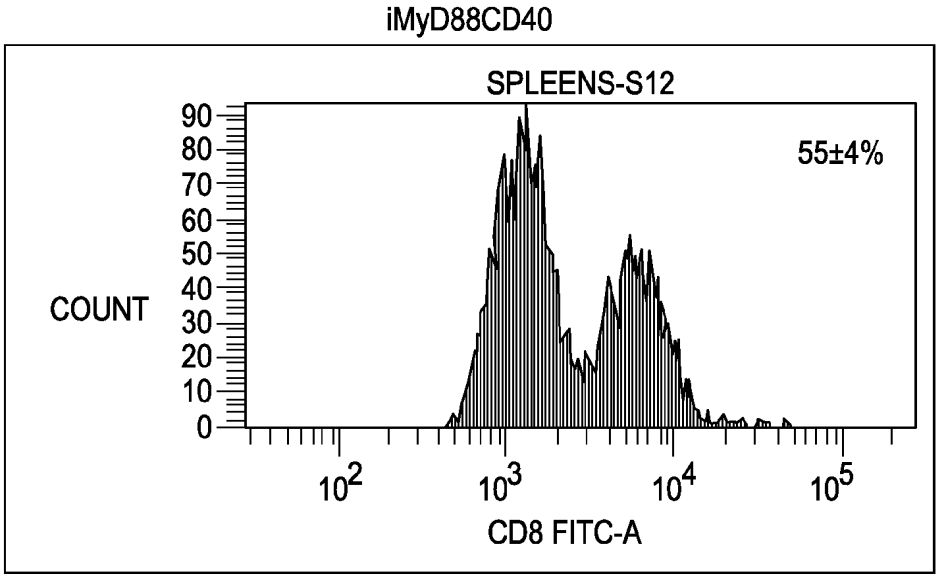


FIG. 24 Continued



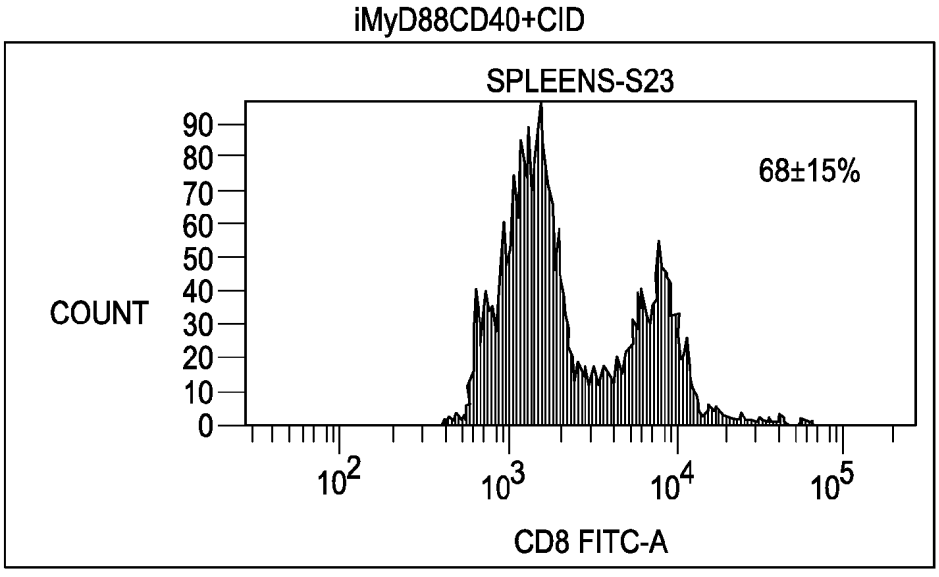


FIG. 24 Continued

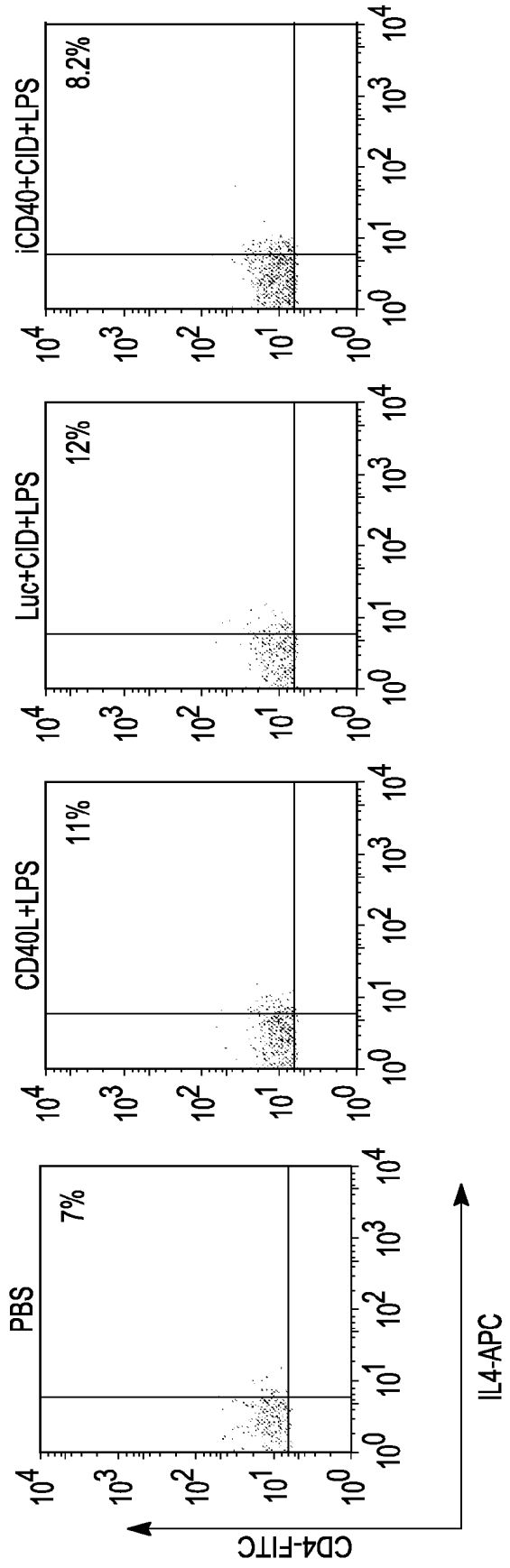

PBS
7%
CD40L+LPS
11%
Luc+CID+LPS
12%
iCD40+CID+LPS
8.2%
CD4-FITC
IL4-APC

FIG. 25

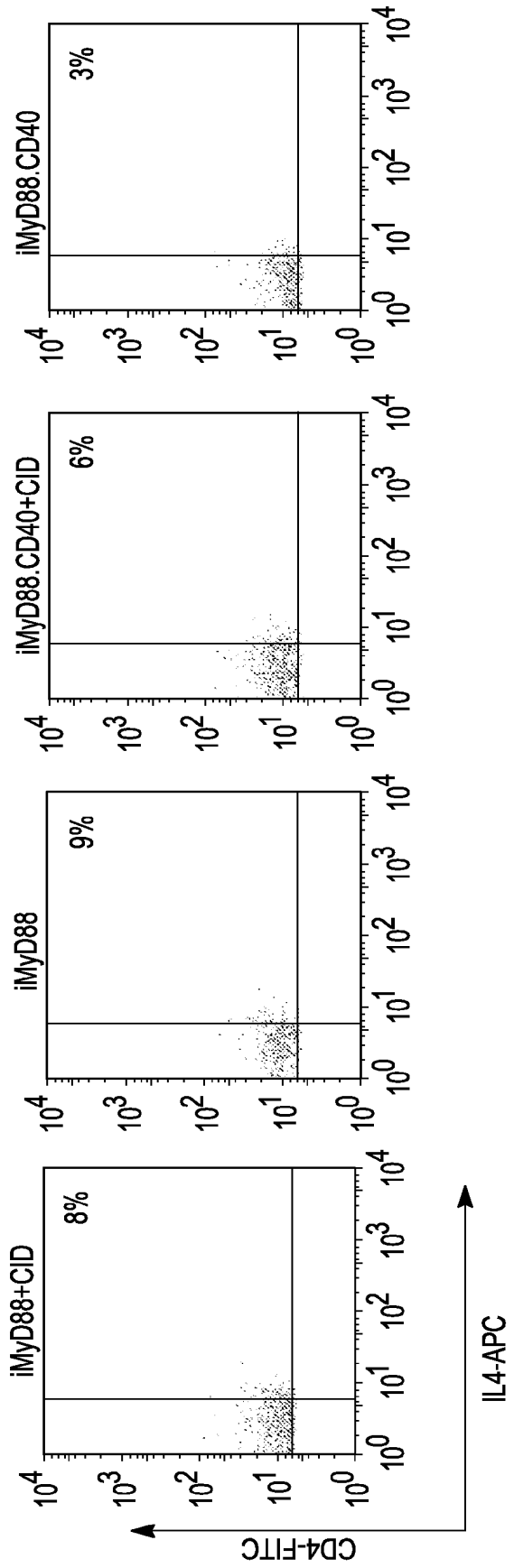


FIG. 25 Continued

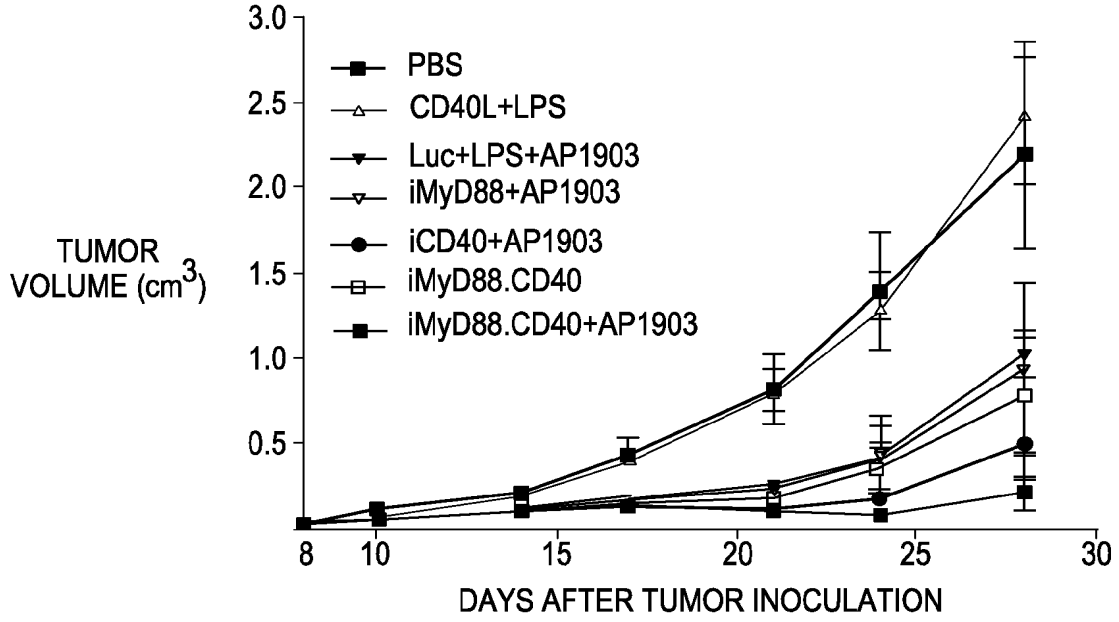


FIG. 26A

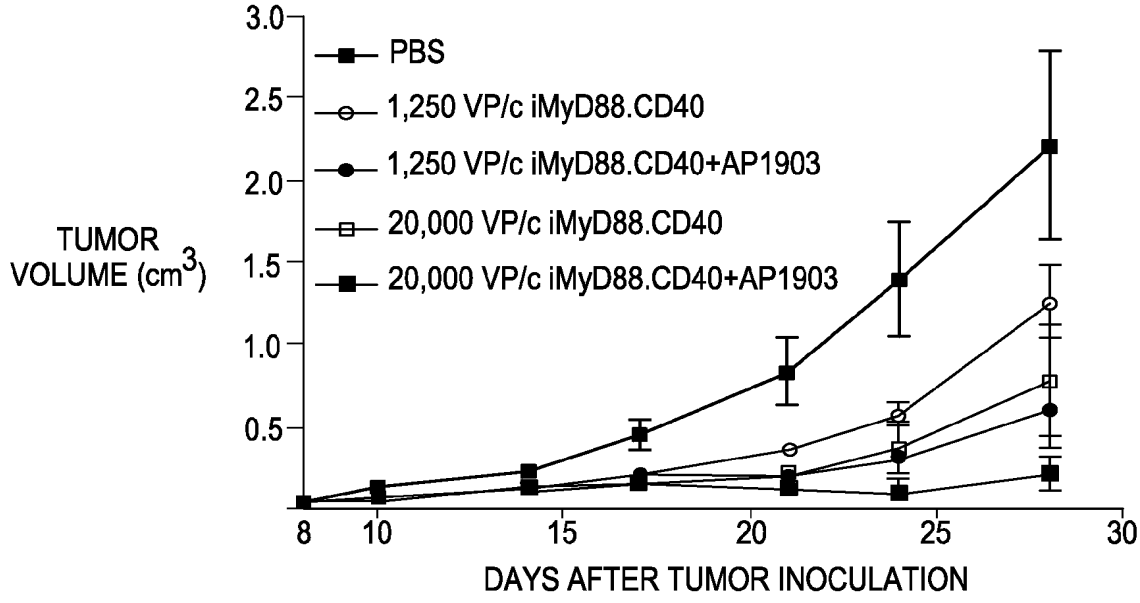


FIG. 26B

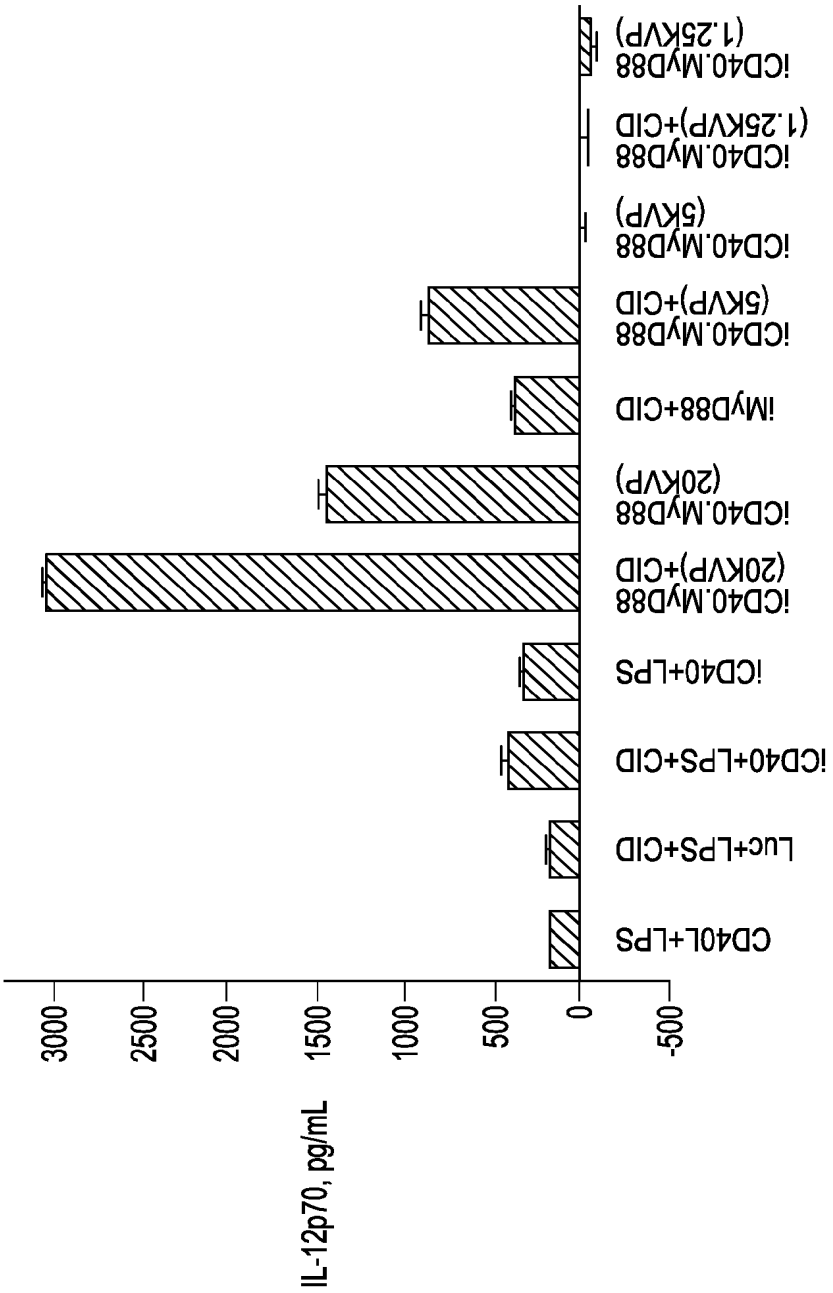

IL-12p70, pg/mL
3000
2500
2000
1500
1000
500
0
-500
CD40L+LPS
Luc+LPS+CID
iCD40+LPS+CID
iCD40+LPS
iCD40.MyD88 (20KVP)+CID
iCD40.MyD88 (20KVP)
iMyD88+CID
iCD40.MyD88 (5KVP)+CID
iCD40.MyD88 (5KVP)
iCD40.MyD88 (1.25KVP)+CID
iCD40.MyD88 (1.25KVP)

FIG. 26C

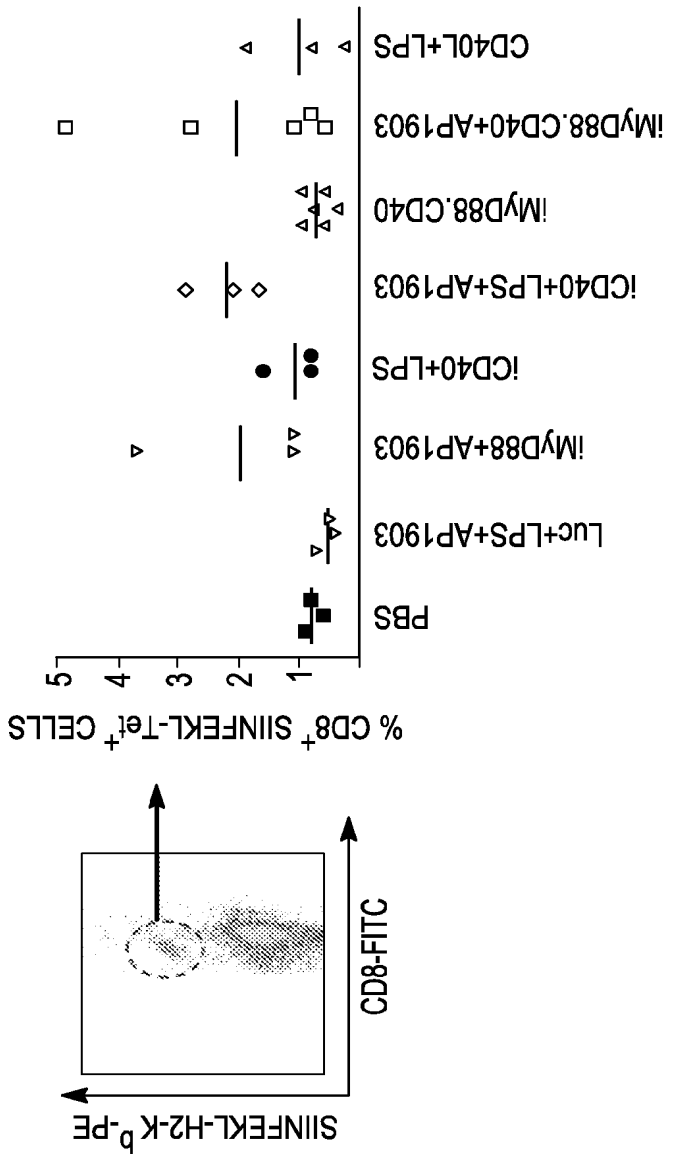

SIINFEKL-H2-K^b-PE
CD8-FITC
% CD8$^+$ SIINFEKL-Tet$^+$ CELLS
1
2
3
4
5
PBS
Luc+LPS+AP1903
iMyD88+AP1903
iCD40+LPS
iCD40+LPS+AP1903
iMyD88.CD40
iMyD88.CD40+AP1903
CD40L+LPS

FIG. 27A

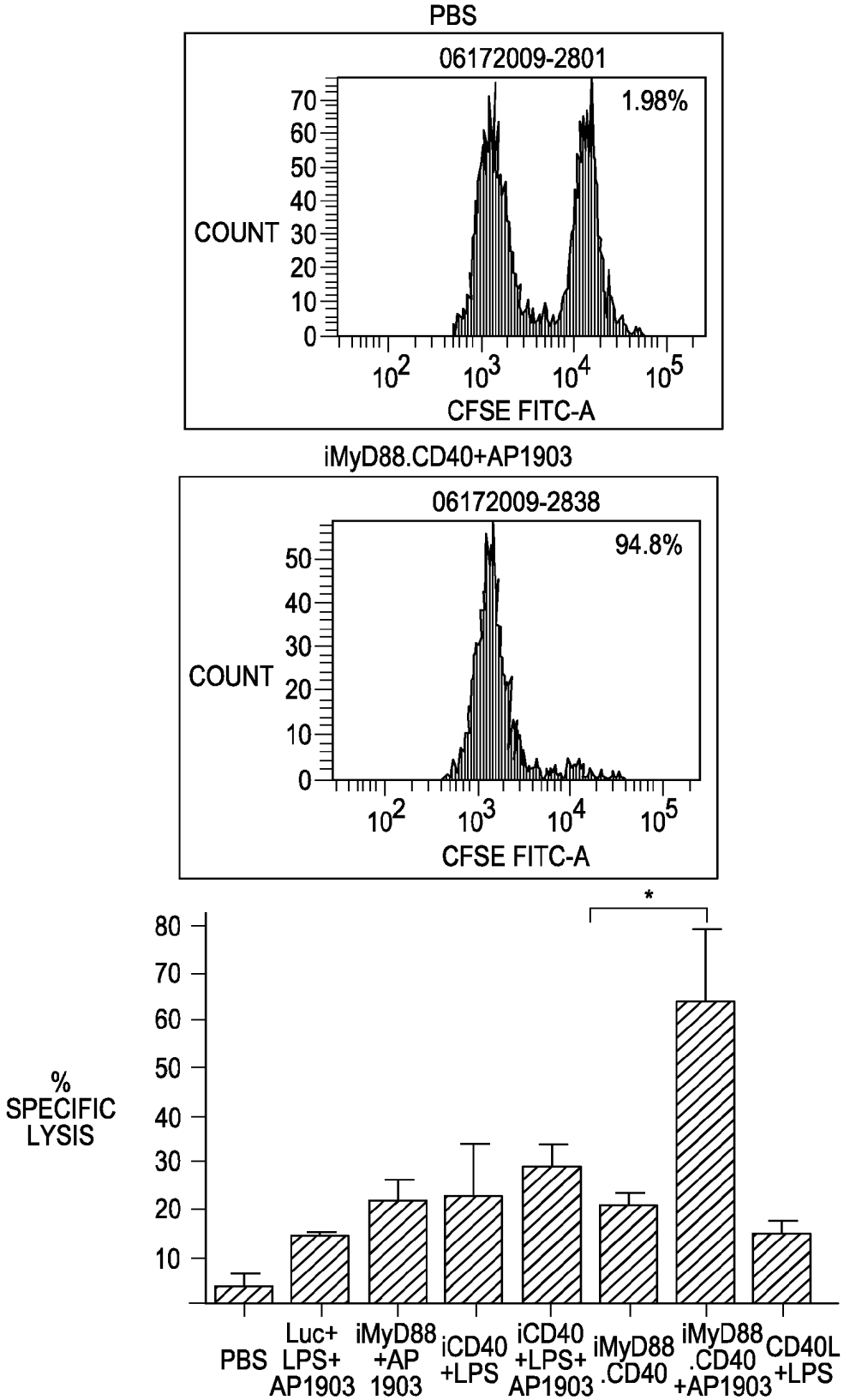

PBS
06172009-2801
1.98%
COUNT
CFSE FITC-A
iMyD88.CD40+AP1903
06172009-2838
94.8%
COUNT
CFSE FITC-A
*
% SPECIFIC LYSIS
PBS
Luc+ LPS+ AP1903
iMyD88 +AP 1903
iCD40 +LPS
iCD40 +LPS+ AP1903
iMyD88 .CD40
iMyD88 .CD40 +AP1903
CD40L +LPS

FIG. 27B

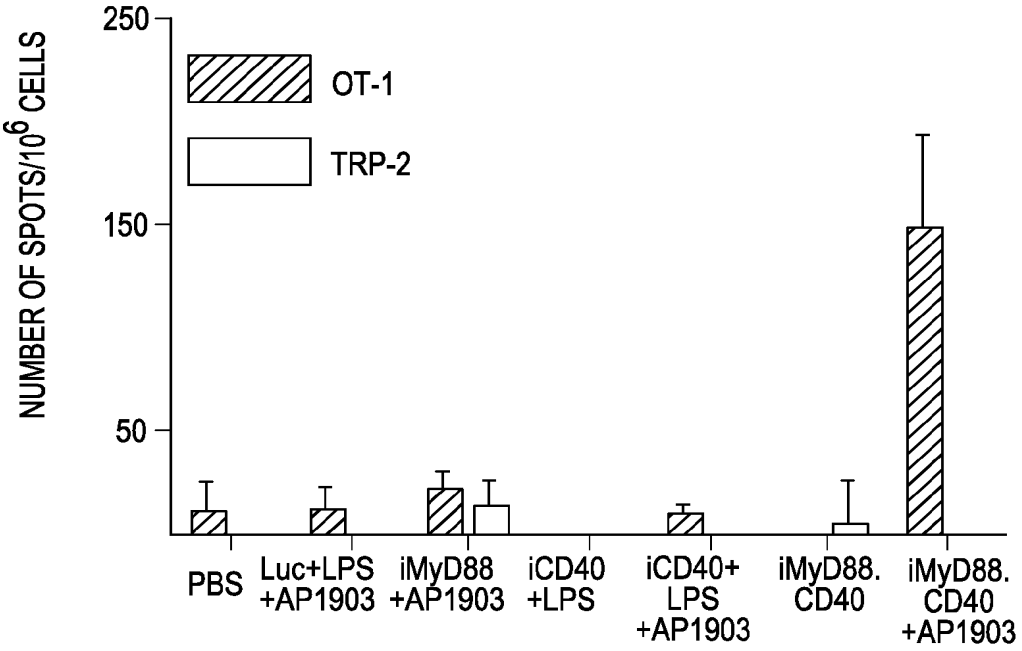


FIG. 27C

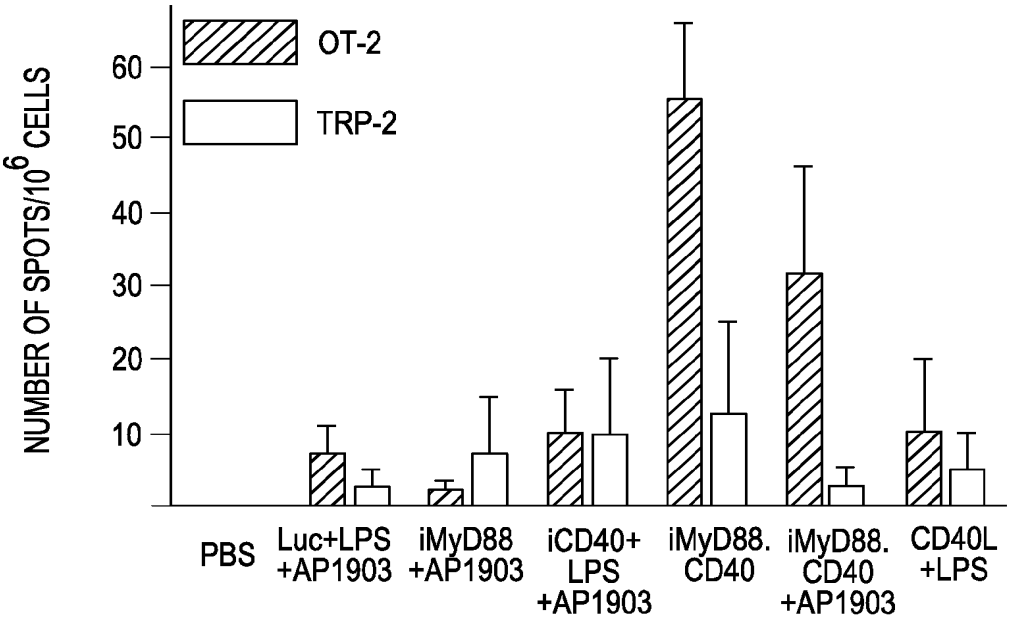


FIG. 27D

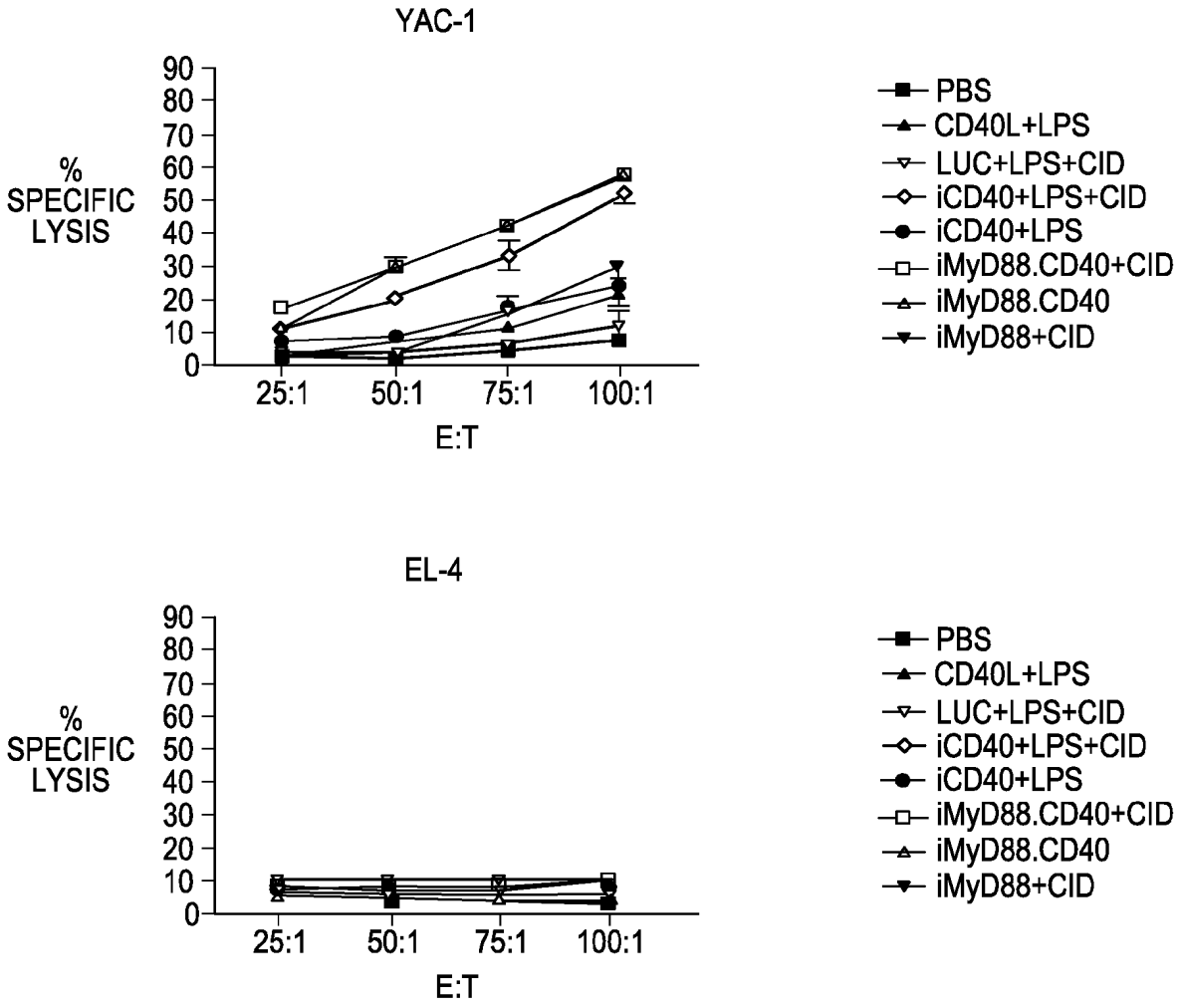

YAC-1
% SPECIFIC LYSIS
90
80
70
60
50
40
30
20
10
0
25:1
50:1
75:1
100:1
E:T
PBS
CD40L+LPS
LUC+LPS+CID
iCD40+LPS+CID
iCD40+LPS
iMyD88.CD40+CID
iMyD88.CD40
iMyD88+CID
EL-4
% SPECIFIC LYSIS
90
80
70
60
50
40
30
20
10
0
25:1
50:1
75:1
100:1
E:T
PBS
CD40L+LPS
LUC+LPS+CID
iCD40+LPS+CID
iCD40+LPS
iMyD88.CD40+CID
iMyD88.CD40
iMyD88+CID

FIG. 28

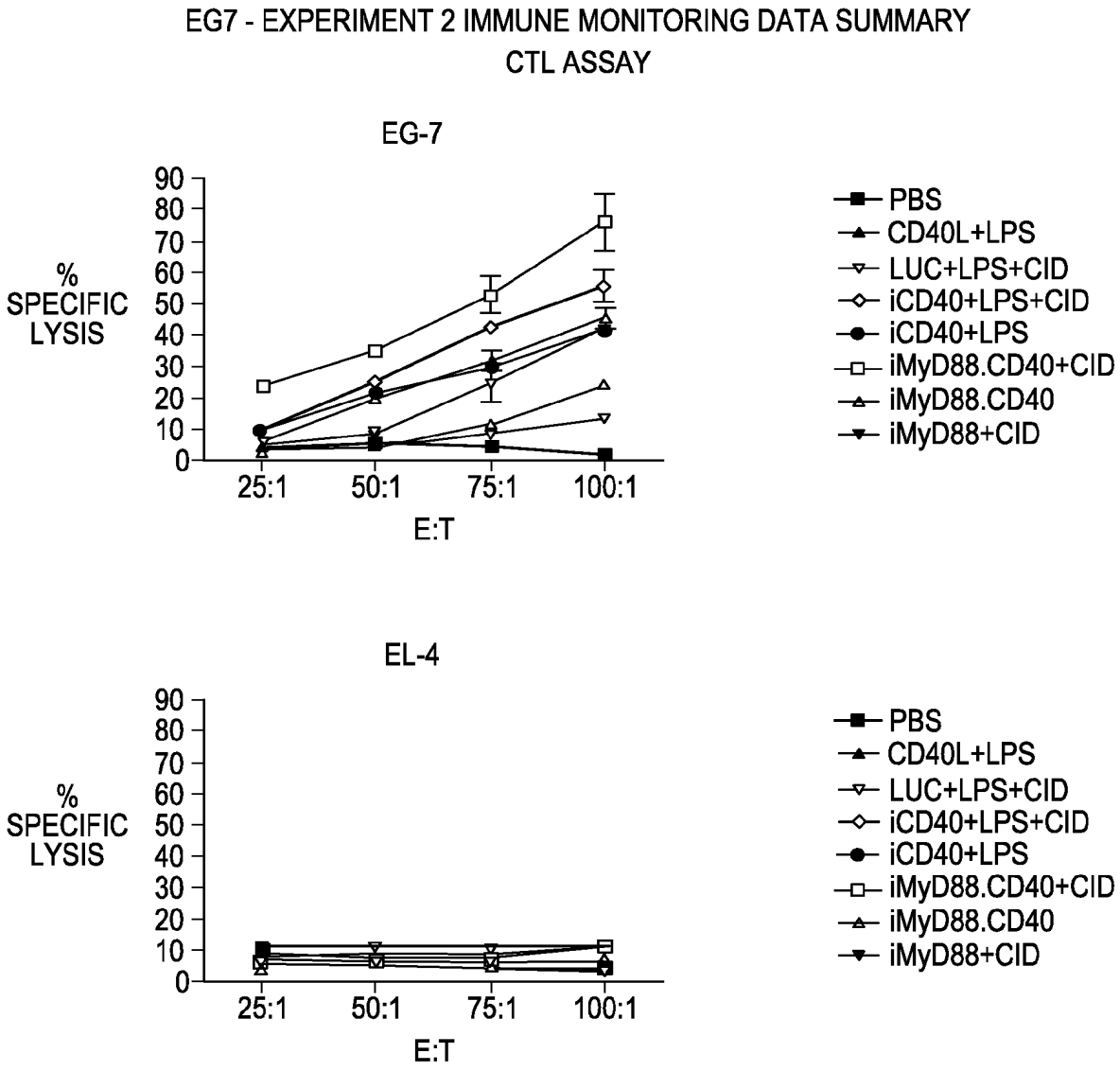

EG7 - EXPERIMENT 2 IMMUNE MONITORING DATA SUMMARY
CTL ASSAY
EG-7
% SPECIFIC LYSIS
90
80
70
60
50
40
30
20
10
0
25:1
50:1
75:1
100:1
E:T
PBS
CD40L+LPS
LUC+LPS+CID
iCD40+LPS+CID
iCD40+LPS
iMyD88.CD40+CID
iMyD88.CD40
iMyD88+CID
EL-4
% SPECIFIC LYSIS
90
80
70
60
50
40
30
20
10
0
25:1
50:1
75:1
100:1
E:T
PBS
CD40L+LPS
LUC+LPS+CID
iCD40+LPS+CID
iCD40+LPS
iMyD88.CD40+CID
iMyD88.CD40
iMyD88+CID

FIG. 29

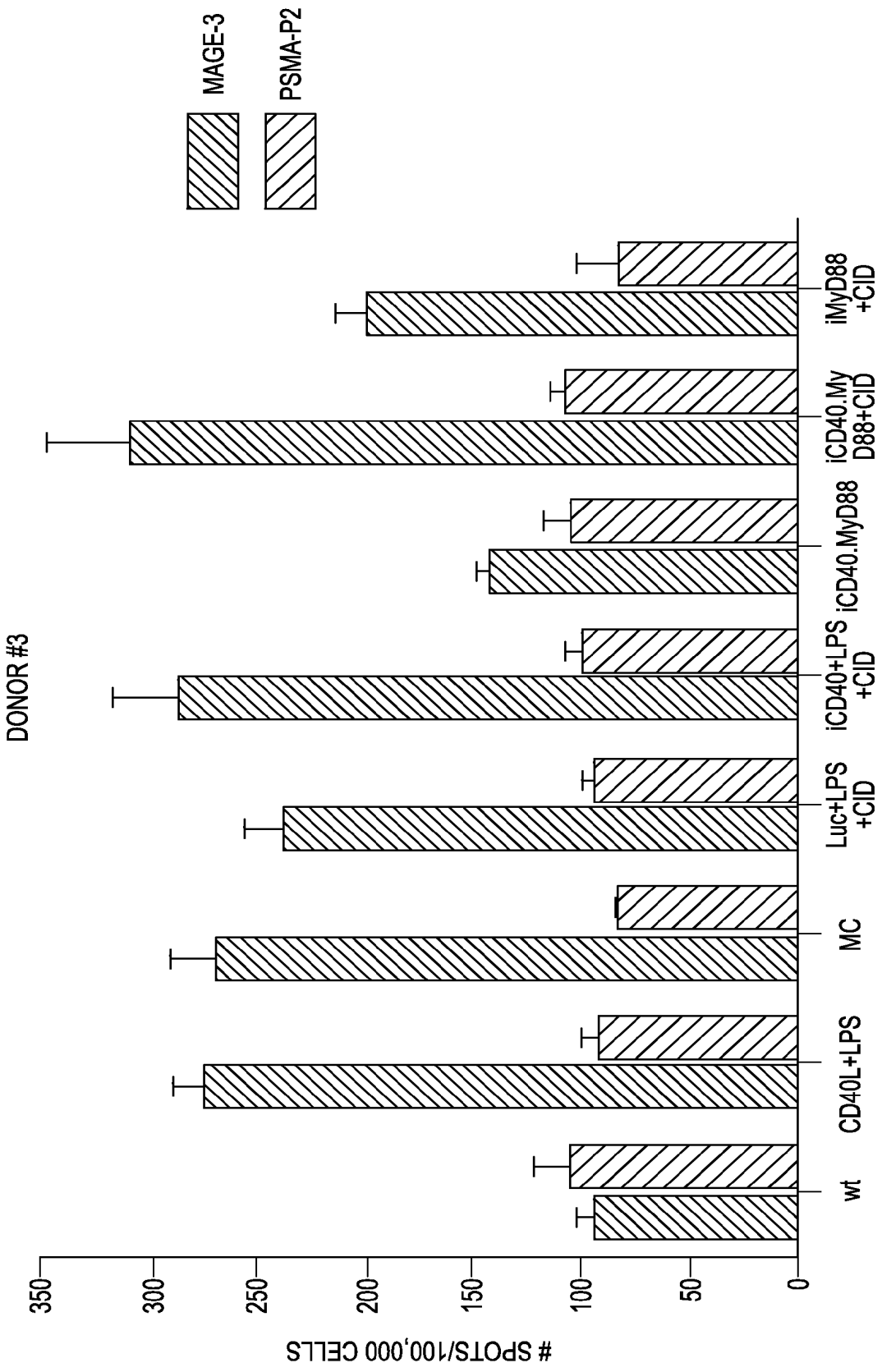

MAGE-3
PSMA-P2
DONOR #3
SPOTS/100,000 CELLS
350
300
250
200
150
100
50
0
wt
CD40L+LPS
MC
Luc+LPS +CID
iCD40+LPS +CID
iCD40.MyD88
iCD40.My D88+CID
iMyD88 +CID

FIG. 30

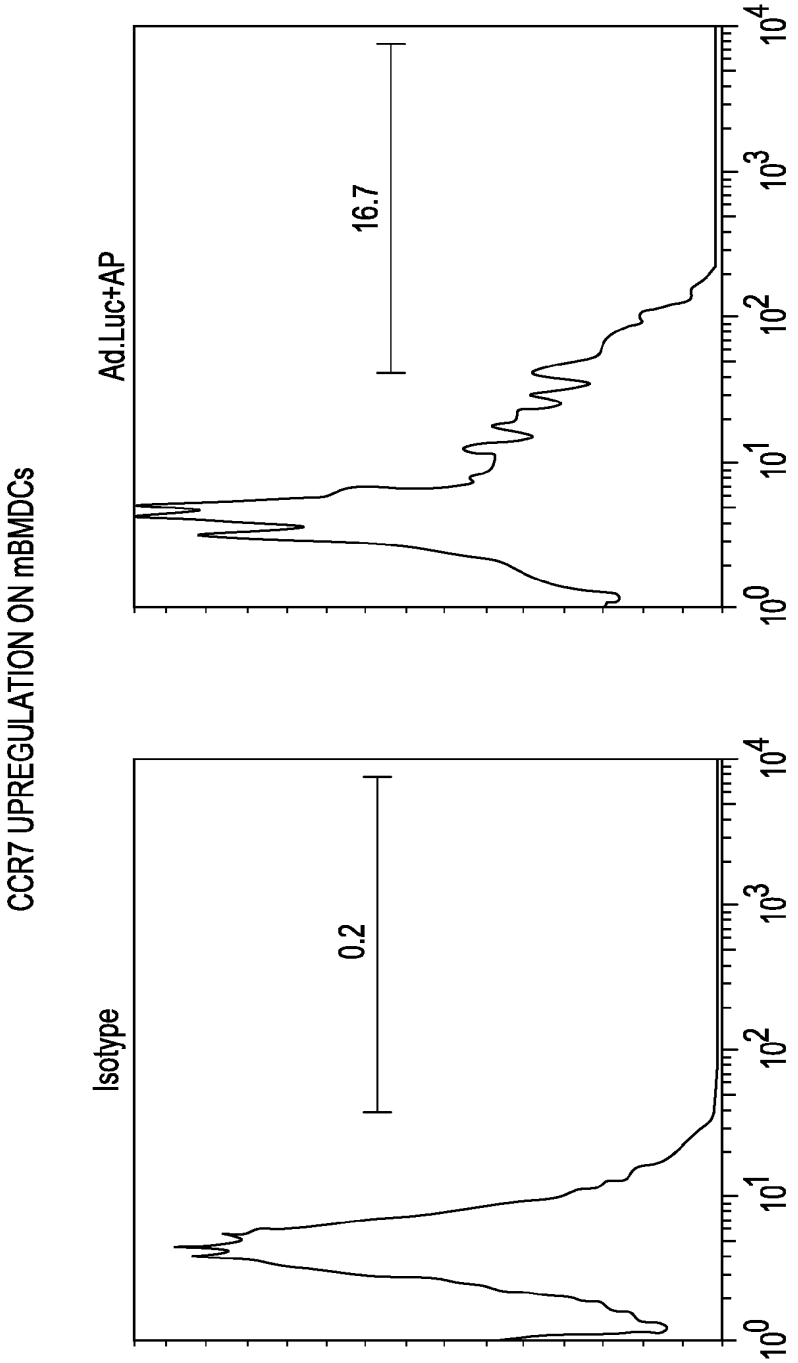

CCR7 UPREGULATION ON mBMDCs
Isotype
0.2
Ad.Luc+AP
16.7
10^0
10^1
10^2
10^3
10^4

FIG. 31

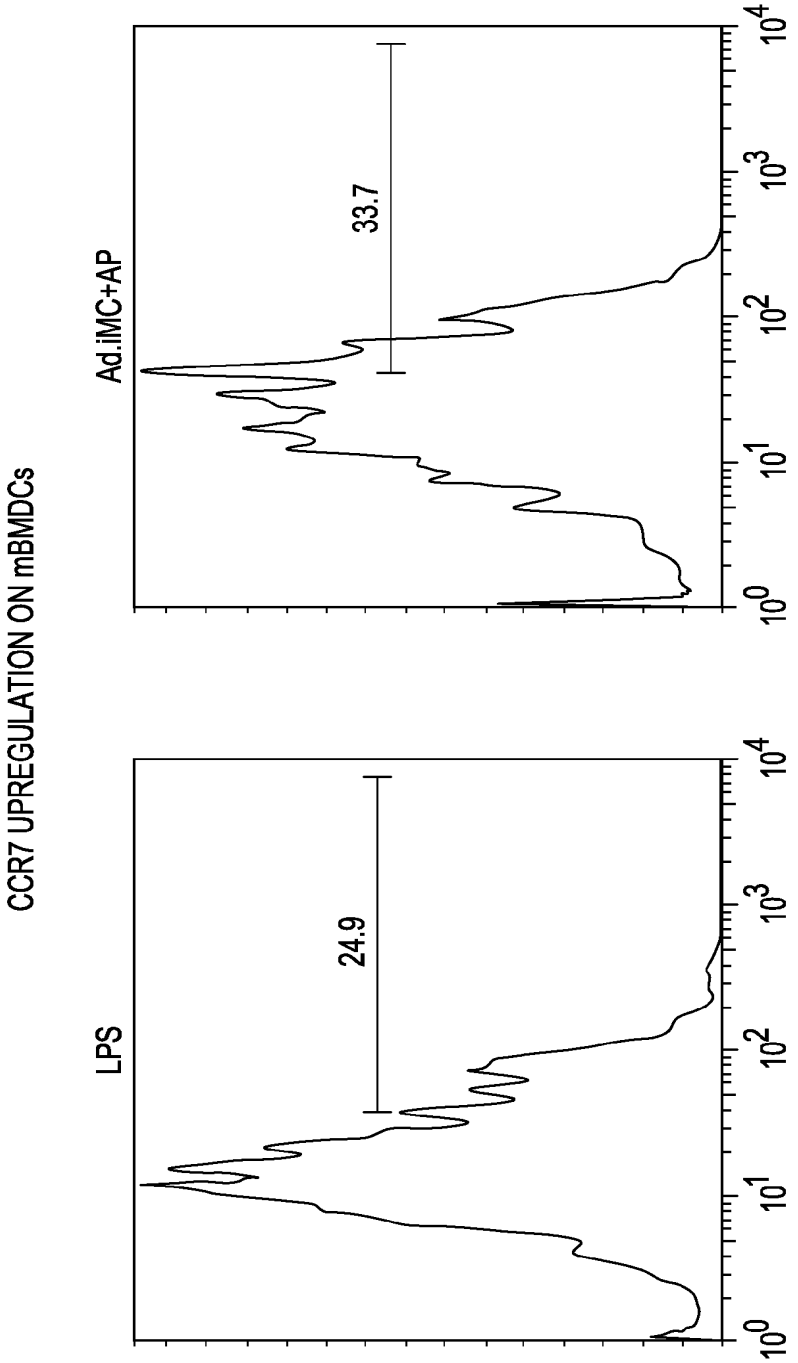


FIG. 31 Continued

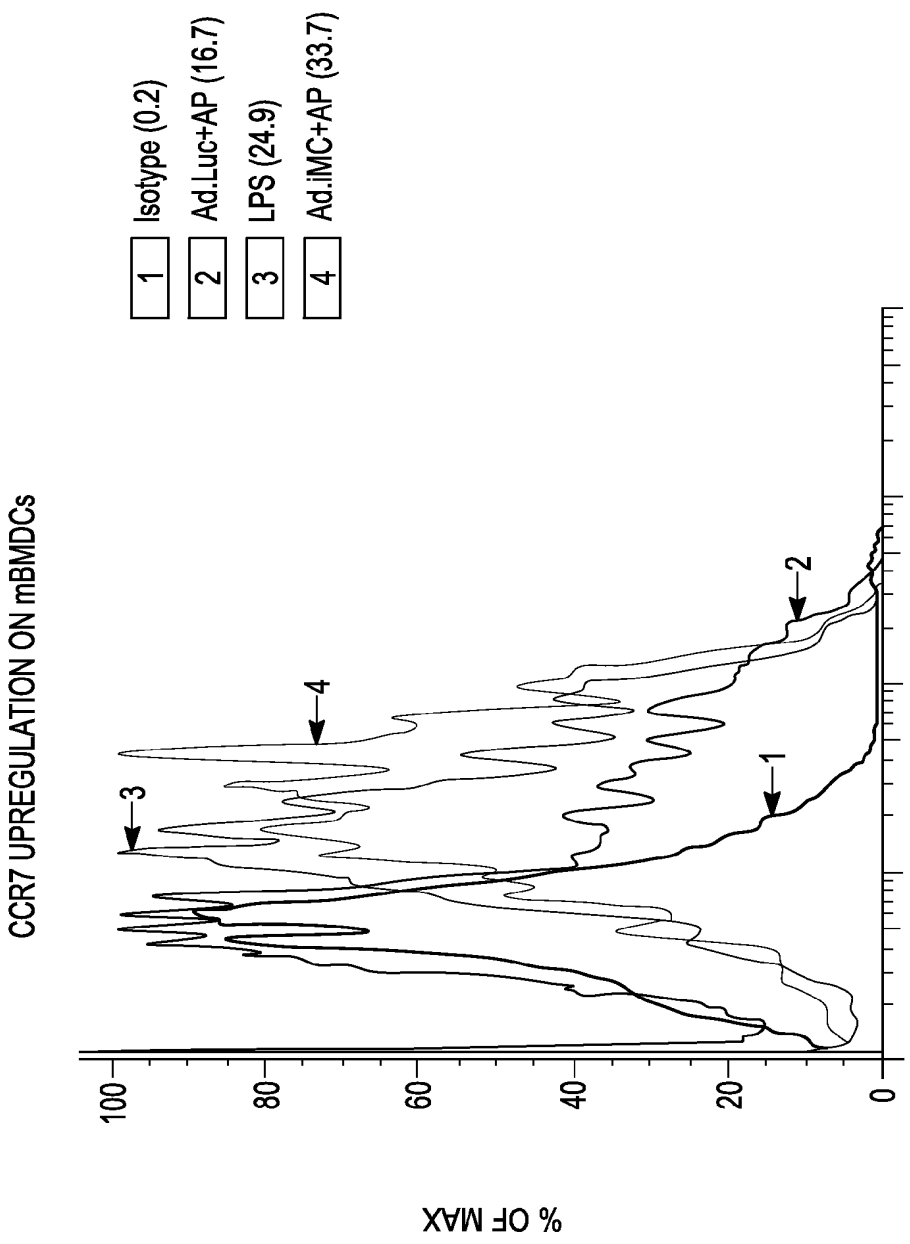

CCR7 UPREGULATION ON mBMDCs
1 Isotype (0.2)
2 Ad.Luc+AP (16.7)
3 LPS (24.9)
4 Ad.iMC+AP (33.7)
% OF MAX
0
20
40
60
80
100
1
2
3
4

FIG. 32

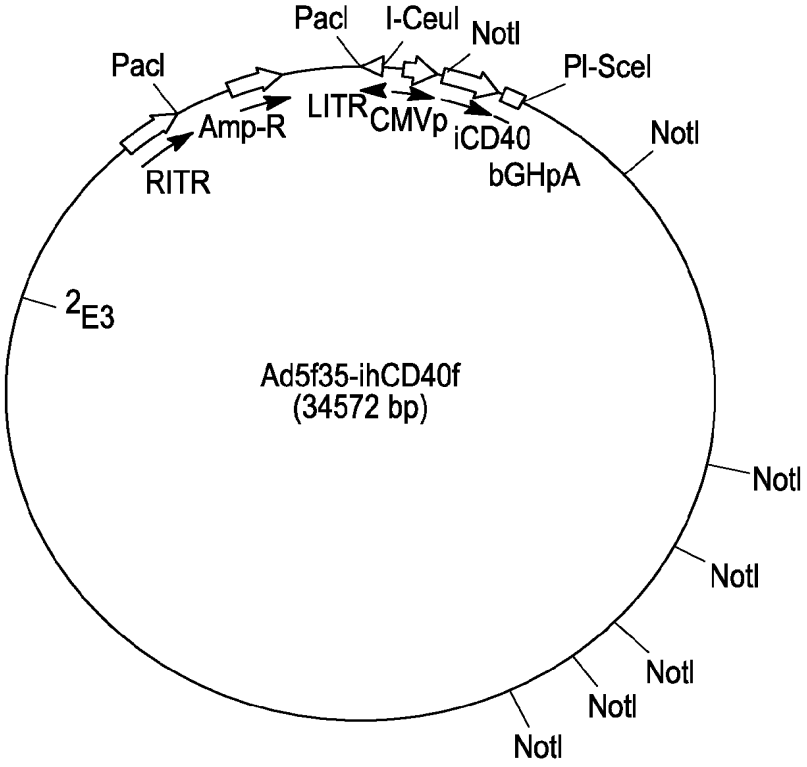

PacI
I-CeuI
NotI
PacI
PI-SceI
LITR
CMVp
Amp-R
iCD40
NotI
RITR
bGHpA
2
E3
Ad5f35-ihCD40f
(34572 bp)
NotI
NotI
NotI
NotI
NotI

FIG. 33

EXPLORATORY EFFICACY ASSESSMENTS

MODALITY		ASSESSMENT	CLASSIFICATION
RADIOGRAPHIC	SOFT TISSUE (CT, MRI)	LESION SIZE; VASCULARITY	CR, PR, SD OR PD[1]
	BONE (BONE SCAN, MRI)	NEW BONE LESIONS	SD OR PD[2]
BIOCHEMICAL	PSA	CHANGE VS. BASELINE	WATERFALL PLOT[3]
		PSADT	INCREASE <25% OR >25%; DECREASE
	CIRCULATING TUMOR CELLS	CELLS PER 7.5 mL	FAVORABLE OR UNFAVORABLE[4]
	IL-6	CHANGE VS. BASELINE	FAVORABLE OR UNFAVORABLE[5]
IMMUNOLOGIC	IMMUNE RESPONSE PROFILE	CTL, CYTOKINES, ELISPOT	CORRELATION WITH CLINICAL OUTCOME
SYMPTOMS	KPS, PAIN SCORE	CHANGE VS. BASELINE	

1. LESION SIZE PER RECIST 1.1 & PROSTATE CANCER WORKING GROUP 2 (PCWG2): COMPLETE RESPONSE (ELIMINATION OF TUMOR BURDEN); PARTIAL RESPONSE (>30% DECLINE IN TUMOR BURDEN); STABLE DISEASE; PROGRESSIVE DISEASE (>20% INCREASE IN TUMOR BURDEN). VASCULARITY PER NON-VALIDATED CR, PR, SD, PD CLASSIFICATIONS, BASED ON CT CONTRAST ENHANCEMENT (DISCUSSED IN LATER SLIDE)
2. PER PCWG2. STABLE DISEASE (≤ 1 NEW LESION) OR PROGRESSIVE DISEASE (≥ 2 NEW LESIONS). RESPONSE NOT RELIABLY MEASURABLE
3. PCWG2 FAVORS USE OF WATERFALL PLOT TO ASSESS PSA RESPONSE, AND DEFINES PSA PROGRESSION AS ≥ 25% INCREASE FROM NADIR
4. CTC VALUE BELOW 5 CELLS PER 7.5 ML SHOWN TO CORRELATE WITH INCREASED EXPECTED OVERALL SURVIVAL
5. IL-6 VALUE BELOW 13.3 PG/ML SHOWN TO CORRELATE WITH INCREASED EXPECTED OVERALL SURVIVAL IN CRPC (CLIN. CAN. RES., 2005)

FIG. 34

12 WEEK IMMUNOLOGICAL & CLINICAL RESPONSE SUMMARY

SUBJECT #	1001	1002	1003	1004	1005	1006
DEMOGRAPHICS & BASELINE METRICS						
AGE	73	72	81	80	66	73
KPS (AT SCREENING)	90%	90%	80%	80%	100%	90%
GLEASON SCORE	N/A	7	9	10	8	8
PRIOR CHEMOTHERAPY	NONE	NONE	TAXOTERE	TAXOTERE	NONE	NONE
CLINICAL SUBTYPE	4	5	3	4	4	5
BASELINE PSA (ng/mL)	5.8	11.1	312.8	46.5	69.0	30.9
PRE-TREATMENT PSADT (MOS.)	4.9	7.3	5.0	1.7	1.4	1.6
IMMUNOLOGICAL RESPONSE @ 12 WEEKS						
AG-SPECIFIC IMMUNE RESPONSE	IFN-γ, IP-10	NOT DETERMINED		IFN-γ, IP-10	IL-6, MCP-1	IL-6, MCP-1
MEAN POST-DOSE CYTOKINE Δ	-2%	-6%	283%	66%	72%	43%
IL-6 DECLINE @ WEEK 12	-98%	-65%	-100%	-16%	+139%	-75%
SAFETY & CLINICAL RESPONSE @ 12 WEEKS						
MAX AE GRADE	1	2	2	1	1	2
RECIST 1.1-SOFT TISSUE	-	SD	SD	-	N/A	PD
RECIST 1.1-BONE	SD	SD	SD	SD	PD	PD
POST-TREATMENT PSADT (MOS.)	19.5	PSA↘	PSA↘	3.7	N/A	2.9
PSADT INCREASE	298%	∞	∞	118%	N/A	80%

FIG. 35

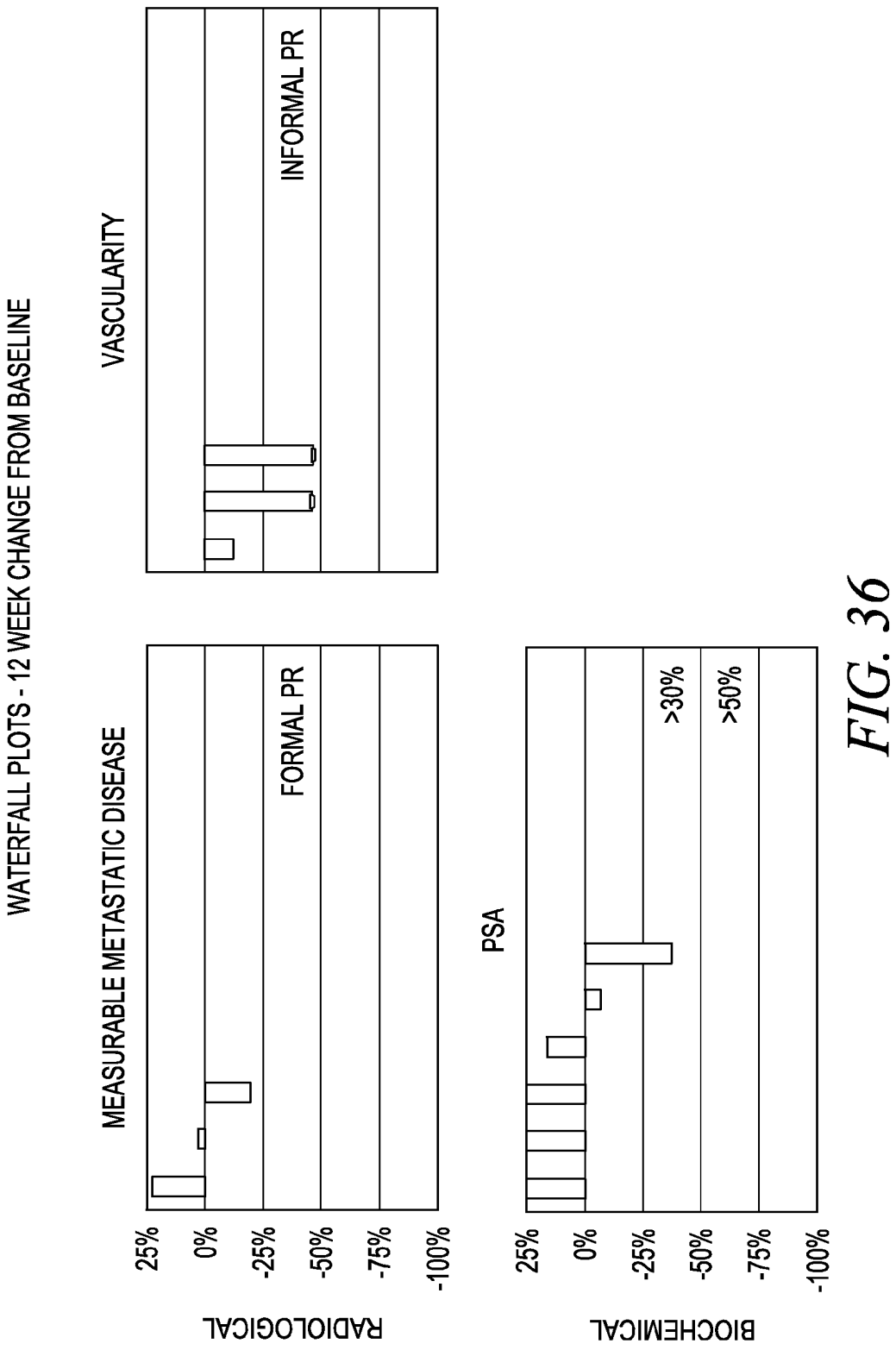

WATERFALL PLOTS - 12 WEEK CHANGE FROM BASELINE
MEASURABLE METASTATIC DISEASE
VASCULARITY
FORMAL PR
INFORMAL PR
25%
0%
-25%
-50%
-75%
-100%
RADIOLOGICAL
PSA
>30%
>50%
BIOCHEMICAL

FIG. 36

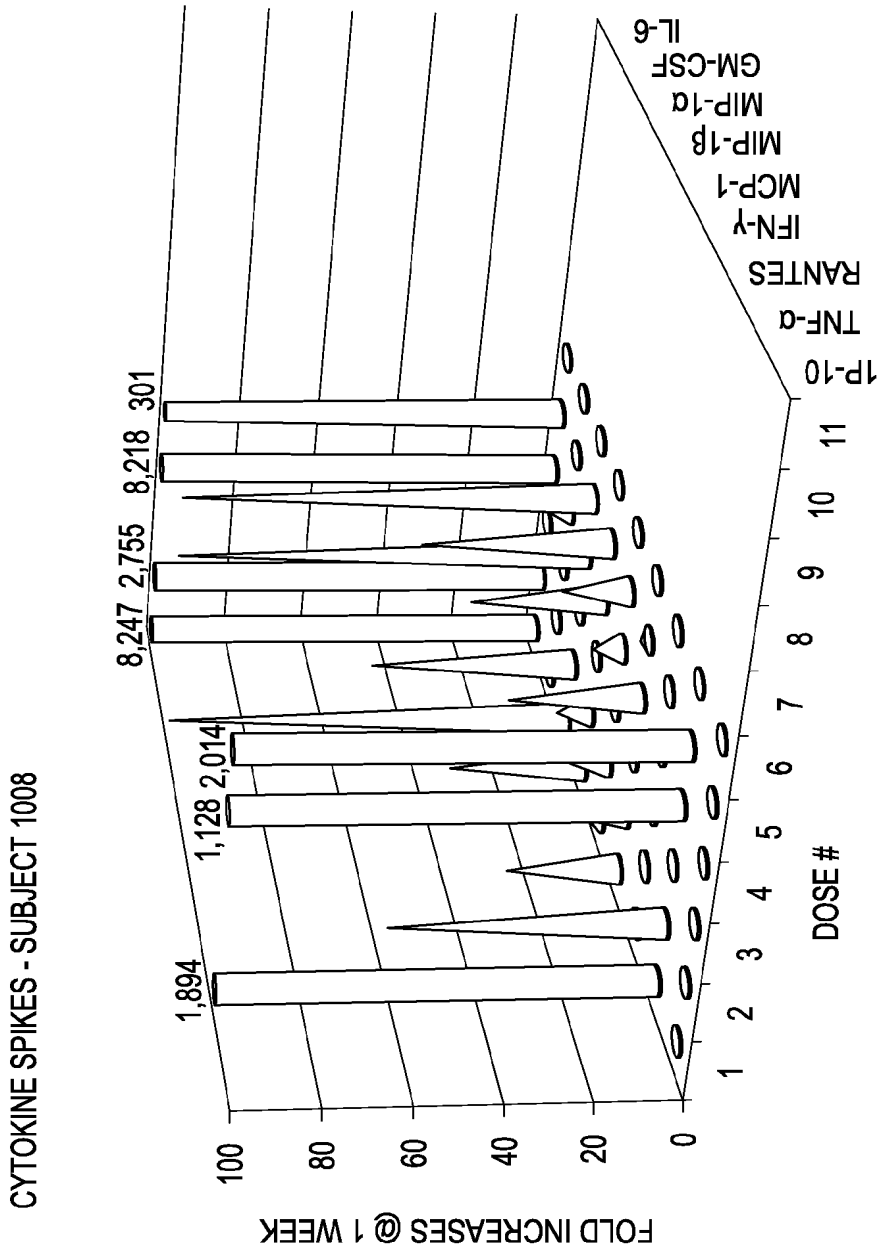

CYTOKINE SPIKES - SUBJECT 1008
FOLD INCREASES @ 1 WEEK
0
20
40
60
80
100
1,894
1,128
2,014
8,247
2,755
8,218
301
DOSE #
1
2
3
4
5
6
7
8
9
10
11
IP-10
TNF-α
RANTES
IFN-γ
MCP-1
MIP-1β
MIP-1α
GM-CSF
IL-6

FIG. 37

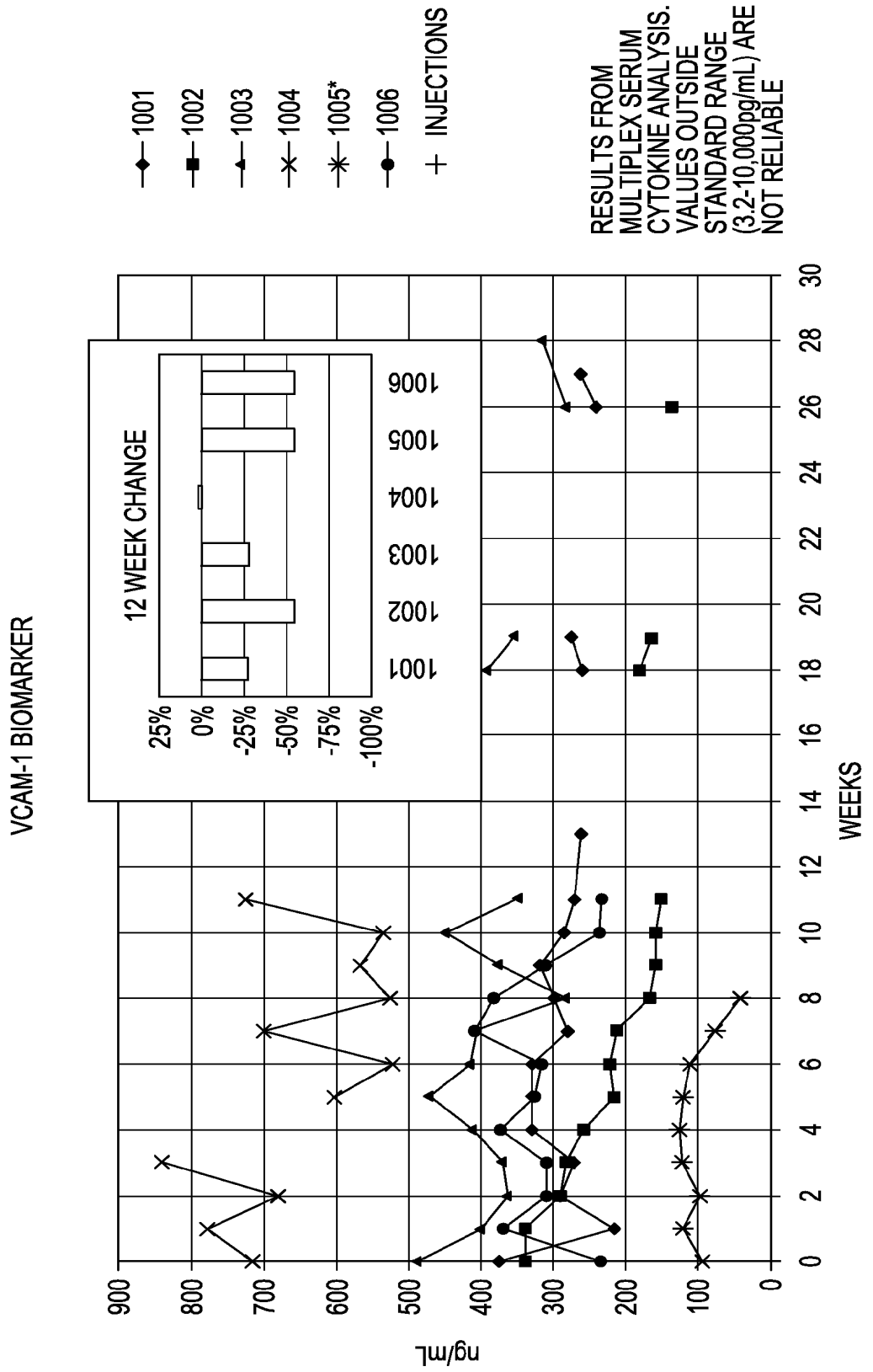

VCAM-1 BIOMARKER
ng/mL
900
800
700
600
500
400
300
200
100
0
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
WEEKS
1001
1002
1003
1004
1005*
1006
INJECTIONS
RESULTS FROM MULTIPLEX SERUM CYTOKINE ANALYSIS. VALUES OUTSIDE STANDARD RANGE (3.2-10,000pg/mL) ARE NOT RELIABLE
12 WEEK CHANGE
25%
0%
-25%
-50%
-75%
-100%
1001
1002
1003
1004
1005
1006

FIG. 38

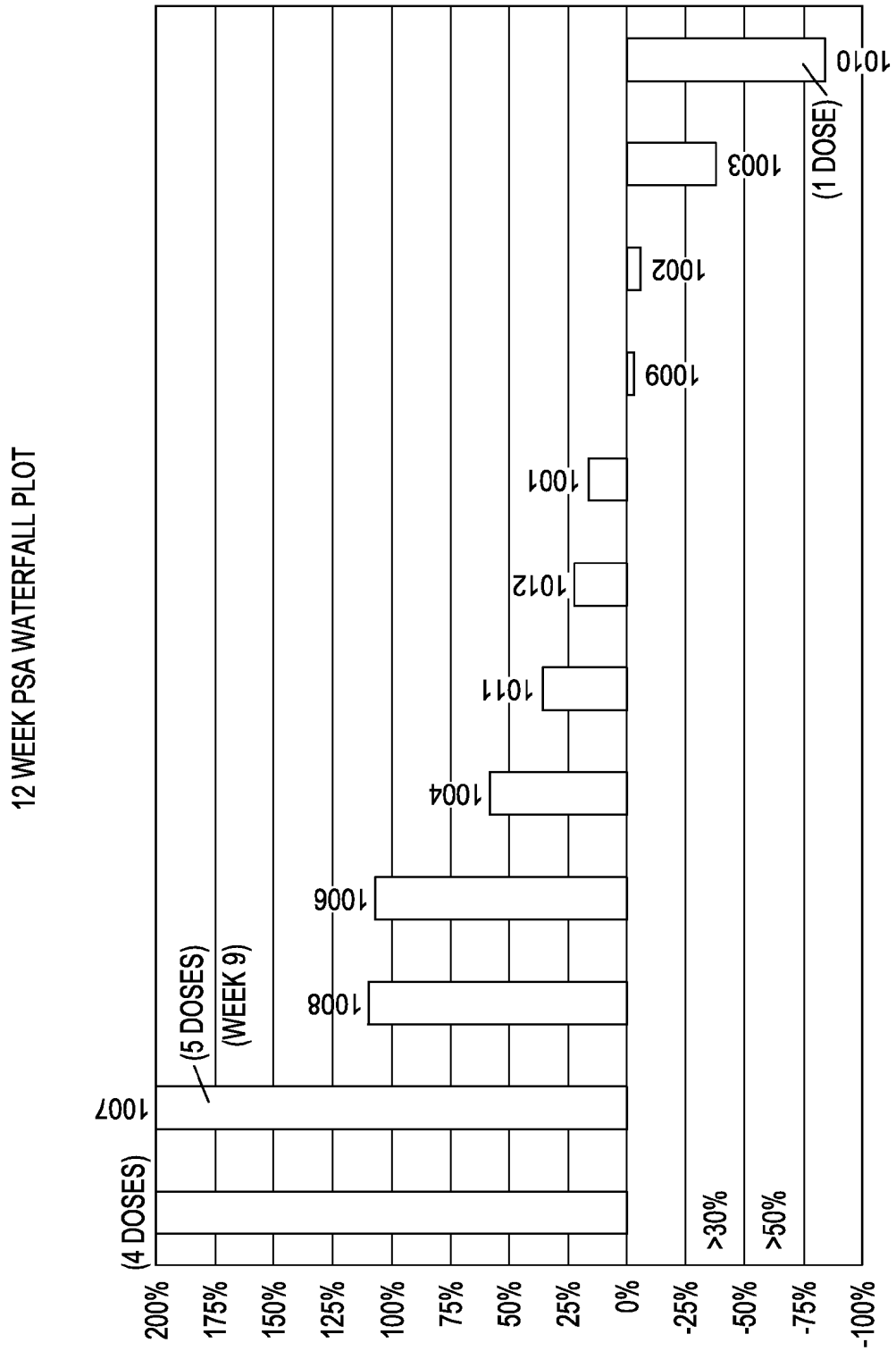

12 WEEK PSA WATERFALL PLOT
200%
175%
150%
125%
100%
75%
50%
25%
0%
-25%
-50%
-75%
-100%
>30%
>50%
(4 DOSES)
1007
(5 DOSES)
(WEEK 9)
1008
1006
1004
1011
1012
1001
1009
1002
1003
1010
(1 DOSE)

FIG. 39

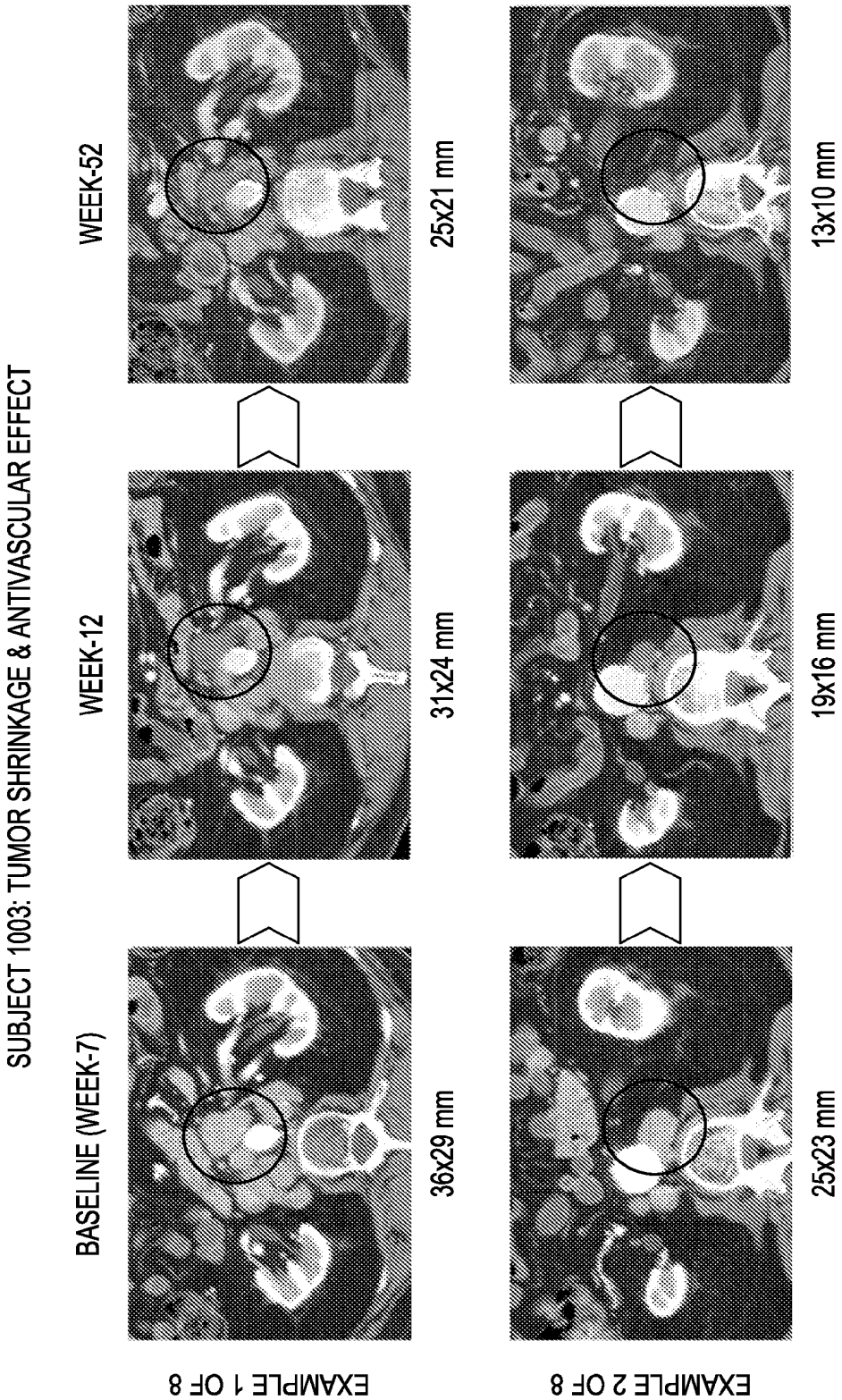

SUBJECT 1003: TUMOR SHRINKAGE & ANTIVASCULAR EFFECT
BASELINE (WEEK-7)
WEEK-12
WEEK-52
36x29 mm
31x24 mm
25x21 mm
25x23 mm
19x16 mm
13x10 mm
EXAMPLE 1 OF 8
EXAMPLE 2 OF 8

FIG. 40

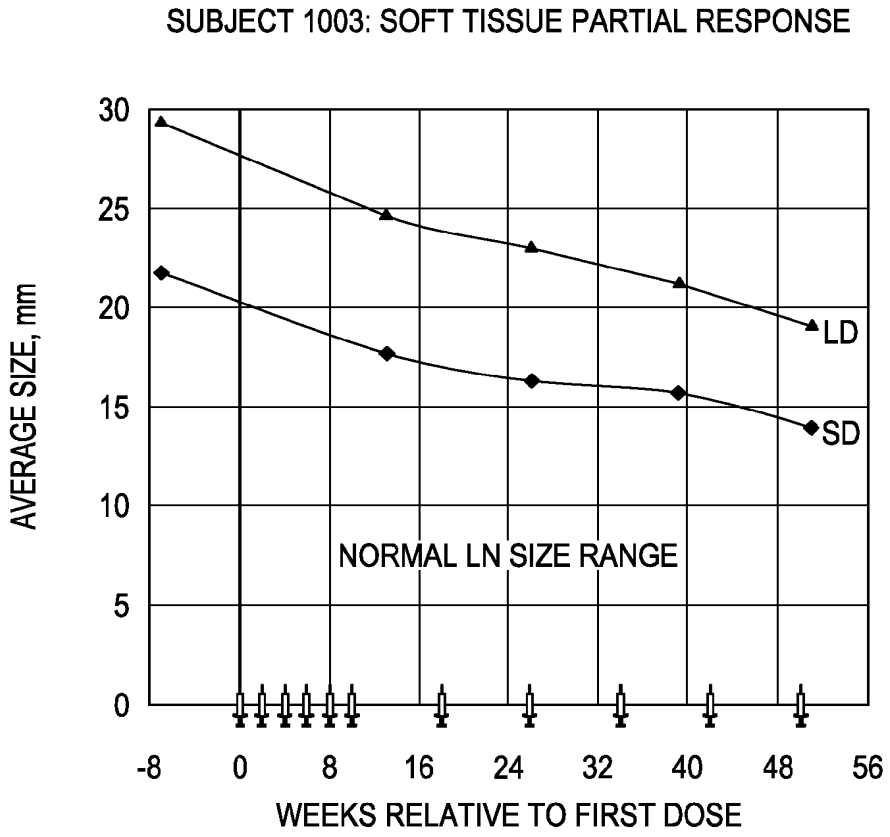

SUBJECT 1003: SOFT TISSUE PARTIAL RESPONSE
AVERAGE SIZE, mm
30
25
20
15
10
5
0
LD
SD
NORMAL LN SIZE RANGE
-8
0
8
16
24
32
40
48
56
WEEKS RELATIVE TO FIRST DOSE

FIG. 41

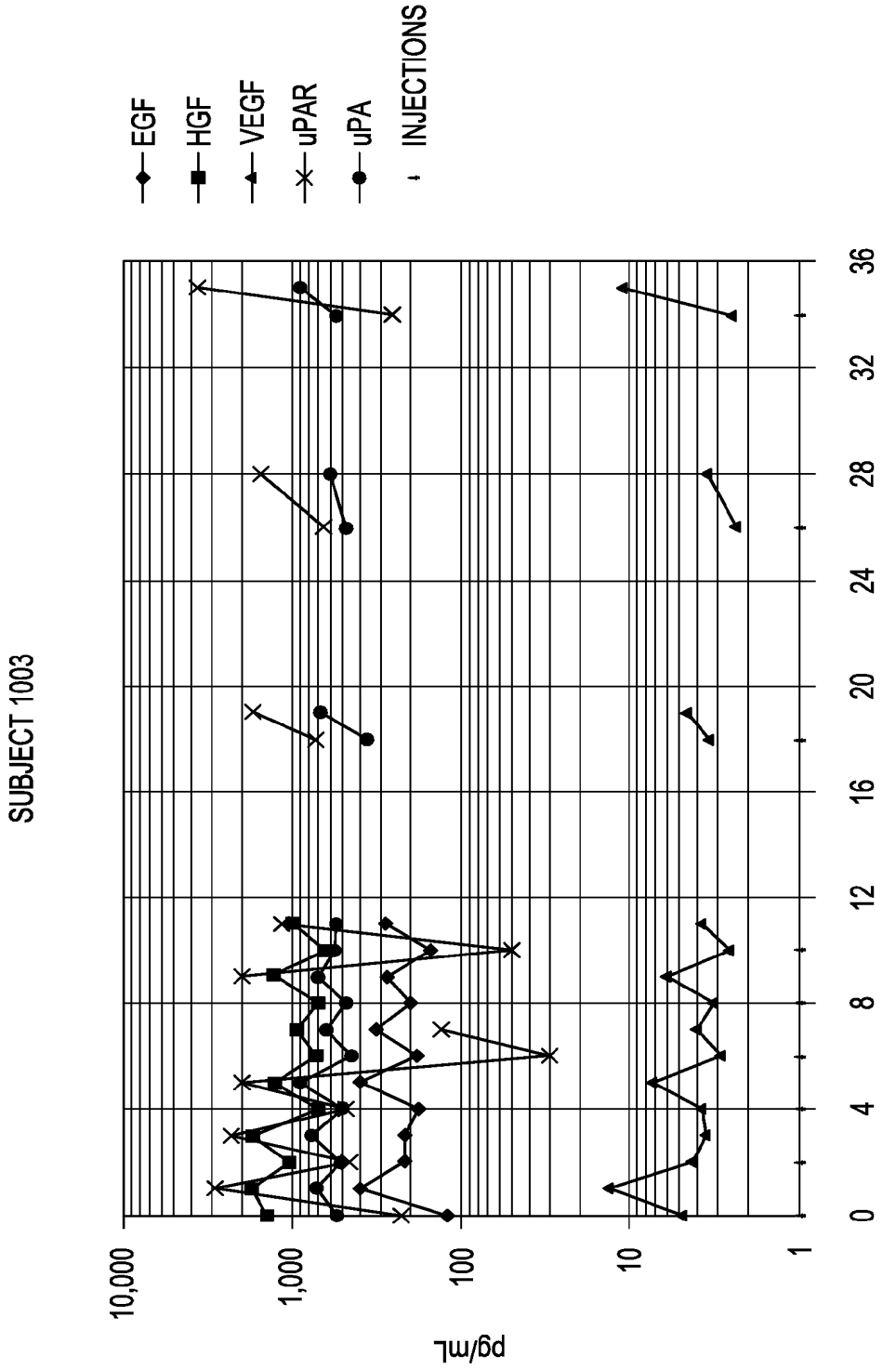

EGF
HGF
VEGF
uPAR
uPA
INJECTIONS
SUBJECT 1003
pg/mL
10,000
1,000
100
10
1
0
4
8
12
16
20
24
28
32
36
WEEKS

FIG. 42

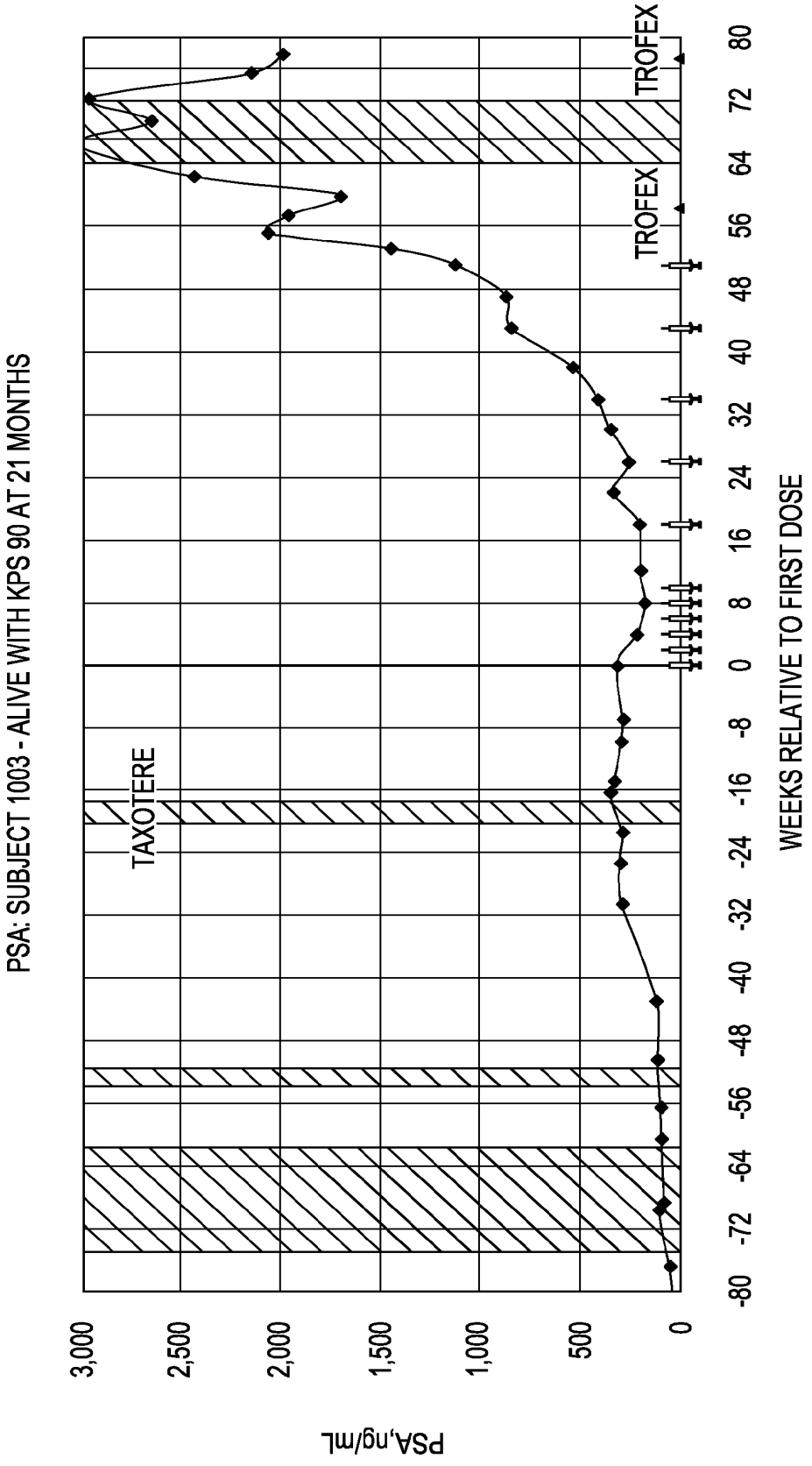

PSA: SUBJECT 1003 - ALIVE WITH KPS 90 AT 21 MONTHS
TAXOTERE
TROFEX
TROFEX
PSA,ng/mL
3,000
2,500
2,000
1,500
1,000
500
0
-80
-72
-64
-56
-48
-40
-32
-24
-16
-8
0
8
16
24
32
40
48
56
64
72
80
WEEKS RELATIVE TO FIRST DOSE

FIG. 43

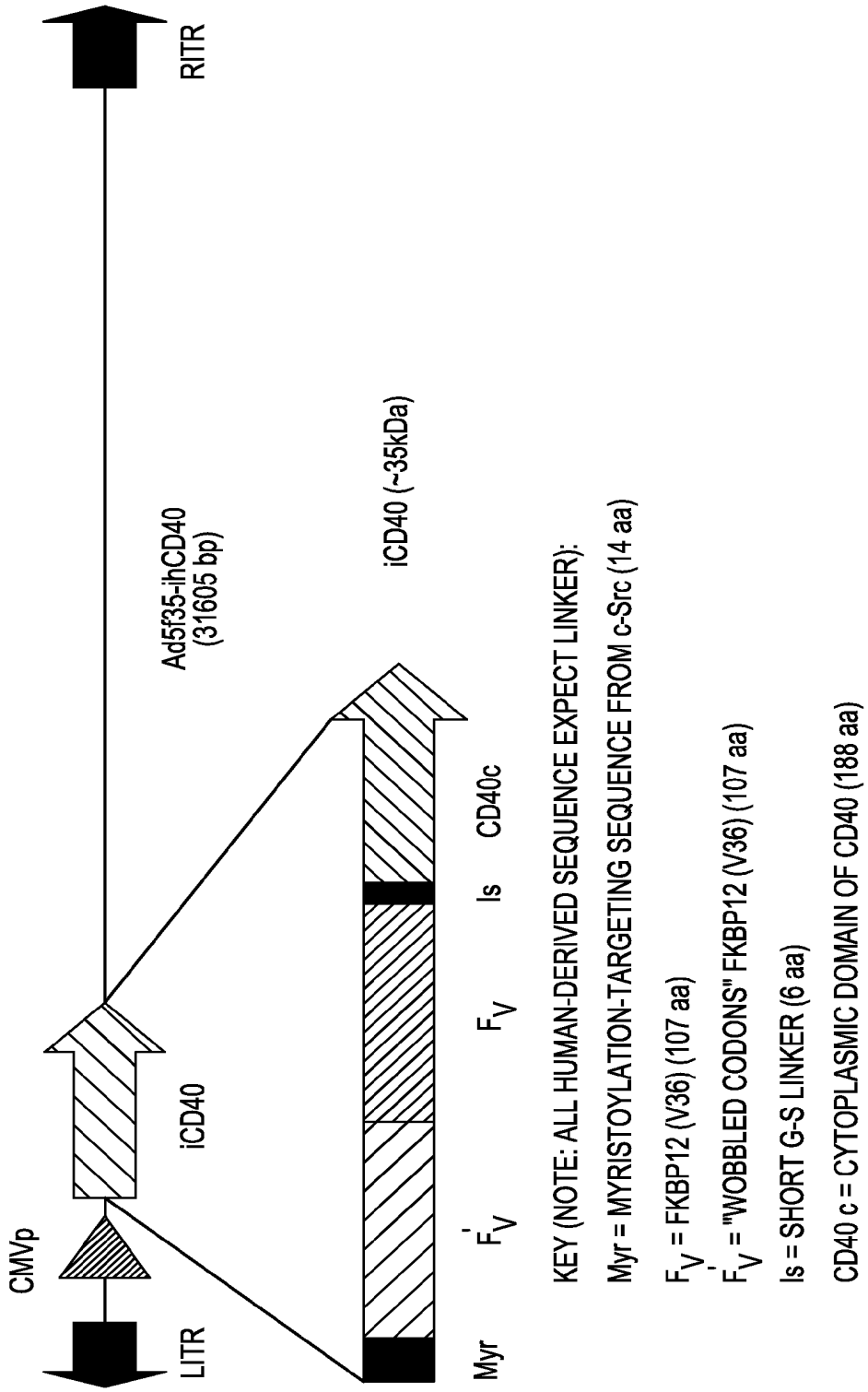

RITR
Ad5f35-ihCD40
(31605 bp)
iCD40 (~35kDa)
CMVp
iCD40
LITR
Myr
F'V
FV
ls
CD40c
KEY (NOTE: ALL HUMAN-DERIVED SEQUENCE EXPECT LINKER):
Myr = MYRISTOYLATION-TARGETING SEQUENCE FROM c-Src (14 aa)
FV = FKBP12 (V36) (107 aa)
F'V = "WOBBLED CODONS" FKBP12 (V36) (107 aa)
ls = SHORT G-S LINKER (6 aa)
CD40 c = CYTOPLASMIC DOMAIN OF CD40 (188 aa)

FIG. 44

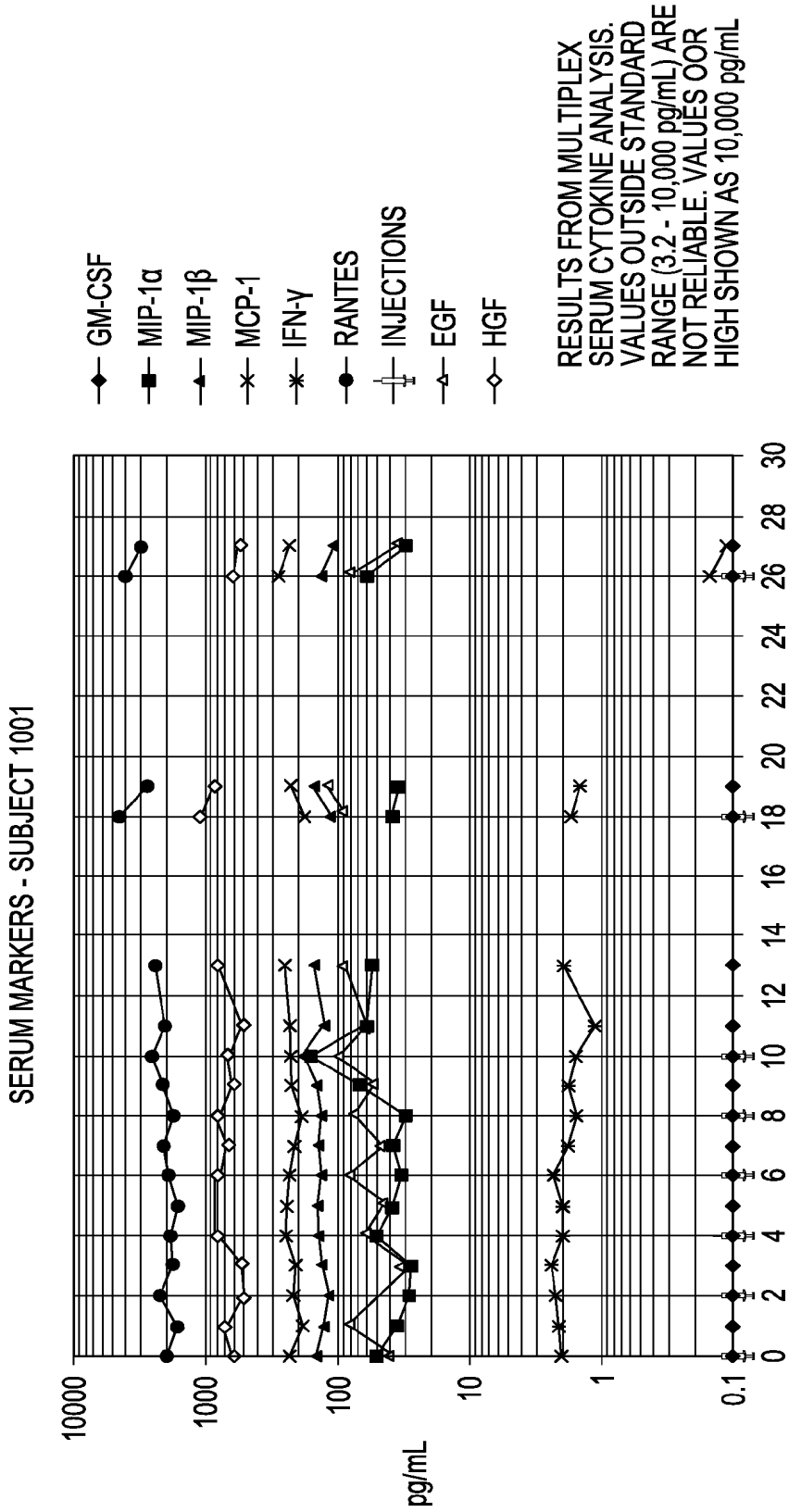

SERUM MARKERS - SUBJECT 1001
GM-CSF
MIP-1α
MIP-1β
MCP-1
IFN-γ
RANTES
INJECTIONS
EGF
HGF
RESULTS FROM MULTIPLEX SERUM CYTOKINE ANALYSIS. VALUES OUTSIDE STANDARD RANGE (3.2 - 10,000 pg/mL) ARE NOT RELIABLE. VALUES OOR HIGH SHOWN AS 10,000 pg/mL
10000
1000
100
10
1
0.1
pg/mL
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
WEEKS

FIG. 45

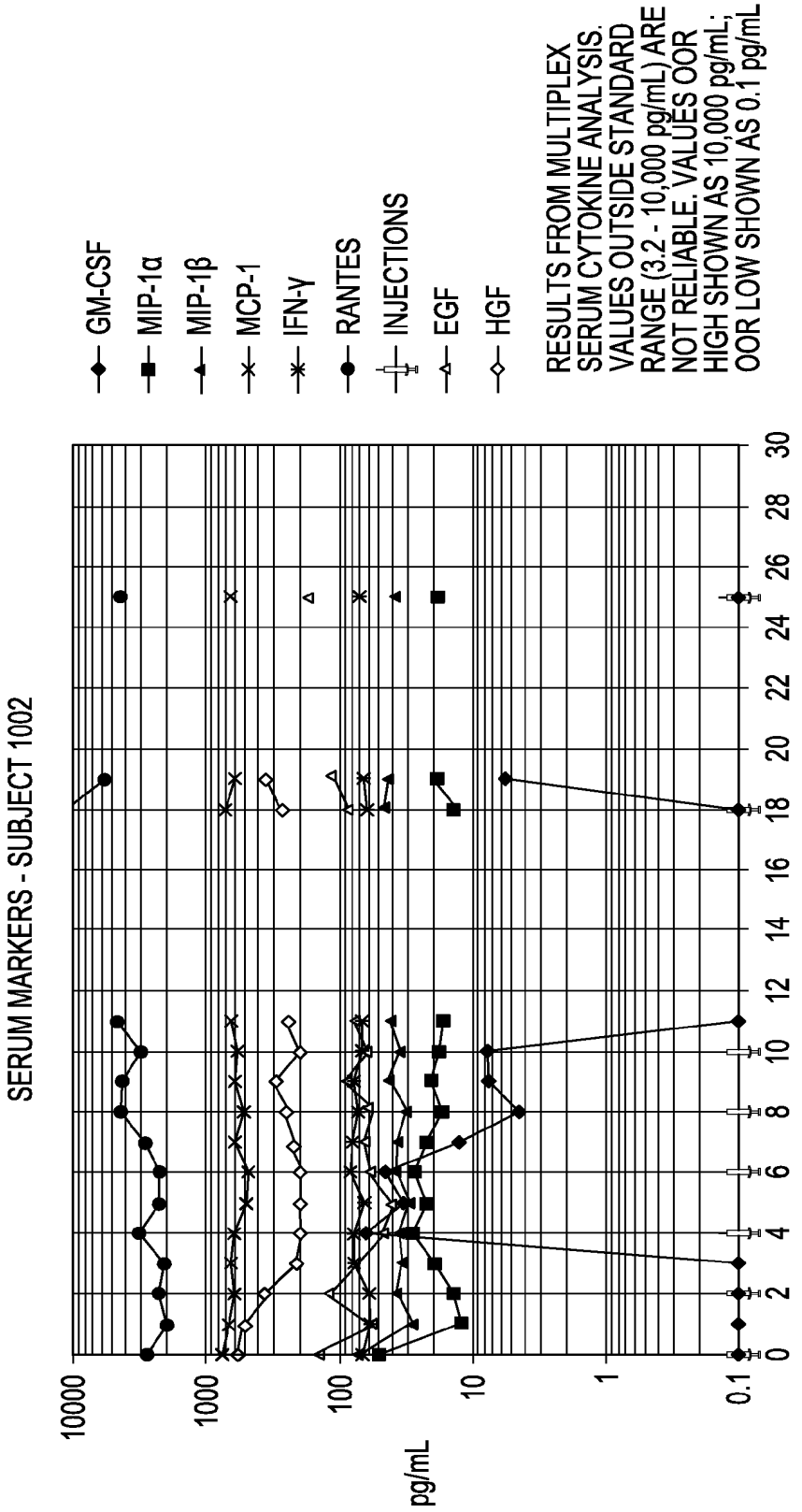

SERUM MARKERS - SUBJECT 1002
GM-CSF
MIP-1α
MIP-1β
MCP-1
IFN-γ
RANTES
INJECTIONS
EGF
HGF
RESULTS FROM MULTIPLEX SERUM CYTOKINE ANALYSIS. VALUES OUTSIDE STANDARD RANGE (3.2 - 10,000 pg/mL) ARE NOT RELIABLE. VALUES OOR HIGH SHOWN AS 10,000 pg/mL; OOR LOW SHOWN AS 0.1 pg/mL
pg/mL
10000
1000
100
10
1
0.1
WEEKS
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30

FIG. 46

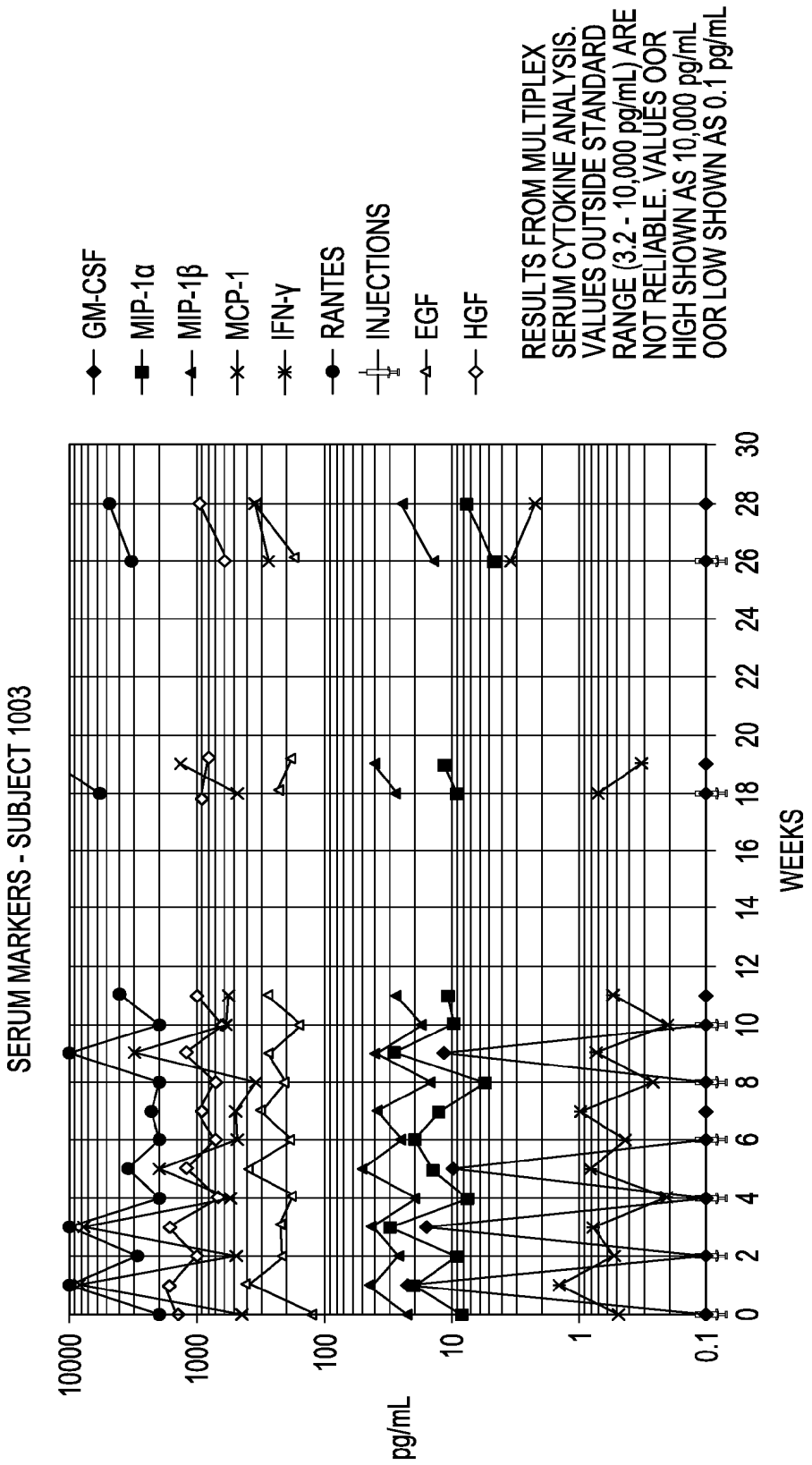

SERUM MARKERS - SUBJECT 1003
GM-CSF
MIP-1α
MIP-1β
MCP-1
IFN-γ
RANTES
INJECTIONS
EGF
HGF
RESULTS FROM MULTIPLEX SERUM CYTOKINE ANALYSIS. VALUES OUTSIDE STANDARD RANGE (3.2 - 10,000 pg/mL) ARE NOT RELIABLE. VALUES OOR HIGH SHOWN AS 10,000 pg/mL OOR LOW SHOWN AS 0.1 pg/mL
pg/mL
10000
1000
100
10
1
0.1
WEEKS
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30

FIG. 47

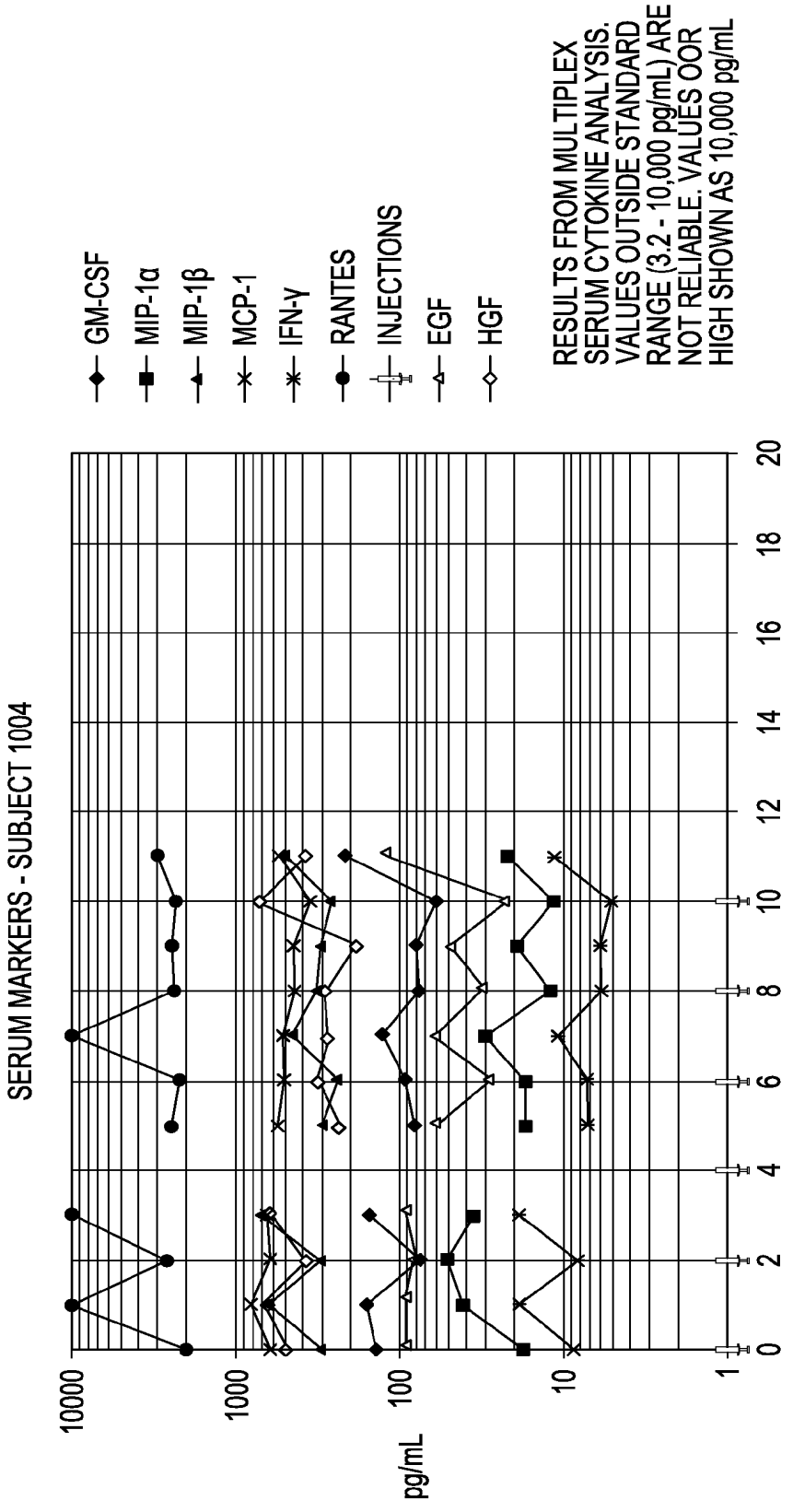

SERUM MARKERS - SUBJECT 1004
GM-CSF
MIP-1α
MIP-1β
MCP-1
IFN-γ
RANTES
INJECTIONS
EGF
HGF
RESULTS FROM MULTIPLEX SERUM CYTOKINE ANALYSIS. VALUES OUTSIDE STANDARD RANGE (3.2 - 10,000 pg/mL) ARE NOT RELIABLE. VALUES OOR HIGH SHOWN AS 10,000 pg/mL
pg/mL
10000
1000
100
10
1
WEEKS
0
2
4
6
8
10
12
14
16
18
20

FIG. 48

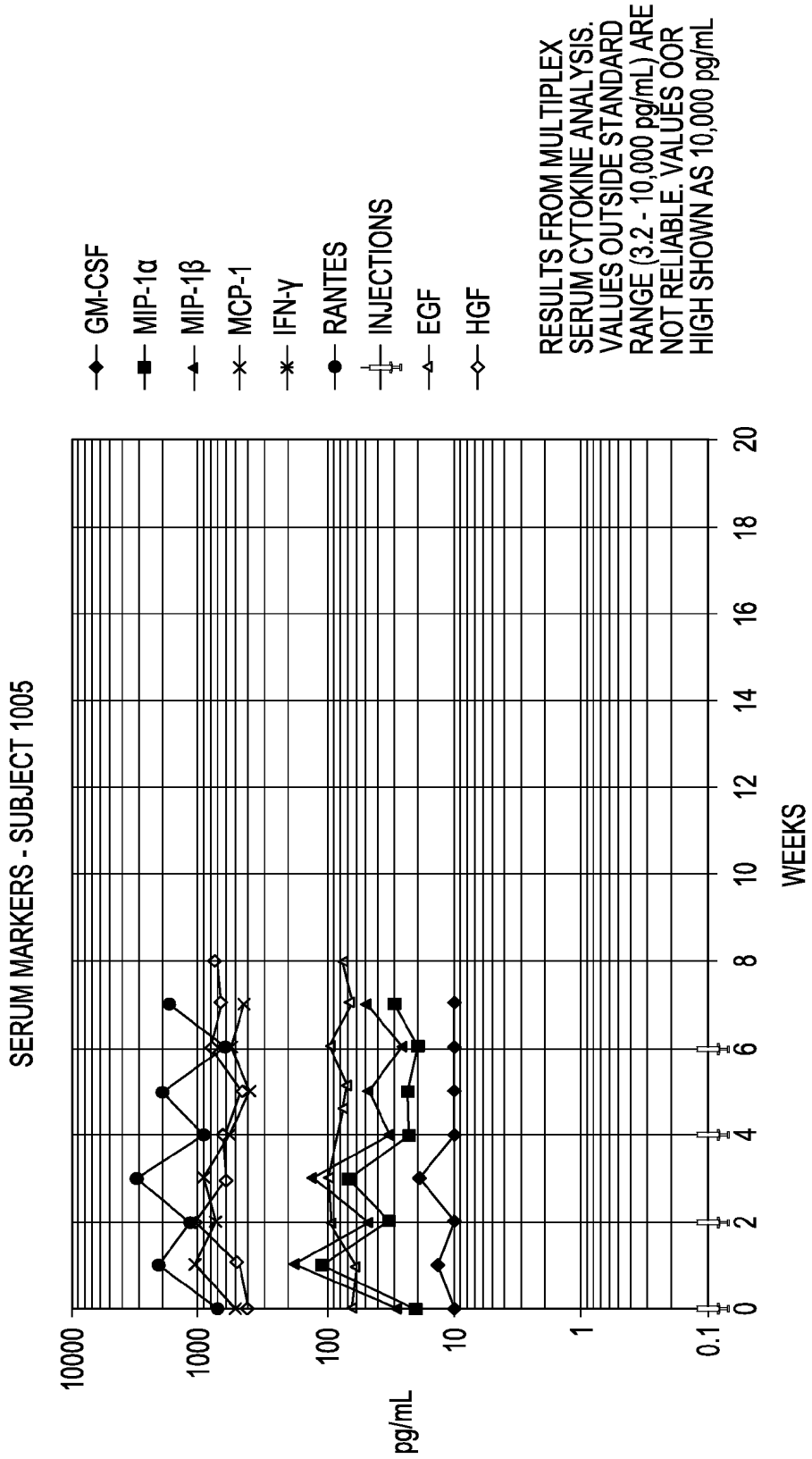

SERUM MARKERS - SUBJECT 1005
GM-CSF
MIP-1α
MIP-1β
MCP-1
IFN-γ
RANTES
INJECTIONS
EGF
HGF
RESULTS FROM MULTIPLEX SERUM CYTOKINE ANALYSIS. VALUES OUTSIDE STANDARD RANGE (3.2 - 10,000 pg/mL) ARE NOT RELIABLE. VALUES OOR HIGH SHOWN AS 10,000 pg/mL
10000
1000
100
10
1
0.1
pg/mL
0
2
4
6
8
10
12
14
16
18
20
WEEKS

FIG. 49

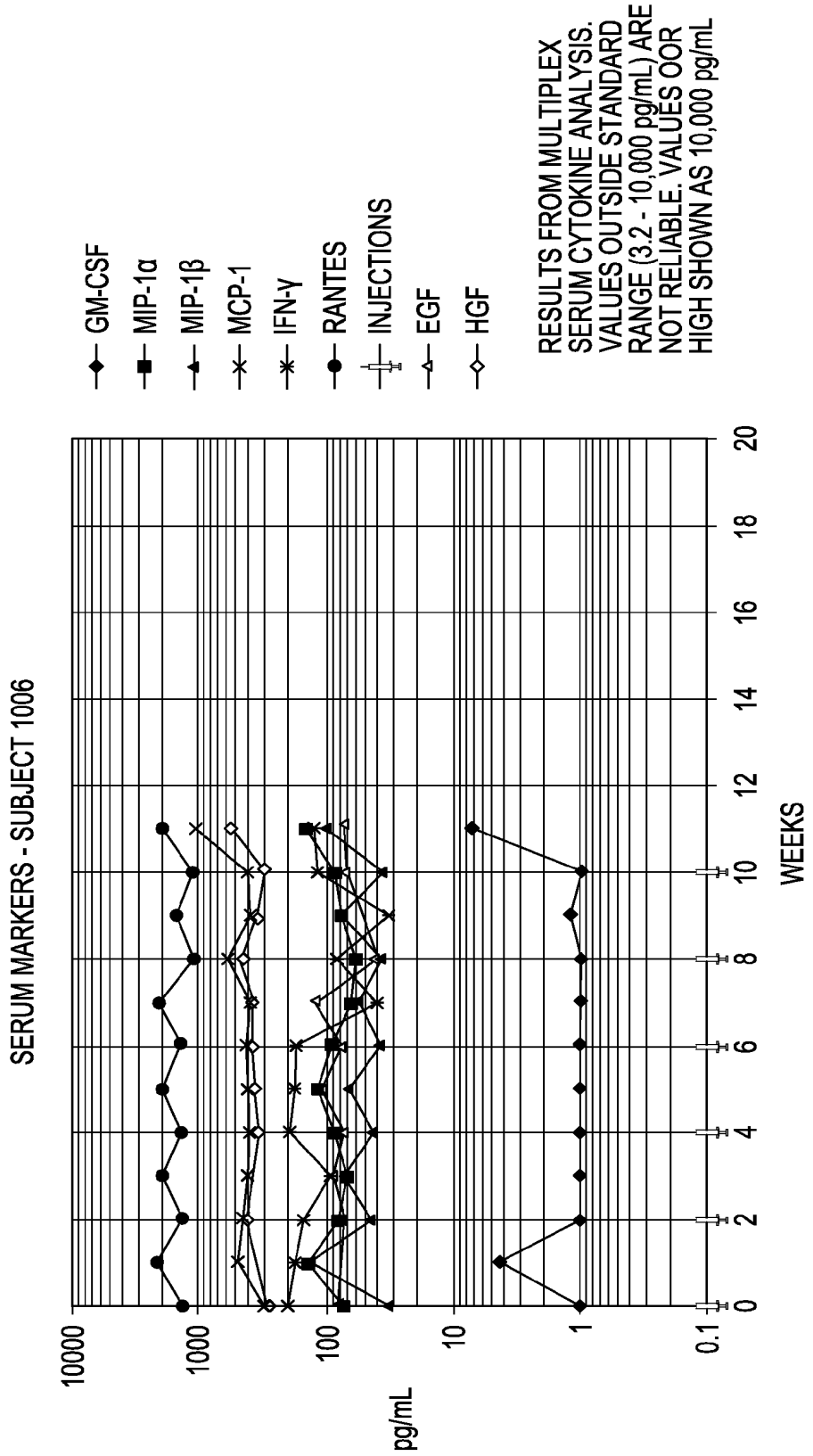

SERUM MARKERS - SUBJECT 1006
GM-CSF
MIP-1α
MIP-1β
MCP-1
IFN-γ
RANTES
INJECTIONS
EGF
HGF
RESULTS FROM MULTIPLEX SERUM CYTOKINE ANALYSIS. VALUES OUTSIDE STANDARD RANGE (3.2 - 10,000 pg/mL) ARE NOT RELIABLE. VALUES OOR HIGH SHOWN AS 10,000 pg/mL
pg/mL
10000
1000
100
10
1
0.1
WEEKS
0
2
4
6
8
10
12
14
16
18
20

FIG. 50

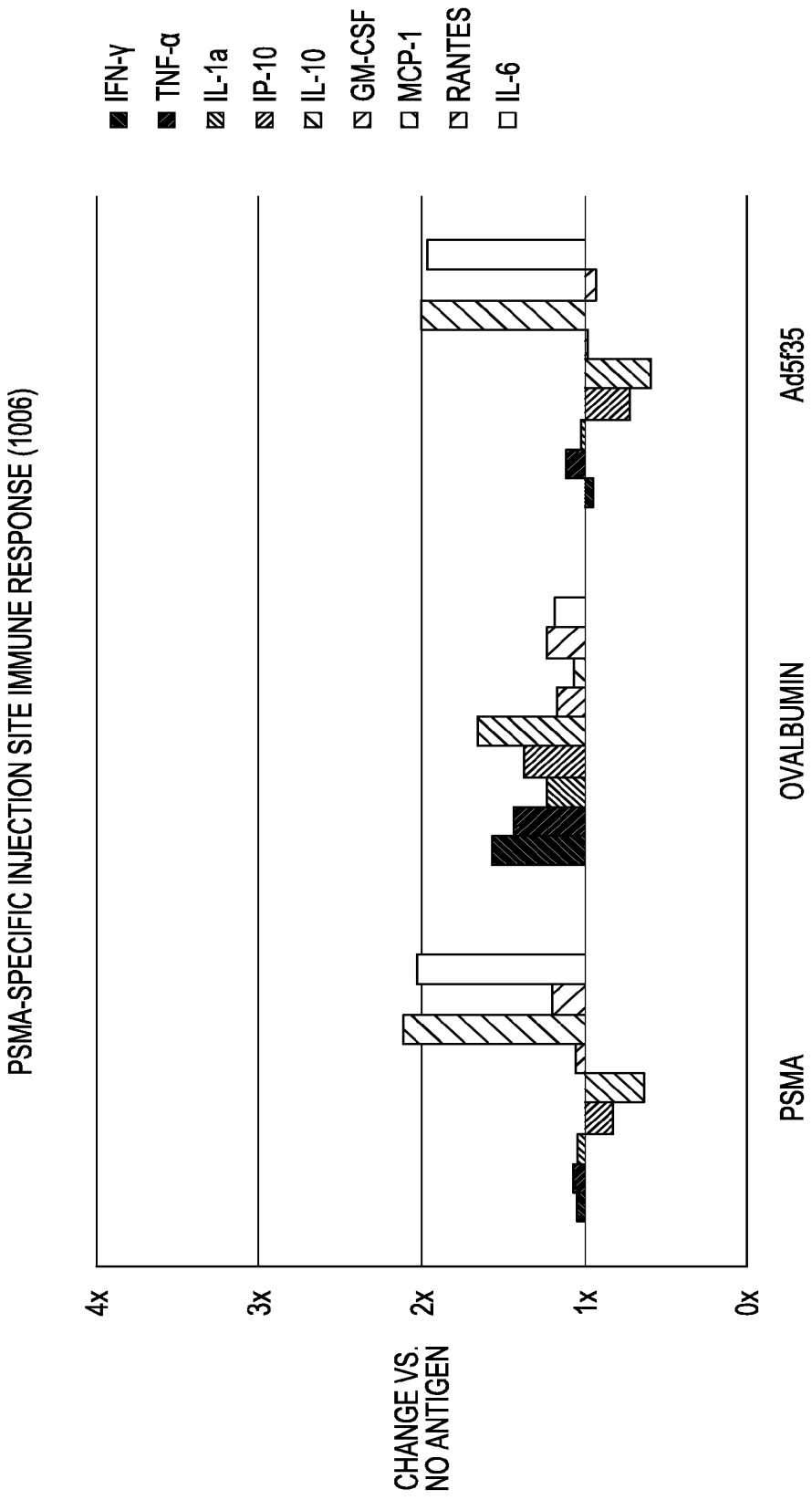

PSMA-SPECIFIC INJECTION SITE IMMUNE RESPONSE (1006)
IFN-γ
TNF-α
IL-1a
IP-10
IL-10
GM-CSF
MCP-1
RANTES
IL-6
CHANGE VS. NO ANTIGEN
4x
3x
2x
1x
0x
PSMA
OVALBUMIN
Ad5f35

FIG. 51

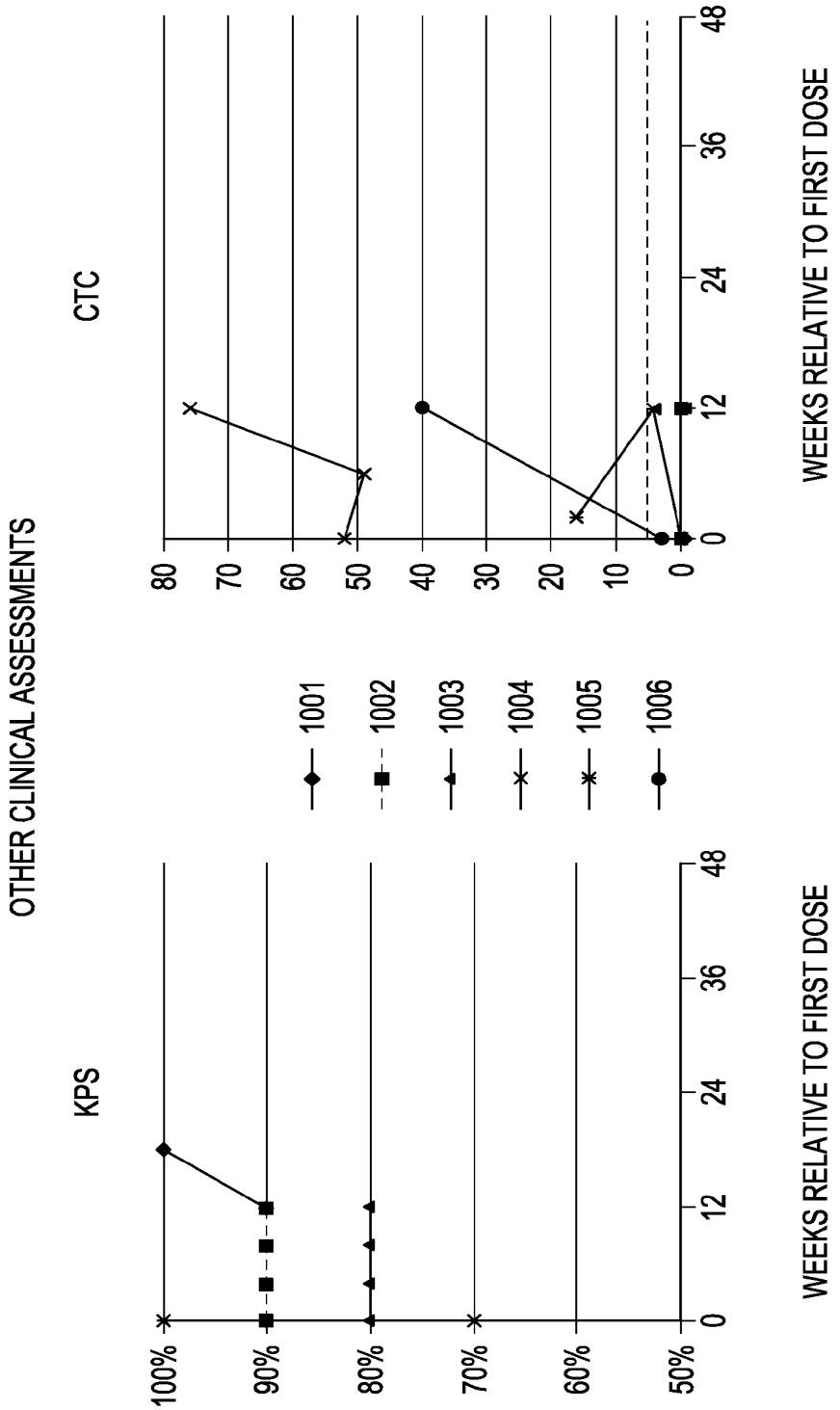

OTHER CLINICAL ASSESSMENTS
KPS
100%
90%
80%
70%
60%
50%
0
12
24
36
48
WEEKS RELATIVE TO FIRST DOSE
CTC
80
70
60
50
40
30
20
10
0
0
12
24
36
48
WEEKS RELATIVE TO FIRST DOSE
1001
1002
1003
1004
1005
1006

FIG. 52

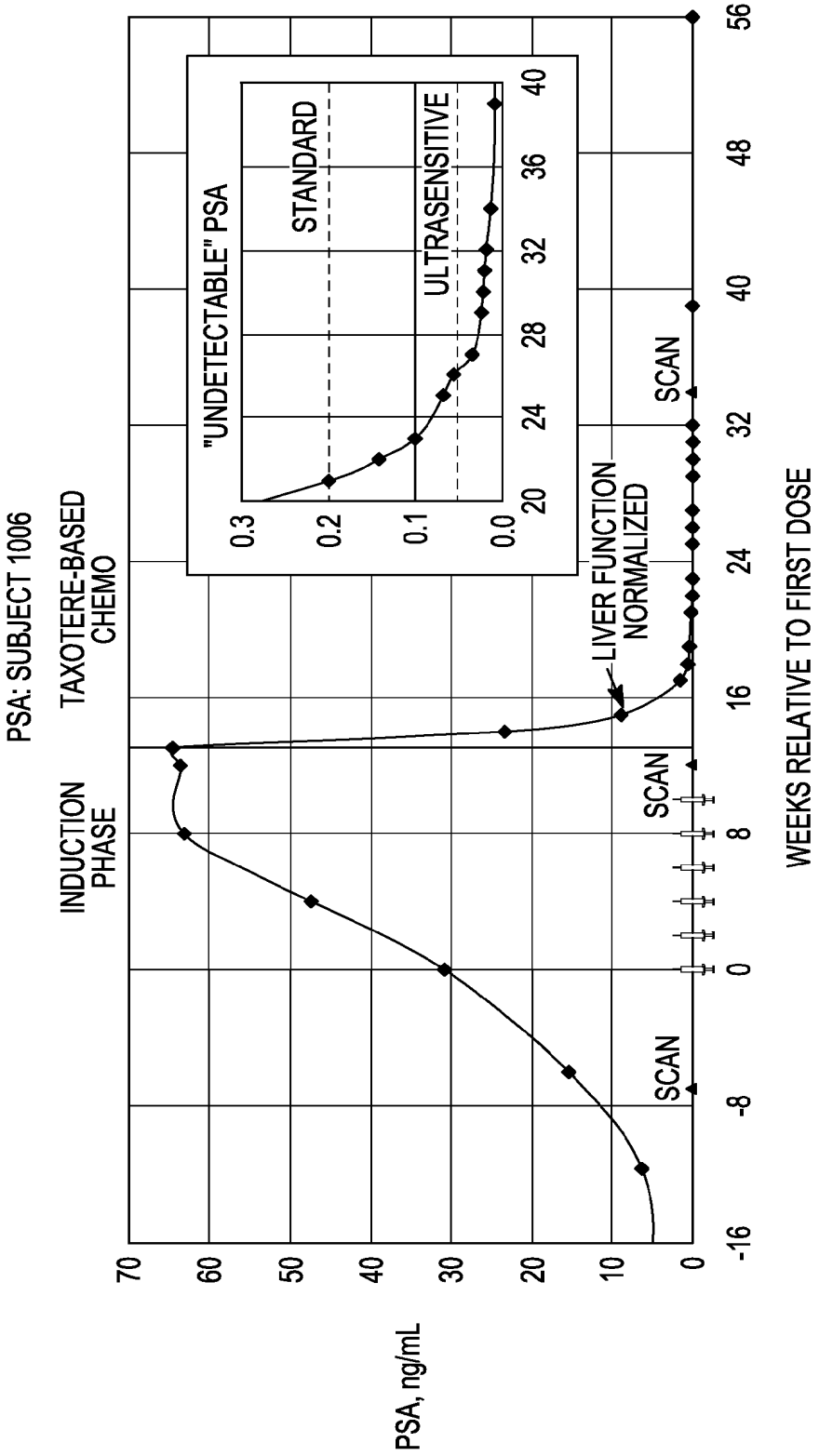

PSA: SUBJECT 1006
TAXOTERE-BASED CHEMO
INDUCTION PHASE
"UNDETECTABLE" PSA
STANDARD
ULTRASENSITIVE
0.3
0.2
0.1
0.0
20
24
28
32
36
40
LIVER FUNCTION NORMALIZED
SCAN
SCAN
SCAN
PSA, ng/mL
70
60
50
40
30
20
10
0
-16
-8
0
8
16
24
32
40
48
56
WEEKS RELATIVE TO FIRST DOSE

FIG. 53

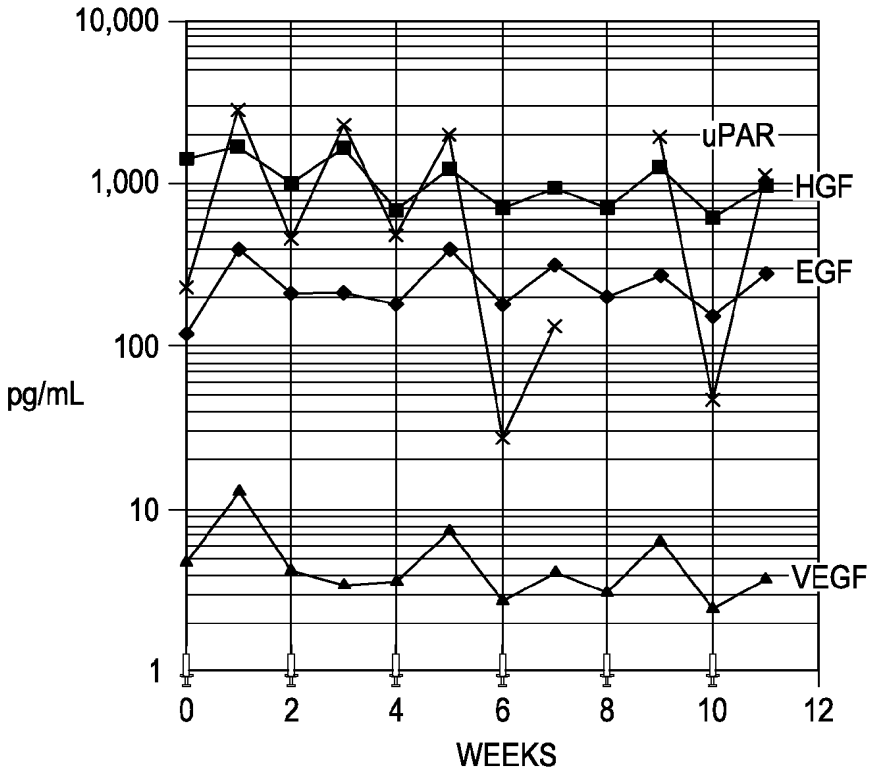


FIG. 54

SAFETY & RESPONSE SUMMARY

SUBJECT#		1001	1002	1003	1004	1005	1006
DEMOGRAPHICS & BASELINE METRICS	AGE	73	72	81	80	66	73
	KPS (AT SCREENING)	90%	90%	80%	80%	100%	90%
	GLEASON SCORE	N/A	7	9	10	8	8
	PRIOR CHEMOTHERAPY	NONE	NONE	TAXOTER	TAXOTER	NONE	NONE
	CLINICAL SUBTYPE	4	5	3	4	4	5
	BASELINE PSA (ng/mL)	5.8	11.1	312.8	46.5	69.0	30.9
	PRE-TREATMENT PSADT (MONTHS)	4.9	7.3	5.0	1.7	1.4	1.6
SAFETY	MAX AE GRADE	1	2	2	1	1	2
IMMUNE RESPONSE	Ag-SPECIFIC IMMUNE RESPONSE	T_H1	NOT DETERMINED		T_H1	T_H2	T_H2
	MEAN POST-DOSE CYTOKINE CHANGE	-2%	-6%	283%	66%	72%	43%
BIOMARKER RESPONSE	12 WK POST-TREATMENT PSADT	19.5	PSA↘	PSA↘	3.7	N/A	2.9
	PSADT INCREASE	298%	∞	∞	118%	N/A	80%
	MEAN POST-DOSE HYPOXIC CHANGE	-3%	2%	231%	70%	47%	22%
CLINICAL RESPONSE	BEST RESPONSE	SD	SD	MMD PR	SD	PD	PD
	TIME ON STUDY (WEEKS FROM BASELINE)	56+	34(W/D)				

FIG. 55

SAFETY & RESPONSE SUMMARY

SUBJECT#		1007	1008	1009	1010	1011	1012
DEMOGRAPHICS & BASELINE METRICS	AGE	67	80	69	85	79	70
	KPS (AT SCREENING)	100%	90%	90%	80%	90%	
	GLEASON SCORE	8	10	8	9	8	
	PRIOR CHEMOTHERAPY	NONE	TAXOTER	NONE	TAXOTER	TAXOTER	TAXOTER
	CLINICAL SUBTYPE	4	5	4	4		
	BASELINE PSA (ng/mL)	2.4	55.8	26.0	1070.0	818.9	3.2
	PRE-TREATMENT PSADT (MONTHS)						
SAFETY	MAX AE GRADE						
IMMUNE RESPONSE	ANTIGEN-SPECIFIC IMMUNE RESPONSE	T_H1	NOT DETERMINED				
	MEAN POST-DOSE CYTOKINE CHANGE	-3%	14,616%	33%	52,247%		
BIOMARKER RESPONSE	12 WK POST-TREATMENT PSADT						
	PSADT INCREASE						
	MEAN POST-DOSE HYPOXIC CHANGE						
CLINICAL RESPONSE	BEST RESPONSE						
	TIME ON STUDY (WEEKS FROM BASELINE)						

FIG. 56

PATIENT DEMOGRAPHICS

SUBJECT#	1001	1002	1003	1004	1005	1006
AGE	73	72	81	80	66	73
KPS (AT SCREENING)	90%	90%	80%	80%	100%	90%
GLEASON SCORE	7	7	9	10	8	8
PRIOR CHEMOTHERAPY	NONE	NONE	TAXOTERE	TAXOTERE	NONE	NONE
CLINICAL SUBTYPE	4	5	3	4	4	5
BASELINE PSA (ng/mL)	5.8	11.1	312.8	46.5	69.0	30.9
PRE-TREATMENT PSADT (MONTHS)	4.9	7.3	5.0	1.7	1.4	1.6
SUBJECT#	1007	1008	1009	1010	1011	1012
AGE	67	80	69	85	79	70
KPS (AT SCREENING)	100%	90%	90%	80%	90%	100%
GLEASON SCORE	8	10	8	9	8	LN BIOPSY
PRIOR CHEMOTHERAPY	(ABIRATERONE)	TAXOTERE	NONE	TAXOTERE	TAXOTERE	TAXOTERE
CLINICAL SUBTYPE	4	5	4	4	4	3
BASELINE PSA (ng/mL)	2.4	55.8	26.0	1070.0	818.9	3.2
PRE-TREATMENT PSADT (MONTHS)	N/A	7.7	9.1	1.8	0.25	6.0

FIG. 57

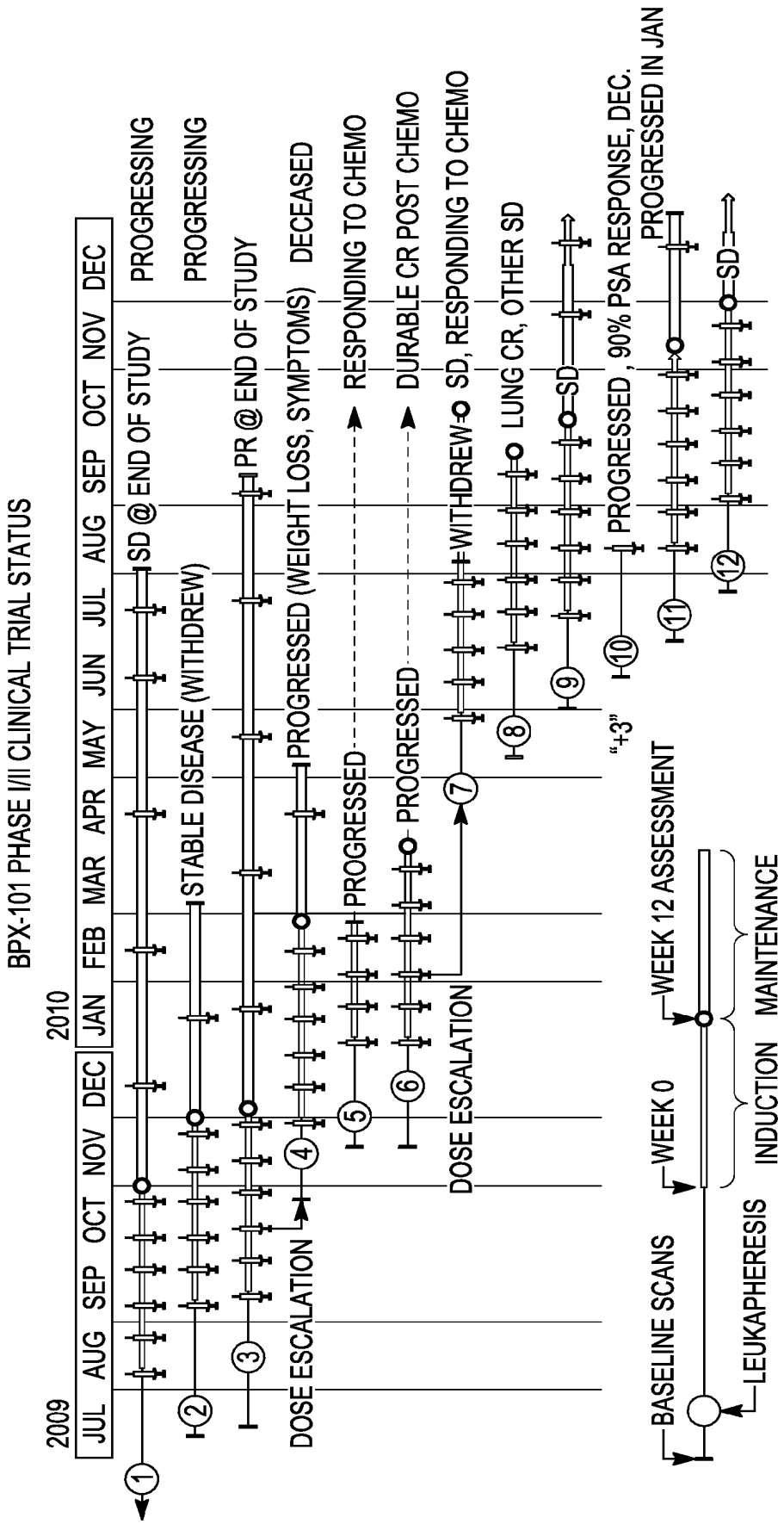

BPX-101 PHASE I/II CLINICAL TRIAL STATUS
2009
2010
JUL AUG SEP OCT NOV DEC JAN FEB MAR APR MAY JUN JUL AUG SEP OCT NOV DEC
PROGRESSING
SD @ END OF STUDY
PROGRESSING
STABLE DISEASE (WITHDREW)
PR @ END OF STUDY
PROGRESSED (WEIGHT LOSS, SYMPTOMS) DECEASED
RESPONDING TO CHEMO
PROGRESSED
DURABLE CR POST CHEMO
PROGRESSED
WITHDREW
SD, RESPONDING TO CHEMO
LUNG CR, OTHER SD
SD
PROGRESSED , 90% PSA RESPONSE, DEC.
PROGRESSED IN JAN
SD
DOSE ESCALATION
DOSE ESCALATION
"+3"
WEEK 12 ASSESSMENT
WEEK 0
BASELINE SCANS
LEUKAPHERESIS
INDUCTION
MAINTENANCE
1
2
3
4
5
6
7
8
9
10
11
12

FIG. 58

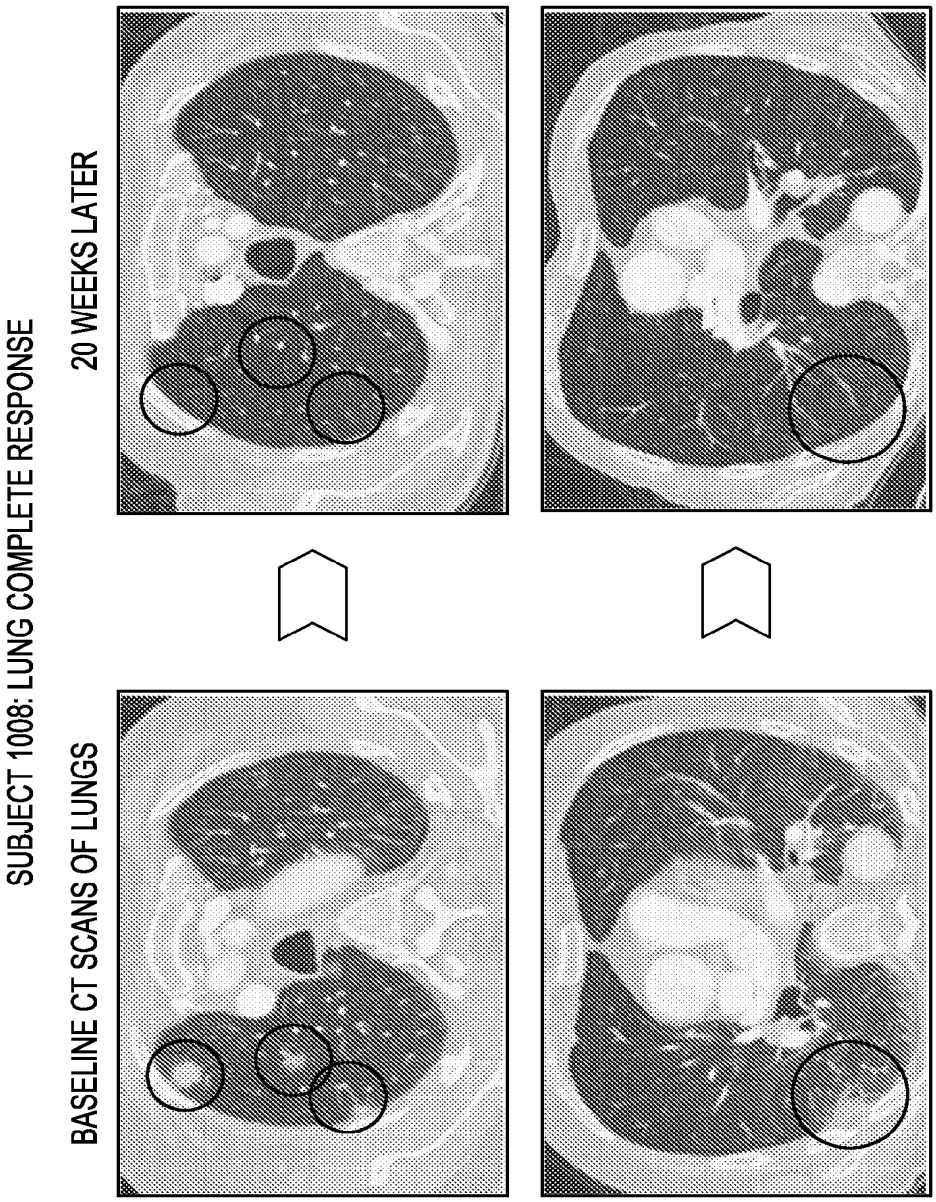

SUBJECT 1008: LUNG COMPLETE RESPONSE
BASELINE CT SCANS OF LUNGS
20 WEEKS LATER

FIG. 59

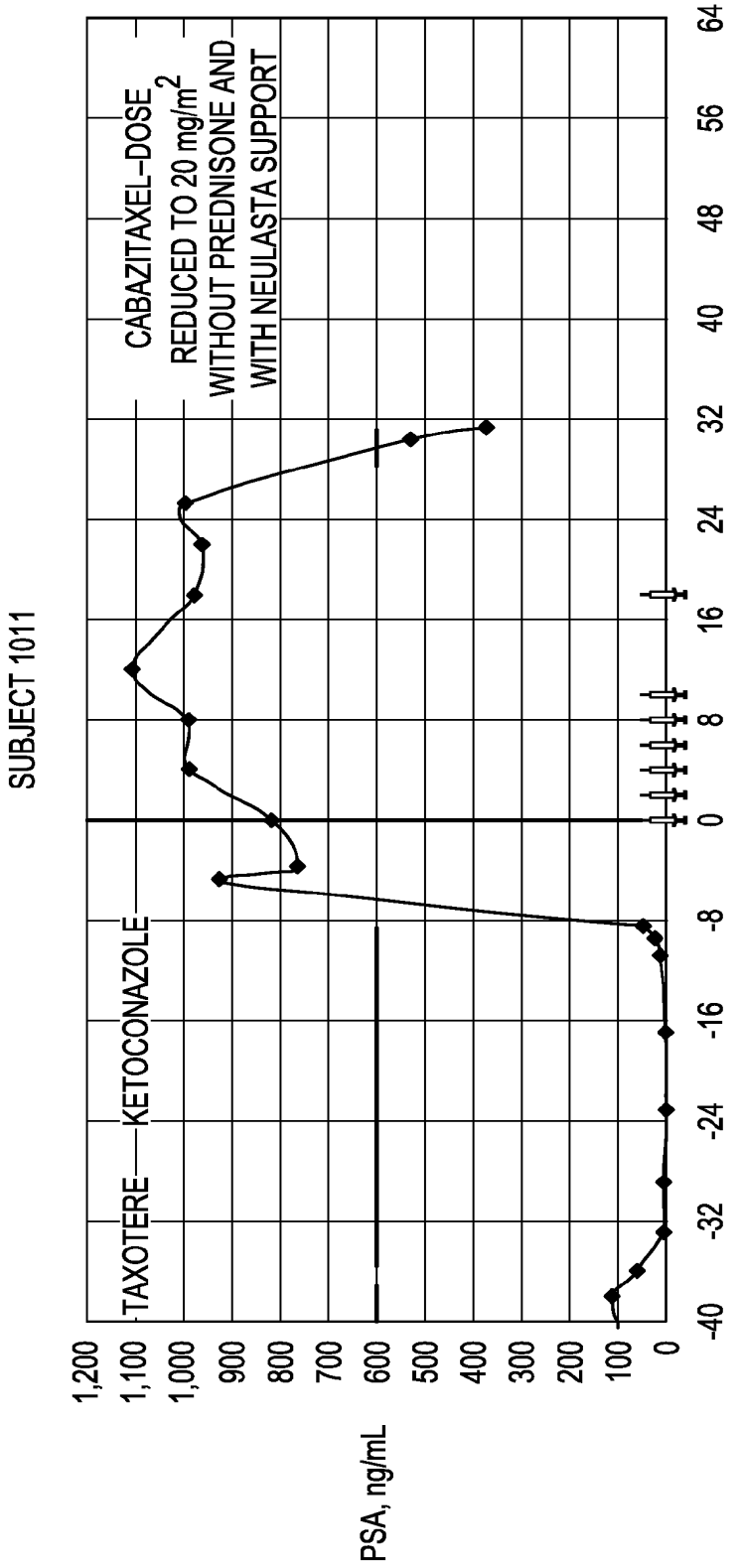

SUBJECT 1011
TAXOTERE
KETOCONAZOLE
CABAZITAXEL–DOSE REDUCED TO 20 mg/m2 WITHOUT PREDNISONE AND WITH NEULASTA SUPPORT
PSA, ng/mL
1,200
1,100
1,000
900
800
700
600
500
400
300
200
100
0
-40
-32
-24
-16
-8
0
8
16
24
32
40
48
56
64
WEEKS RELATIVE TO FIRST DOSE

FIG. 60

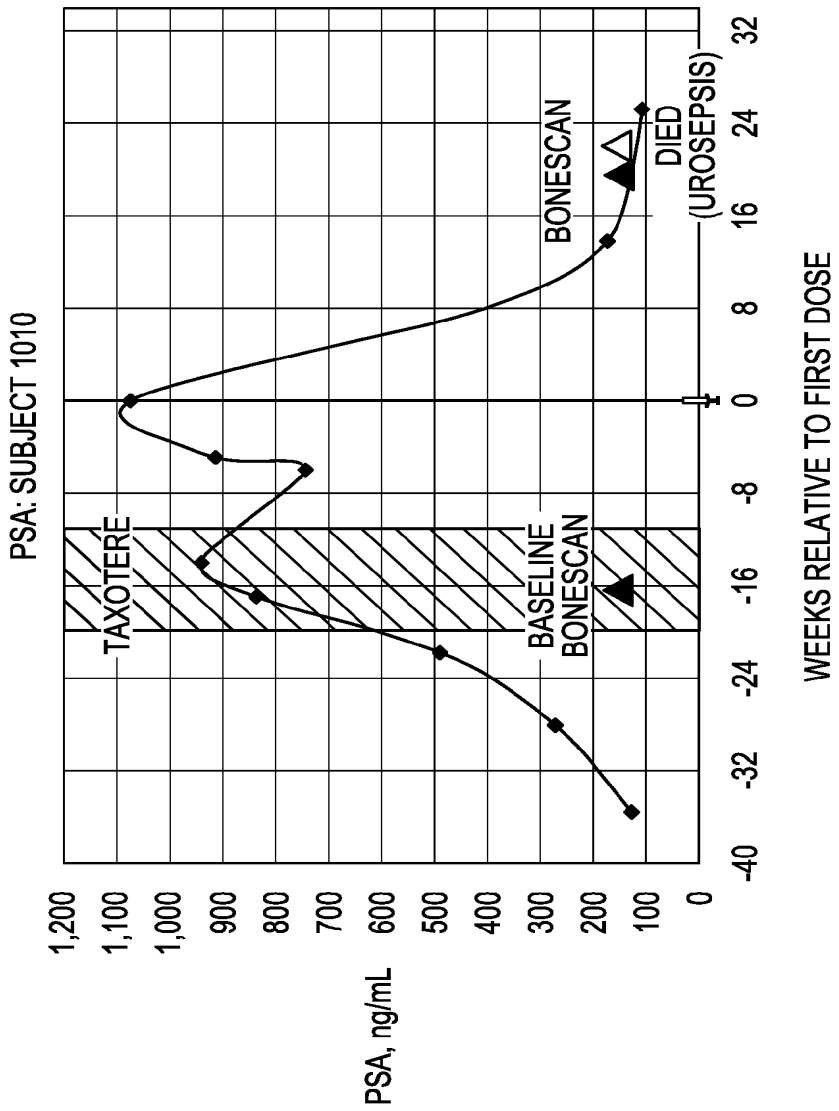

PSA: SUBJECT 1010
PSA, ng/mL
1,200
1,100
1,000
900
800
700
600
500
400
300
200
100
0
TAXOTERE
BASELINE BONESCAN
BONESCAN
DIED (UROSEPSIS)
-40
-32
-24
-16
-8
0
8
16
24
32
WEEKS RELATIVE TO FIRST DOSE

FIG. 61

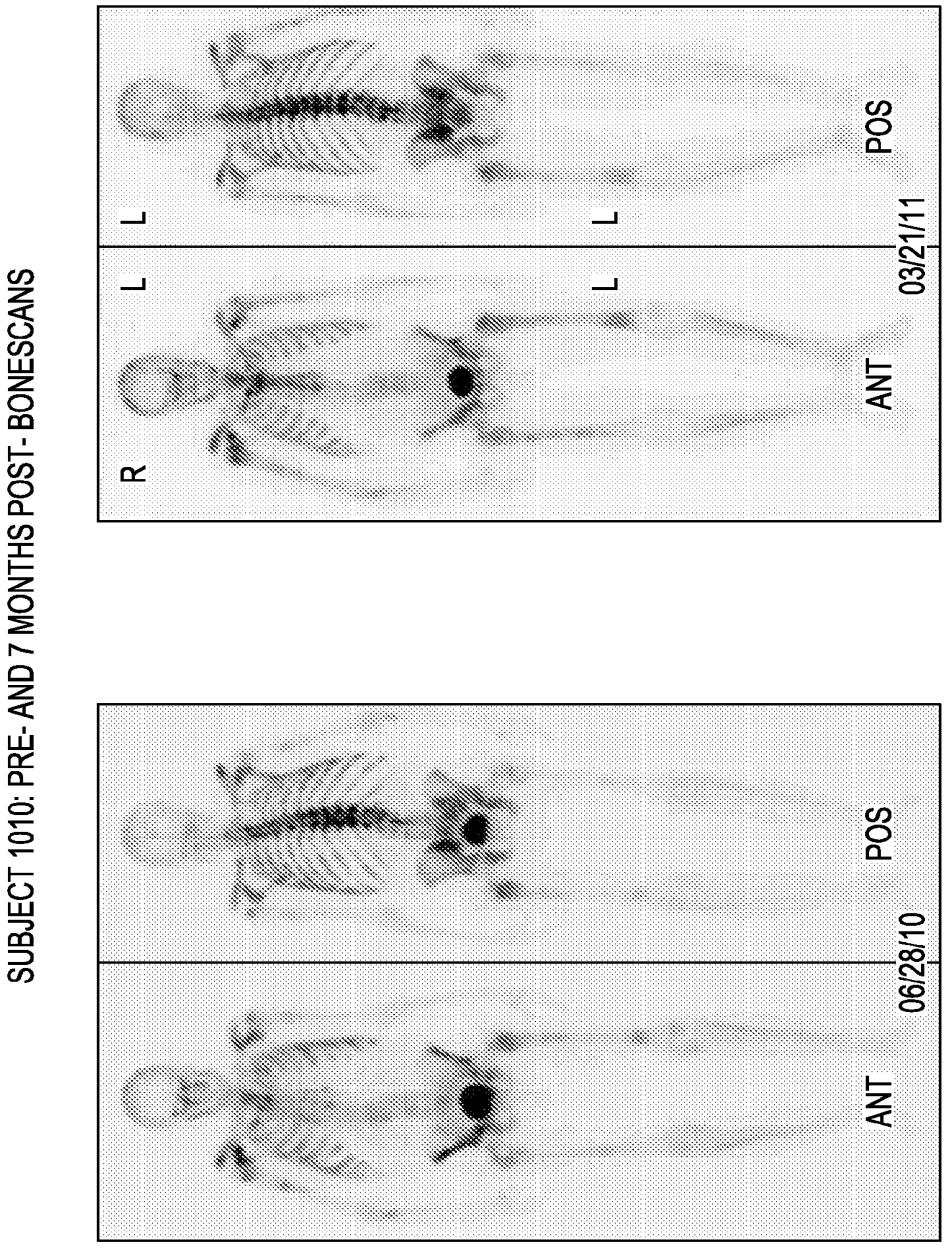

SUBJECT 1010: PRE- AND 7 MONTHS POST- BONESCANS
ANT
06/28/10
POS
R
L
L
ANT
03/21/11
L
L
POS

FIG. 62

SEQUENCING WITH TAXANE-BASED CHEMOTHERAPY

SUBJECT	RESPONSE TO BPX POST-CHEMO	RESPONSE TO CHEMO POST BPX
1003	46% MAX PSA DECLINE, LN PR	>30% PSA DECLINE (AFTER 3 CYCLES DOCETAXEL), SOFT TISSUE AND BONE DISEASE MIXED RESPONSE (VS. MINIMAL RESPONSE PRE-BPX)
1004	SYMPTOMATIC IMPROVEMENT	N/A
1006	N/A	>99% PSA DECLINE (AFTER TWO CYCLES DOCETAXEL/CARBOPLATIN-BASED CHEMOTHERAPY), DURABLE VISCERAL, LN, BONE CRs
1007	N/A (ABIRATERONE)	MMD REDUCTION (DOCETAXEL/CARBOPLATIN)
1008	LUNG CR	N/A
1010	90% PSA DECLINE AFTER SINGLE DOSE	N/A
1011	SD	>60% PSA DECLINE (AFTER TWO CYCLES CABAZITAXEL)
1012	SD	N/A

FIG. 63

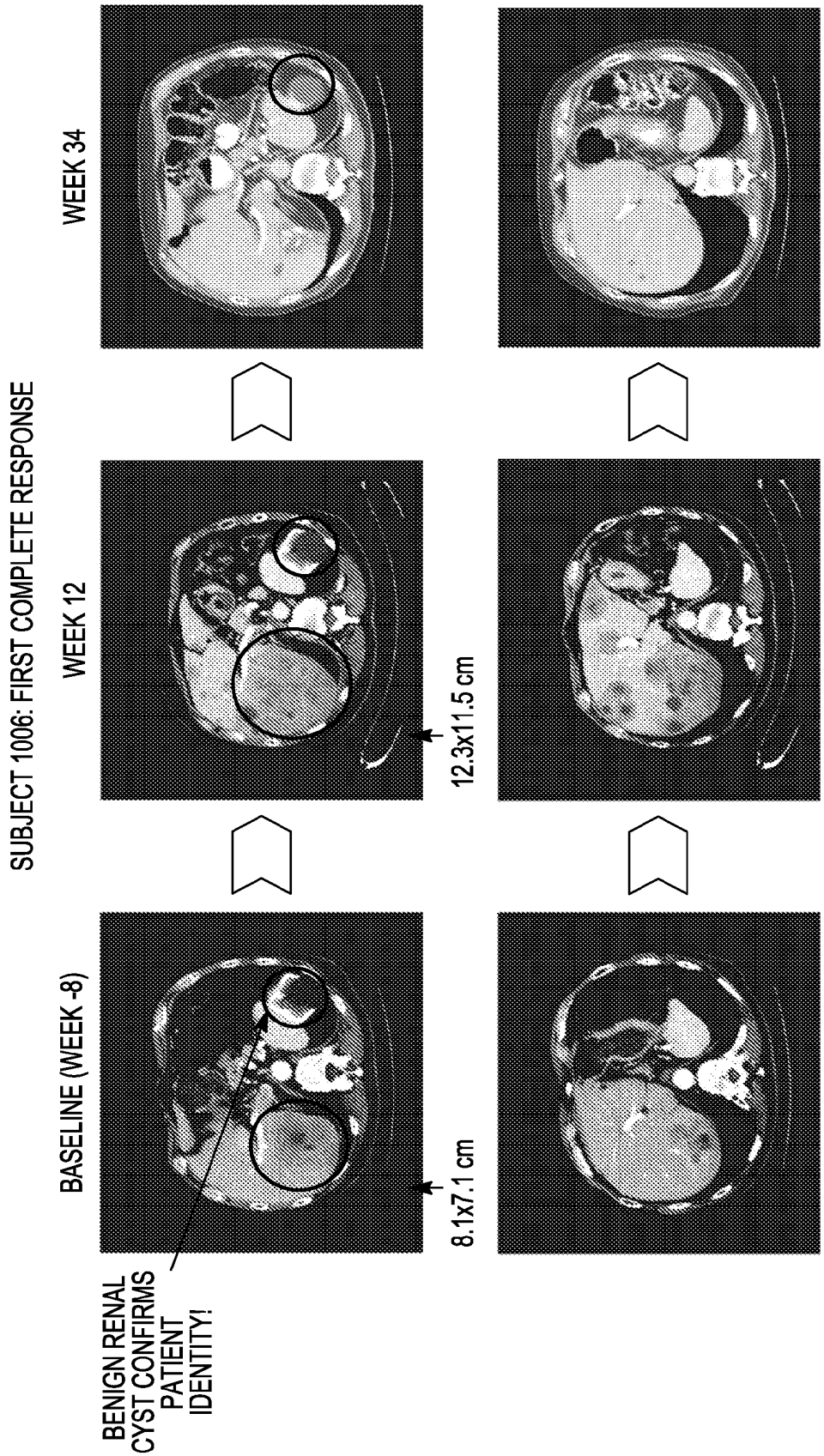

SUBJECT 1006: FIRST COMPLETE RESPONSE
BASELINE (WEEK -8)
WEEK 12
WEEK 34
BENIGN RENAL CYST CONFIRMS PATIENT IDENTITY!
8.1x7.1 cm
12.3x11.5 cm

FIG. 64

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(25) Filing Language: English

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

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **WOLFGANG, Marc** [US/US]; 53 Stagecoach Road, Holliston, MA 01746 (US). **REITER, Lawrence, A.** [US/US]; 32 West Mystic Avenue, Mystic, CT 06355 (US). **CRAWFORD, Thomas, C.** [US/US]; 13 Clark Lane, Essex, CT 06426 (US). **FETZER, Oliver, S.** [US/US]; 130 Beard Way, Needham, MA 02492 (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 (AL, 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, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

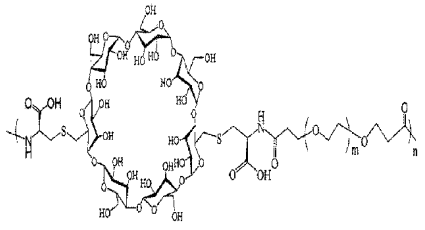
— *with international search report (Art. 21(3))*

(54) **Title**: CYCLODEXTRIN-BASED POLYMERS FOR THERAPEUTIC DELIVERY

(57) **Abstract**: Methods and compositions relating to CDP-taxane conjugates are described herein.

Figure 1

The CDP as shown in Figure 1 is provided below:



wherein the group  has a Mw of 3.4 kDa or less and n is at least 4. Note that the taxane is conjugated to the CDP through the carboxylic acid moieties of the polymer as provided above. Full loading of the taxane on to the CDP is not required. In some embodiments, at least one of the carboxylic acid moieties remains unreacted with the taxane after conjugation (e.g., a plurality of the carboxylic acid moieties remain unreacted).

WO 2011/063421 A1

CYCLODEXTRIN-BASED POLYMERS FOR THERAPEUTIC DELIVERY

Claim of Priority

This application claims priority to U.S.S.N. 61/263,749, filed 11/23/2009 and U.S.S.N. 61/391,922, filed 10/11/2010, the entire contents of each of which are incorporated herein by reference.

Background of the Invention

Drug delivery of some small molecule therapeutic agents, such as taxane, has been problematic due to their poor pharmacological profiles. These therapeutic agents often have low aqueous solubility, their bioactive forms exist in equilibrium with an inactive form, or high systemic concentrations of the agents lead to toxic side-effects. Some approaches to circumvent the problem of their delivery have been to conjugate the agent directly to a water-soluble polymer such as hydroxypropyl methacrylate (HPMA), polyethyleneglycol, and poly-L-glutamic acid. In some cases, such conjugates have been successful in solubilizing or stabilizing the bioactive form of the therapeutic agent, or achieving a sustained release formulation which circumvents complications associated with high systemic concentrations of the agent.

Another approach to the drug delivery problem has been to form host/guest inclusion complexes between the therapeutic agent and cyclodextrins or derivatives thereof. Cyclodextrins (alpha, beta, and gamma) and their oxidized forms have unique physico-chemical properties such as good water solubility, low toxicity and low immune response. To date, most of the drug delivery studies with cyclodextrins have focused on their ability to form supra-molecular complexes, wherein cyclodextrins form host/guest inclusion complexes with therapeutic molecules and thus alter the physical, chemical, and/or biological properties of these guest molecules.

Summary of the Invention

In one aspect, the disclosure features a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-larotaxel conjugate or CDP-cabazitaxel conjugate, described

herein, and methods of making the CDP-taxane conjugates, e.g., a CDP-docetaxel conjugates, a CDP-larotaxel conjugates or CDP-cabazitaxel conjugates, described herein.

In one embodiment, CDP is not biodegradable.

In one embodiment, CDP is biocompatible.

In one embodiment, the CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-larotaxel conjugate or CDP-cabazitaxel conjugate, includes an inclusion complex between a taxane, e.g., docetaxel, larotaxel or cabazitaxel, attached or conjugated to the CDP, e.g., via a covalent linkage or via a linker such as a linker described herein, and another molecule in the CDP. In one embodiment, the CDP-taxane conjugate forms a nanoparticle. In one embodiment, the CDP-taxane conjugate including an inclusion complex forms a nanoparticle. The nanoparticle ranges in size from 10 to 300 nm in diameter, e.g., 10 to 280, 20 to 280, 30 to 250, 30 to 200, 20 to 150, 30 to 100, 20 to 80, 10 to 80, 10 to 70, 20 to 60 or 20 to 50 nm 10 to 70, 10 to 60 or 10 to 50 nm diameter. In one embodiment, the nanoparticle is 20 to 60 nm in diameter. In one embodiment, the composition comprises a population or a plurality of nanoparticles with an average diameter from 10 to 300 nm, e.g., 20 to 280, 15 to 250, 15 to 200, 20 to 150, 15 to 100, 20 to 80, 15 to 80, 15 to 70, 15 to 60 or , 15 to 50, 20 to 50 nm. In one embodiment, the average nanoparticle diameter is from 15 to 60 nm (e.g., 20-60. In one embodiment, the surface charge of the molecule is neutral, or slightly negative. In some embodiments, the zeta potential of the particle surface is from about -80 mV to about 50 mV, about -20 mV to about 20 mV, about -20 mV to about -10 mV, or about -10 mV to about 0.

In one embodiment, the taxane (e.g., docetaxel, paclitaxel, larotaxel or cabazitaxel), conjugated to the CDP is more soluble when conjugated to the CDP, than when not conjugated to the CDP.

In one embodiment, the composition comprises a population, mixture or plurality of CDP-taxane conjugates. In one embodiment, the population, mixture or plurality of CDP-taxane conjugates comprises a plurality of different taxane conjugated to a CDP (e.g., two different taxanes are in the composition such that two different taxanes are attached to a single CDP; or a first taxane is attached to a first CDP and a second taxane is attached to a second CDP and both CDP-taxane conjugates are present in the composition). In one embodiment, the population, mixture or plurality of CDP-taxane

conjugates comprises a CDP having a single taxane attached thereto in a plurality of positions (e.g., a CDP has a single taxane attached thereto such that the single taxane for some occurrences is attached through a first position (e.g., a 2'-OH) and for other occurrences is attached through a second position (e.g., a 7-OH) to thereby provide a CDP having a single taxane attached through a plurality of positions on the taxane). In some embodiments, for example, where a third position is available (e.g., a 10-OH), a single taxane can be attached to the CDP through a first, second, and third position (e.g., 2'-OH, 7-OH, and 10-OH). In one embodiment, the population, mixture or plurality of CDP-taxane comprises a first CDP attached to a taxane through a first position (e.g., a 2'-OH) and a second CDP attached to the same taxane through a second position (e.g., a 7-OH) and both CDP-taxane conjugates are present in the composition. In one embodiment, the population, mixture or plurality of CDP-taxane comprises a first CDP attached to a taxane through a first position (e.g., a 2'-OH), a second CDP attached to the same taxane through a second position (e.g., a 7-OH), and a third CDP attached to the same taxane through a third position (e.g., a 10-OH) and all three CDP-taxane conjugates are present in the composition. In some embodiments, a single CDP includes a single taxane attached through a plurality of positions (e.g., the 2'-OH, 7-OH, and/or 10-OH).

In one aspect, the disclosure 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 CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to a subject in an amount effective to treat the disorder, to thereby treat the proliferative disorder. In an embodiment, the CDP-taxane conjugate comprises a taxane molecule (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled, e.g., via a linker such as a linker described herein, to a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane molecule, coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the composition is administered in combination with one or more additional anticancer agent, e.g., chemotherapeutic agent, e.g., a chemotherapeutic agent or combination of chemotherapeutic agents described herein, and radiation.

In an embodiment, the method further comprises administering a chemotherapeutic agent as a free agent.

In an embodiment, the taxane associated with the CDP and the free agent are the same chemotherapeutic agent. E.g., the agent is a taxane (e.g., docetaxel, paclitaxel, larotaxel or cabazitaxel).

In an embodiment, the taxane associate with the CDP and the free agent are different chemotherapeutic agents.

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, lung adenocarcinoma 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, small cell lung cancer, lung adenocarcinoma, and squamous cell cancer, e.g., unresectable, locally advanced or metastatic non-small cell lung cancer, small cell lung cancer, lung adenocarcinoma, and squamous cell 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 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 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 CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein, and e.g., the CDP-docetaxel conjugate 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 docetaxel, to thereby treat the disorder. In one embodiment, the conjugate 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, e.g., the subject is administered at least two, three, four, five, six, seven, eight, nine, ten or eleven additional doses of the conjugate. In one embodiment, the conjugate is administered once every two, three, four, five, six weeks. In another embodiment, the CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein, and e.g., the CDP-docetaxel conjugate 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) of docetaxel, to thereby treat the disorder. In one embodiment, the conjugate 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, e.g., the subject is administered at least two, three, four, five, six, seven, eight, nine, ten or eleven additional doses of the conjugate. In one embodiment, the conjugate 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 CDP-docetaxel conjugate. 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 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 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 CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein, and the conjugate 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) 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, four, five or six doses, wherein the subject is administered a dose of the conjugate once every two, three, four, five or six weeks.

In one embodiment, the CDP-taxane conjugate is a CDP -docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein, and the conjugate 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) 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, four, five or six doses, wherein the subject is administered a dose of the conjugate once a week for two, three four, five, six doses, e.g., followed by one, two or three weeks without administration of the CDP-docetaxel conjugate.

In one embodiment, the composition includes a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP 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) of docetaxel, to thereby treat the disorder. In one embodiment, the dose is administered once every 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 CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP 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) 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 CDP-docetaxel conjugate. 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 CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein and, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein, and, e.g., the conjugate 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) of paclitaxel, to thereby treat the disorder. In one embodiment, the CDP-paclitaxel conjugate 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, e.g., the subject is administered at least two, three, four, five, six, seven, eight, nine or ten additional doses of the conjugate. In one embodiment, the CDP-paclitaxel conjugate 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) 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 CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate includes a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP -paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein, and the conjugate 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) 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, four, five, six, seven or eight doses, wherein the subject is administered a dose of the conjugate once every one, two, three, four, five or six weeks.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP -paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP 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) 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 CDP-taxane conjugate is a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., directly or via linker, to a CDP described herein, and the CDP-cabazitaxel conjugate is administered to the subject in an amount that includes 5 mg/m^2 or greater (e.g., 10 mg/m^2, 12 mg/m^2, 15 mg/m^2, 20 mg/m^2, 25 mg/m^2, 30 mg/m^2, 35 mg/m^2, 40 mg/m^2, 45

mg/m^2, 50 mg/m^2, 55 mg/m^2, or 60 mg/m^2) of cabazitaxel, 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 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 5 mg/m^2 or greater (e.g., 10 mg/m^2, 12 mg/m^2, 15 mg/m^2, 20 mg/m^2, 25 mg/m^2, 30 mg/m^2, 35 mg/m^2, 40 mg/m^2, 45 mg/m^2, 50 mg/m^2, 55 mg/m^2, or 60 mg/m^2) of cabazitaxel. 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 one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., directly or via linker, to a CDP described herein, and the CDP-cabazitaxel conjugate is administered to the subject in an amount of the composition that includes 5 mg/m^2 or greater (e.g., 10 mg/m^2, 12 mg/m^2, 15 mg/m^2, 20 mg/m^2, 25 mg/m^2, 30 mg/m^2, 35 mg/m^2, 40 mg/m^2, 45 mg/m^2, 50 mg/m^2, 110 mg/m^2, 55 mg/m^2, or 60 mg/m^2) of cabazitaxel, 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, four, 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 CDP-taxane conjugate is a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., directly or via linker, to a CDP 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 5 mg/m^2 or greater (e.g., 10 mg/m^2, 12 mg/m^2, 15 mg/m^2, 20 mg/m^2, 25 mg/m^2, 30 mg/m^2, 35 mg/m^2, 40 mg/m^2, 45 mg/m^2, 50 mg/m^2, 55 mg/m^2, or 60 mg/m^2) of cabazitaxel, 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 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 CDP-taxane conjugate, e.g., a CDP-taxane conjugate comprising a taxane molecule (e.g., a docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecule), coupled, e.g., via linkers, to a CDP 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 CDP-taxane conjugate 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., CRLX101, formerly known as IT-101)); a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin), an antibiotic (e.g., mitomycin, actinomycin, bleomycin), an antimetabolite (e.g., an antifolate, a purine analogue, a pyrimidine analogue (e.g., capecitabine)); an anthracycline (e.g., doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone, valrubicin); a steroid (e.g., prednisone or prednisolone) and a taxane (e.g., paclitaxel, docetaxel, larotaxel or cabazitaxel).

In one embodiment, the CDP-taxane conjugate, e.g., a CDP-taxane conjugate comprising a taxane molecule, coupled, e.g., via a linker, to a CDP 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 CDP-taxane conjugate 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 yet another aspect, the invention features a method of identifying a subject, e.g., a human, having a proliferative disorder, e.g., cancer, for treatment with a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel described herein, the method comprising identifying a subject having a proliferative disorder who has received an anticancer agent; and administering a composition comprising a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel described herein, to a subject, e.g., a human, in an amount effective to treat the disorder, to thereby treat the proliferative disorder.

In another aspect, the disclosure features a method of treating a chemotherapeutic sensitive, a chemotherapeutic refractory, a chemotherapeutic resistant, and/or a relapsed cancer. The method comprises: administering a composition comprising a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel described herein, to a subject, e.g., a human, in an amount effective to treat the disorder, to thereby treat the proliferative disorder.

In an embodiment, the CDP-taxane conjugate comprises a taxane molecule (e.g., a docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecule), coupled, e.g., via a linker such as a linker described herein, to a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane molecule (e.g., a docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecule), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in 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, a purine analogue, a pyrimidine analogue (e.g., capecitabine)), 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., CRLX101)), a taxane (e.g., docetaxel, paclitaxel, larotaxel or cabazitaxel) 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 CDP-taxane conjugate (e.g., a CDP-cabazitaxel conjugate) is administered to a subject who cancer is refractory to, resistant to and/or has relapsed during or after treatment with a taxane (e.g., docetaxel or paclitaxel).

In one embodiment, the CDP-taxane conjugate is administered in combination with a second chemotherapeutic agent, e.g., a chemotherapeutic agent described herein. For example, the CDP-taxane conjugate can be administered in combination with a vinca alkaloid (e.g., vinblastine, vincristine, vindesine, vinorelbine), a steroid (e.g., prednisone or prednisolone) 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, lung adenocarcinoma and squamous cell cancer), genitourinary tract, e.g., ovary (including fallopian tube and peritoneal cancers), cervix, prostate (e.g., hormone refractory prostate cancer), 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, small cell lung cancer, lung adenocarcinoma, and squamous cell cancer, e.g., unresectable, locally advanced or metastatic non-small cell lung cancer, small cell lung cancer, lung adenocarcinoma, and squamous cell 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 composition includes a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel molecules, coupled, e.g., via linkers, to a CDP described herein.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the composition includes a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel molecules, coupled, e.g., via linkers, to a CDP described herein. In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the composition includes a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel molecules, coupled, e.g., via linkers, to a CDP described herein. In one

embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the composition includes a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel molecules, coupled, e.g., via linkers, to a CDP described herein. In one embodiment, the CDP-cabazitaxel conjugate 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 CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in 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 CDP-taxane conjugate 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 CDP-taxane conjugate is administered with trastuzumab.

In some embodiments, the CDP-taxane conjugate is administered in combination with a second chemotherapeutic agent. For example, the CDP-taxane conjugate 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 and AZD2171). In one embodiment, the CDP-taxane conjugate is administered in combination with bevacizumab.

In some embodiments, the CDP-taxane conjugate is administered in combination with an anthracycline (e.g., daunorubicin, doxorubicin, epirubicin, valrubicin and idarubicin).

In some embodiments, the CDP-taxane conjugate 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 CDP-taxane conjugate 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 CDP-taxane conjugate is administered in combination with a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin).

In some embodiments, the CDP-taxane conjugate 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 CDP-taxane conjugate is administered in combination with a vinca alkaloid (e.g., vinblastine, vincristine, vindesine, vinorelbine).

In some embodiments, the CDP-taxane conjugate is administered in combination with an antibiotic (e.g., mitomycin, actinomycin, bleomycin).

In some embodiments, the CDP-taxane conjugate is administered in combination with an alkylating agent (e.g., cyclophosphamide, dacarbazine, melphalan, ifosfamide, temozolomide).

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate 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 CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in 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 CDP-taxane conjugate 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 CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate 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 CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate

described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is administered in combination with prednisone or prednisolone, e.g., prednisone or prednisolone at a dose of 5 mg, 10 mg or 15 mg).

In one embodiment, the CDP-taxane conjugate is administered in combination with estramustine.

In one embodiment, the CDP-taxane conjugate is administered in combination with an anthracenedione (e.g., mitoxantrone) and prednisone or prednisolone, e.g., prednisone or prednisolone at a dose of 5 mg, 10 mg or 15 mg).

In one embodiment, the CDP-taxane conjugate 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 and AZD2171).

In one embodiment, the CDP-taxane conjugate 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 CDP-taxane conjugate is administered in combination with a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin).

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker

shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate 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 CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the subject has been treated with a taxane (e.g., docetaxel or paclitaxel) that did not effectively treat the cancer (e.g., the subject has a taxane refractory, taxane resistant and/or relapsed cancer), and the subject is administered a CDP-taxane conjugate (e.g., a CDP-cabazitaxel conjugate and/or a CDP-larotaxel conjugate).

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate

comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is administered in combination with prednisone or prednisolone, e.g., prednisone or prednisolone at a dose of 5 mg, 10 mg or 15 mg).

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 CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate

described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is administered in combination with a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin).

In one embodiment, the CDP-taxane conjugate is administered in combination with an alkylating agent (e.g., cyclophosphamide, dacarbazine, melphalan, ifosfamide, temozolomide).

In one embodiment, the CDP-taxane conjugate 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 CDP-taxane conjugate 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, cytrarabine, gemcitabine, 5-fluorouracil); an alkylating agent (e.g., cyclophosphamide, dacarbazine, melphalan, ifosfamide, temozolomide); a topoisomerase inhibitor (e.g., etoposide, topotecan, irinotecan, tenoposide, 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 CDP-taxane conjugate 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 and AZD2171.

In one embodiment, the CDP-taxane conjugate is administered in combination with an mTOR inhibitor, e.g., rapamycin, everolimus, AP23573, CCI-779 or SDZ-RAD.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an

embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate 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 CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in 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 subject has been treated with a taxane (e.g., docetaxel or paclitaxel) which did not effectively treat the cancer.

In one embodiment, the CDP-taxane conjugate is administered in combination with a pyrimidine analog, e.g., capecitabine or gemcitabine.

In one embodiment, the CDP-taxane conjugate is administered in combination with capecitabine and gemcitabine.

In one embodiment, the CDP-taxane conjugate 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 CDP-taxane conjugate is administered in combination with a topoisomerase I inhibitor, e.g., irinotecan, topotecan, tenoposide, lamellarin D, SN-38, camptothecin (e.g., CRLX101). In one embodiment the topoisomerase I inhibitor is topotecan. In another embodiment, the topoisomerase I inhibitor is irinotecan or etoposide.

In one embodiment, the CDP-taxane conjugate 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, cytrarabine, 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 CDP-taxane conjugate 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 CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate 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 (e.g., unresectable, locally advanced or metastatic non-small cell lung cancer) in a subject, e.g., a human. The method comprises: administering a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., a via linker such as a liner described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate 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 and AZD2171.

In one embodiment, the CDP-taxane conjugate 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 CDP-taxane conjugate is administered in combination with a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin). In one embodiment, the CDP-taxane conjugate 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 CDP-taxane conjugate 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 CDP-taxane conjugate 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 CDP-taxane conjugate is administered in combination with a vinca alkaloid (e.g., vinblastine, vincristine, vindesine, vinorelbine).

In one embodiment, the CDP-taxane conjugate is administered in combination with an alkylating agent (e.g., cyclophosphamide, dacarbazine, melphalan, ifosfamide, temozolomide).

In one embodiment, the CDP-taxane conjugate is administered in combination with an mTOR inhibitor, e.g., rapamycin, everolimus, AP23573, CCI-779 or SDZ-RAD.

In one embodiment, the CDP-taxane conjugate, either alone or with any of the combinations described herein, is administered in combination with radiation.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an

embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate 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 CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in 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 or AZD2171 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 subject has been treated with a taxane (e.g., docetaxel or paclitaxel) which did not effectively treat the cancer.

In one embodiment, the CDP-taxane conjugate 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 CDP-taxane conjugate 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 CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising

larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate 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 CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to a subject in an amount effective to treat the myeloma, to thereby treat the myeloma.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is administered as a primary treatment for multiple myeloma.

In one embodiment, the CDP-taxane conjugate is administered in combination with dexamethasone. In one embodiment, the CDP-taxane conjugate is further

administered in combination with an anthracycline (e.g., daunorubicin, doxorubicin (e.g., liposomal doxorubicin), epirubicin, valrubicin and idarubicin), thalidomide or thalidomide derivative (e.g., lenalidomide).

In one embodiment, the CDP-taxane conjugate is administered in combination with a proteasome inhibitor (e.g., bortezomib) and dexamethasone. In one embodiment, the CDP-taxane conjugate is further administered in combination with an anthracycline (e.g., daunorubicin, doxorubicin (e.g., liposomal doxorubicin), epirubicin, valrubicin and idarubicin), thalidomide or thalidomide derivative (e.g., lenalidomide).

In one embodiment, the CDP-taxane conjugate is administered in combination with a vinca alkaloid (e.g., vinblastine, vincristine, vindesine and vinorelbine) and dexamethasone. In one embodiment, the CDP-taxane conjugate is further administered in combination with an anthracycline (e.g., daunorubicin, doxorubicin (e.g., liposomal doxorubicin), epirubicin, valrubicin and idarubicin).

In one embodiment, the CDP-taxane conjugate is administered in combination with thalidomide or thalidomide derivative (e.g., lenalidomide).

In one embodiment, after the subject has received a primary treatment, e.g., a primary treatment described herein, the subject is further administered a high dose treatment. For example, the subject can be administered a high dose treatment of dexamethasone, an alkylating agent (e.g., cyclophosphamide or melphalan) and/or a CDP-taxane conjugate described herein.

In one embodiment, after the primary treatment, e.g., after the primary treatment and the high dose treatment, stem cells are transplanted into the subject. In one embodiment, a subject who has received a stem cell transplant is administered thalidomide. In one embodiment, the subject is further administered a corticosteroid (e.g., prednisone).

In one embodiment, the CDP-taxane conjugate 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 one embodiment, the VEGF receptor inhibitor is selected from CP-547632 and AZD2171.

In some embodiments, the CDP-taxane conjugate 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 CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker

shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate 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 comprising:

providing a subject who has multiple myeloma and has been treated with a chemotherapeutic agent that did not effectively treat the myeloma (e.g., the subject has a chemotherapeutic refractory myeloma, a chemotherapeutic resistant myeloma and/or a relapsed myeloma) or who had an unacceptable side effect (e.g., the subject has a chemotherapeutic sensitive myeloma), and

administering a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to a subject in an amount effective to treat the myeloma, to thereby treat the myeloma.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the subject has been treated with a proteosome inhibitor, e.g., bortezomib, which did not effectively treat the myeloma (e.g., the subject has a bortezomib refractory, a bortezomib resistant and/or relapsed myeloma).

In one embodiment, the subject has been treated with an anthracycline (e.g., daunorubicin, doxorubicin, epirubicin, valrubicin or idarubicin) which did not effectively treat the cancer (e.g., the subject has a doxorubicin refractory, a doxorubicin resistant and/or a relapsed myeloma).

In one embodiment, the subject has been treated with a thalidomide or thalidomide derivative (e.g., lenalidomide) which did not effectively treat the myeloma

(e.g., the subject has thalidomide or thalidomide derivative refractory, thalidomide or thalidomide derivative resistant and/or a relapsed myeloma).

In one embodiment, the subject has been treated with a taxane (e.g., docetaxel or paclitaxel) which did not effectively treat the myeloma.

In one embodiment, the CDP-taxane conjugate is administered in combination with an anthracycline (e.g., daunorubicin, doxorubicin (e.g., liposomal doxorubicin), epirubicin, valrubicin and idarubicin). In one embodiment, the CDP-taxane conjugate is administered in combination with an anthracycline (e.g., daunorubicin, doxorubicin (e.g., liposomal doxorubicin), epirubicin, valrubicin and idarubicin) and a proteosome inhibitor, e.g., bortezomib.

In another embodiment, the CDP-taxane conjugate is administered in combination with a proteosome inhibitor, e.g., bortezomib.

In one embodiment, the CDP-taxane conjugate is administered in combination with thalidomide or a thalidomide derivative (e.g. lenalidomide) and dexamethasone.

In one embodiment, the CDP-taxane conjugate is administered in combination with dexamethaxone and cyclophosphamide. In one embodiment, the CDP-taxane conjugate is further administered in combination with a topoisomerase inhibitor (e.g., etoposide, topotecan, irinotecan, tenoposide, SN-38, lamellarin D) and/or a platinum based agent (carboplatin, cisplatin, oxaliplatin). In one embodiment, the CDP-taxane conjugate is further administered in combination with an anthracycline (e.g., daunorubicin, doxorubicin (e.g., liposomal doxorubicin), epirubicin, valrubicin and idarubicin).

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In yet another aspect, the invention features a method of treating AIDS-related Kaposi's Sarcoma in a subject, e.g., a human. The method comprises: administering a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to a subject in an amount effective to treat the sarcoma, to thereby treat the sarcoma.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker

such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is administered in combination with an antiviral agent, e.g., a nucleoside or a nucleotide reverse transcriptase inhibitor, a non-nucleoside reverse transcriptase inhibitor, a protease inhibitor, an integrase inhibitor, and entry or fusion inhibitor, a maturation inhibitor, or a broad spectrum inhibitor. Examples of nucleoside reverse transcriptase inhibitors include zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, emtricitabine and apricitabine. Nucleotide reverse transcriptase include, e.g., tenofovir and adefovir. Examples of a non-nucleoside reverse transcriptase inhibitor include efavirenz, nevirapine, delavirdine and etravirine. Protease inhibitors include, e.g., saquinavir, ritonavir, indinavir, nelfinavir and amprenavir. An exemplary integrase inhibitor is raltegravir. Examples of entry inhibitors and fusion inhibitors include maraviroc and enfuvirtide. Maturation inhibitors include, e.g., bevirimat and vivecon.

In one embodiment, the CDP-taxane conjugate is administered in combination with cryosurgery. In one embodiment, CDP-taxane conjugate is administered in combination alitretinoin.

In one embodiment, the CDP-taxane conjugate is administered in combination with an anthracycline (e.g., daunorubicin, doxorubicin (e.g., liposomal doxorubicin), epirubicin, valrubicin and idarubicin). In one embodiment, the CDP-taxane conjugate is further administered with a vinca alkaloid (e.g., vinblastine, vincristine, vindesine and vinorelbine) and an antibiotic (e.g., actinomycin, bleomycin, hydroxyurea and mitomycin).

In one embodiment, the CDP-taxane conjugate is administered in combination with a taxane (e.g., paclitaxel or docetaxel). In one embodiment, the CDP-taxane conjugate is further administered with a vinca alkaloid (e.g., vinblastine, vincristine, vindesine and vinorelbine).

In one embodiment, the CDP-taxane is administered in combination with a vinca alkaloid (e.g., vinblastine, vincristine, vindesine and vinorelbine).

In some embodiments, the CDP-taxane conjugate 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 and AZD2171). In one embodiment, the CDP-taxane conjugate is administered in combination with bevacizumab.

In some embodiments, the CDP-taxane conjugate 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 CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a

CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In yet another aspect, the invention features a method of treating AIDS-related Kaposi's Sarcoma, in a subject, e.g., a human. The method comprises:

providing a subject who has AIDS-related Kaposi's Sarcoma and has been treated with a chemotherapeutic agent which did not effectively treat the sarcoma (e.g., the subject has a chemotherapeutic refractory, a chemotherapeutic resistant and/or a relapsed sarcoma) or which had an unacceptable side effect (e.g., the subject has a chemotherapeutic sensitive sarcoma), and

administering a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the sarcoma is refractory to, resistant to, and/or relapsed with treatment with one or more of: a taxane (e.g., paclitaxel and docetaxel), an anthracycline, a vinca alkaloid (e.g., vinblastine, vincristine, vindesine and vinorelbine) and an anthracycline (e.g., daunorubicin, doxorubicin, epirubicin, valrubicin and idarubicin).

In one embodiment, the cancer is a multidrug resistant sarcoma.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In yet another aspect, the invention features a method of treating gastric cancer in a subject, e.g., a human. The method comprises: administering a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the gastric cancer is gastroesophageal junction adenocarcinoma.

In one embodiment, the CDP-taxane conjugate is administered prior to surgery, after surgery or before and after surgery to remove the cancer.

In one embodiment, the CDP-taxane conjugate is administered in combination with one or more of an anthracycline (e.g., daunorubicin, doxorubicin (e.g., liposomal doxorubicin), epirubicin, valrubicin and idarubicin), 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 some embodiments, the CDP-taxane conjugate is administered in combination with an anti-metabolite, e.g., an antifolate (e.g., floxuridine, pemetrexed) or pyrimidine

analogue (e.g., capecitabine, 5FU)). In one embodiment, the CDP-taxane conjugate is further administered with a taxane (e.g., paclitaxel or docetaxel).

In one embodiment, the CDP-taxane conjugate is administered in combination with radiation.

In some embodiments, the CDP-taxane conjugate 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 and AZD2171). In one embodiment, the CDP-taxane conjugate is administered in combination with bevacizumab.

In some embodiments, the CDP-taxane conjugate 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 CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising

larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In yet another aspect, the invention features a method of treating gastric cancer, e.g. a gastric cancer described herein such as gastroesophageal junction adenocarcinoma, in a subject, e.g., a human. The method comprises:

providing a subject who has gastric cancer and has been treated with a chemotherapeutic agent which did not effectively treat the cancer (e.g., the subject has a non-resectable cancer, 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 CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g.,

a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the cancer is refractory to, resistant to, and/or relapsed with treatment with one or more of: a taxane (e.g., paclitaxel and docetaxel), an anthracycline (e.g., daunorubicin, doxorubicin, epirubicin, valrubicin and idarubicin), an anti-metabolite, e.g., an antifolate (e.g., floxuridine, pemetrexed) or pyrimidine analogue (e.g., capecitabine, 5FU)), and a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin).

In one embodiment, the cancer is a multidrug resistant cancer.

In one embodiment, the CDP-taxane conjugate is administered in combination with a pyrimidine analogue, e.g., a pyrimidine analogue described herein (e.g., capecitabine and 5FU).

In one embodiment, the CDP-taxane conjugate is administered in combination with a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin). In one embodiment, the CDP-taxane conjugate is further administered in combination with a pyrimidine analogue, e.g., a pyrimidine analogue described herein (e.g., capecitabine and 5FU). In another embodiment, the CDP-taxane conjugate is further administered in combination with a topoisomerase inhibitor (e.g., etoposide, topotecan, irinotecan, tenoposide, SN-38, lamellarin D).

In one embodiment, the CDP-taxane conjugate is administered in combination with a topoisomerase inhibitor (e.g., etoposide, topotecan, irinotecan, tenoposide, SN-38, lamellarin D). In one embodiment, the CDP-taxane conjugate is further administered in combination with a pyrimidine analogue, e.g., a pyrimidine analogue described herein (e.g., capecitabine and 5FU).

In some embodiments, the CDP-taxane conjugate is administered in combination with a taxane (e.g., paclitaxel and docetaxel). In one embodiment, the CDP-taxane conjugate is further administered in combination with a pyrimidine analogue, e.g., a pyrimidine analogue described herein (e.g., capecitabine and 5FU).

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker

shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In yet another aspect, the invention features a method of treating a soft tissue sarcoma (e.g., non-resectable, advanced, metastatic or relapsed soft tissue sarcoma) in a

subject, e.g., a human. The method comprises: administering a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to a subject in an amount effective to treat the sarcoma, to thereby treat the sarcoma.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the soft tissue sarcoma is rhabdomyosarcoma, leiomyosarcoma, hemangiosarcoma, lymphangiosarcoma, synovial sarcoma, neurofibrosarcoma, liposarcoma, fibrosarcoma, malignant fibrous histiocytoma and dermatofibrosarcoma.

In one embodiment, the CDP-taxane conjugate is administered in combination with an anthracycline, e.g., daunorubicin, doxorubicin (e.g., liposomal doxorubicin), epirubicin, valrubicin and idarubicin.

In one embodiment, the CDP-taxane conjugate is administered in combination with an alkylating agent (e.g., cyclophosphamide, dacarbazine, melphalan, ifosfamide, temozolomide). In one embodiment, the CDP-taxane conjugate is further administered in combination with mesna. In one embodiment, the CDP-taxane conjugate is further administered in combination with an anthracycline, e.g., daunorubicin, doxorubicin (e.g., liposomal doxorubicin), epirubicin, valrubicin and idarubicin.

In one embodiment, the CDP-taxane conjugate is administered in combination with an anti-metabolite, e.g., an antifolate (e.g., pemetrexed, floxuridine, raltitrexed) or pyrimidine analog (e.g., capecitabine, cytrarabine, gemcitabine, 5FU).

In one embodiment, the CDP-taxane conjugate is administered in combination with a vinca alkaloid (e.g., vinblastine, vincristine, vindesine, vinorelbine).

In some embodiments, the CDP-taxane conjugate 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 and AZD2171). In one embodiment, the CDP-taxane conjugate is administered in combination with bevacizumab.

In some embodiments, the CDP-taxane conjugate 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 CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In yet another aspect, the invention features a method of treating a soft tissue sarcoma, in a subject, e.g., a human. The method comprises:

providing a subject who has a soft tissue sarcoma and has been treated with a chemotherapeutic agent which did not effectively treat the sarcoma (e.g., the subject has a chemotherapeutic refractory, a chemotherapeutic resistant and/or a relapsed sarcoma) or which had an unacceptable side effect (e.g., the subject has a chemotherapeutic sensitive sarcoma), and

administering a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to a subject in an amount effective to treat the sarcoma, to thereby treat the sarcoma.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the sarcoma is refractory to, resistant to, and/or relapsed with treatment with one or more of: a taxane (e.g., paclitaxel and docetaxel), an anthracycline (e.g., doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone, valrubicin), a vinca alkaloid (e.g., vinblastine, vincristine, vindesine and vinorelbine) and an alkylating agent (e.g., cyclophosphamide, dacarbazine, melphalan, ifosfamide, temozolomide).

In one embodiment, the sarcoma is a multidrug resistant cancer.

In one embodiment, the soft tissue sarcoma is rhabdomyosarcoma, leiomyosarcoma, hemangiosarcoma, lymphangiosarcoma, synovial sarcoma, neurofibrosarcoma, liposarcoma, fibrosarcoma, malignant fibrous histiocytoma and dermatofibrosarcoma.

In one embodiment, the CDP-taxane conjugate is administered in combination with an anthracycline, e.g., daunorubicin, doxorubicin (e.g., liposomal doxorubicin), epirubicin, valrubicin and idarubicin.

In one embodiment, the CDP-taxane conjugate is administered in combination with an alkylating agent (e.g., cyclophosphamide, dacarbazine, melphalan, ifosfamide, temozolomide). In one embodiment, the CDP-taxane conjugate is further administered in combination with mesna. In one embodiment, the CDP-taxane conjugate is further administered in combination with an anthracycline, e.g., daunorubicin, doxorubicin (e.g., liposomal doxorubicin), epirubicin, valrubicin and idarubicin.

In one embodiment, the CDP-taxane conjugate is administered in combination with an anti-metabolite, e.g., an antifolate (e.g., pemetrexed, floxuridine, raltitrexed) or pyrimidine analog (e.g., capecitabine, cytrarabine, gemcitabine, 5FU).

In one embodiment, the CDP-taxane conjugate is administered in combination with a vinca alkaloid (e.g., vinblastine, vincristine, vindesine, vinorelbine).

In some embodiments, the CDP-taxane conjugate 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 and AZD2171). In one embodiment, the CDP-taxane conjugate is administered in combination with bevacizumab.

In some embodiments, the CDP-taxane conjugate 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 CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker

shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one aspect, the disclosure features a method of treating pancreatic cancer (e.g., locally advanced or metastatic pancreatic cancer) in a subject, e.g., a human. The method

comprises: administering a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

In one embodiment, the cancer is refractory to, resistant to, and/or relapsed with treatment with one or more of: a taxane (e.g., paclitaxel and docetaxel).

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is administered after surgery or before and after surgery to remove the cancer.

In one embodiment, the CDP-taxane conjugate is administered in combination with one or more of an anti-metabolite, e.g., an antifolate, e.g., floxuridine, a pyrimidine analogue, e.g., 5FU, capecitabine, and/or a nucleoside analog, e.g., gemcitabine. For example, in one embodiment, the CDP-taxane conjugate is administered in combination with a nucleoside analog, e.g., gemcitabine. In one embodiment, the CDP-taxane conjugate is further administered in combination with a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin) and a pyrimidine analogue (e.g., 5FU and/or capecitabine). In one embodiment, the CDP-taxane conjugate is further 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 some embodiments, the CDP-taxane conjugate is administered in combination with an anti-metabolite, e.g., 5FU, and leucovorin. In one embodiment, the CDP-taxane conjugate is administered in combination with radiation.

In some embodiments, the CDP-taxane conjugate 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 and AZD2171). In one embodiment, the CDP-taxane conjugate is administered in combination with bevacizumab.

In some embodiments, the CDP-taxane conjugate 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 CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one aspect, the disclosure features a method of treating pancreatic cancer, e.g. locally advanced or metastatic pancreatic cancer, in a subject, e.g., a human. The method comprises:

providing a subject who has pancreatic cancer and has been treated with a chemotherapeutic agent which did not effectively treat the cancer (e.g., the subject has a non-resectable cancer, 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 CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the cancer is refractory to, resistant to, and/or relapsed with treatment with one or more of: a taxane (e.g., paclitaxel, docetaxel, larotaxel, cabazitaxel), an anthracycline (e.g., daunorubicin, doxorubicin, epirubicin, valrubicin and idarubicin), an anti-metabolite, e.g., an antifolate (e.g., floxuridine, pemetrexed) or

pyrimidine analogue (e.g., capecitabine, 5FU)), and a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin).

In one embodiment, the cancer is a multidrug resistant cancer.

In one embodiment, the CDP-taxane conjugate is administered in combination with a pyrimidine analogue, e.g., a pyrimidine analogue described herein (e.g., capecitabine and/or 5FU). In one embodiment, the CDP-taxane conjugate is administered in combination with a pyrimidine analogue, e.g., 5FU, and leucovorin. In one embodiment, the CDP-taxane conjugate is further administered in combination with a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin).

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a

CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In yet another aspect, the invention features a method of treating advanced or metastatic colorectal cancer in a subject, e.g., a human. The method comprises: administering a composition comprising a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the cancer is refractory to, resistant to, and/or relapsed with treatment with one or more of: a taxane (e.g., paclitaxel and docetaxel).

In one embodiment, the CDP-taxane conjugate is administered in combination with an antimetabolite, e.g., an antifolate (e.g., pemetrexed, raltitrexed). In one embodiment, the CDP-taxane conjugate is administered in combination with an

antimetabolite, e.g., 5FU, and leucovorin. In one embodiment, the CDP-taxane conjugate is further administered in combination with a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin). For example, in one embodiment, the CDP-taxane conjugate is administered in combination with an antimetabolite, e.g., 5FU, leucovorin, and a platinum-based agent, e.g., oxaliplatin. In another embodiment, the antimetabolite is a pyrimidine analog, e.g., capecitabine.

In one embodiment, the CDP-taxane conjugate is administered in combination with a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin).

In one embodiment, the CDP-taxane conjugate 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 one embodiment, the VEGF receptor inhibitor is selected from CP-547632 and AZD2171. In one embodiment, the CDP-taxane conjugate is administered in combination with a VEGF pathway inhibitor, e.g., bevacizumab, and an antimetabolite, e.g., an antifolate (e.g., pemetrexed, raltitrexed) or pyrimidine analogue (e.g., 5FU). In one embodiment, the CDP-taxane conjugate is administered with a VEGF pathway inhibitor, e.g., bevacizumab, an antimetabolite, e.g., a pyrimidine analogue (e.g., 5FU), and leucovorin. In another embodiment, the CDP-taxane conjugate is administered with a VEGF pathway inhibitor, e.g., bevacizumab, an antimetabolite, e.g., a pyrimidine analogue (e.g., 5FU), leucovorin, a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin) and/or a topoisomerase inhibitor (e.g., irinotecan, topotecan, etoposide, teniposide, lamellarin D, SN-38, camptothecin (e.g., CRLX101)). For example, in one embodiment, the CDP-taxane conjugate is administered with the following combination: a VEGF pathway inhibitor, e.g., bevacizumab, an antimetabolite (e.g., 5FU), leucovorin and a platinum-based agent (e.g., oxaliplatin); a VEGF pathway inhibitor, e.g., bevacizumab, an antimetabolite (e.g., 5FU), leucovorin, a platinum-based agent (e.g., oxaliplatin) and a topoisomerase inhibitor (e.g., irinotecan); or a VEGF pathway inhibitor, e.g., bevacizumab, an antimetabolite (e.g., 5FU), leucovorin and a topoisomerase inhibitor (e.g., irinotecan).

In another embodiment, the CDP-taxane conjugate is administered in combination with a VEGF pathway inhibitor, e.g., bevacizumab, and an antimetabolite wherein the

antimetabolite is a pyrimidine analog, e.g., capecitabine. In one embodiment, the CDP-taxane conjugate is further administered in combination with a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin) or a topoisomerase inhibitor (e.g., irinotecan, topotecan, etoposide, teniposide, lamellarin D, SN-38, camptothecin (e.g., CRLX101)). For example, in one embodiment, the CDP-taxane conjugate is administered with the following combination: a VEGF pathway inhibitor, e.g., bevacizumab, a pyrimidine analog, e.g., capecitabine, and a platinum-based agent (e.g., oxaliplatin); or a VEGF pathway inhibitor, e.g., bevacizumab, a pyrimidine analog, e.g., capecitabine, and a topoisomerase inhibitor (e.g., irinotecan).

In one embodiment, the CDP-taxane conjugate is administered in combination with an epidermal growth factor (EGF) pathway inhibitor, e.g., an EGF inhibitor or EGF receptor inhibitor. The EGF receptor inhibitor can be, e.g., cetuximab, erlotinib, gefitinib, panitumumab. In one embodiment, the CDP-taxane conjugate is administered in combination with an EGF pathway inhibitor, e.g., cetuximab or panitumumab, and a VEGF pathway inhibitor, e.g., bevacizumab.

In one embodiment, the CDP-taxane conjugate is administered in combination with a topoisomerase inhibitor (e.g., irinotecan, topotecan, etoposide, teniposide, lamellarin D, SN-38, camptothecin (e.g., CRLX101)). In one embodiment, the CDP-taxane conjugate is administered in combination with a topoisomerase inhibitor (e.g., irinotecan) and a VEGF pathway inhibitor, e.g., bevacizumab.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an

embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In yet another aspect, the invention features a method of treating advanced or metastatic colorectal cancer in a subject, e.g., a human, the method comprising:

providing a subject who has advanced or metastatic colorectal cancer and has been treated with a chemotherapeutic agent that did not effectively treat the cancer (e.g., the subject has a chemotherapeutic refractory cancer, a chemotherapeutic resistant cancer and/or a relapsed cancer) or who had an unacceptable side effect (e.g., the subject has a chemotherapeutic sensitive cancer), and

administering a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate

described herein, to a subject in an amount effective to treat the cancer, to thereby treat the cancer.

In one embodiment, the cancer is refractory to, resistant to, and/or relapsed with treatment with one or more of: a taxane (e.g., paclitaxel and docetaxel).

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the subject has been treated with an anti-metabolite, e.g., a pyrimidine analogue which did not effectively treat the cancer (e.g., the subject has a capecitabine and/or 5FU refractory, a capecitabine and/or 5FU resistant and/or relapsed cancer).

In one embodiment, the subject has been treated with a pyrimidine analog which did not effectively treat the cancer (e.g., the subject has a capecitabine refractory, a capecitabine resistant and/or a relapsed cancer).

In one embodiment, the CDP-taxane conjugate 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 one embodiment, the VEGF receptor inhibitor is selected from CP-547632 and AZD2171. In one embodiment, the CDP-taxane conjugate is administered in combination with a VEGF pathway inhibitor, e.g., bevacizumab, and an antimetabolite, e.g., an antifolate (e.g., pemetrexed, raltitrexed) or pyrimidine analogue (e.g., 5FU). In one embodiment, the CDP-taxane conjugate is administered with a VEGF pathway inhibitor, e.g., bevacizumab, an antimetabolite (e.g., 5FU) and leucovorin. In another embodiment, the CDP-taxane conjugate is administered with a VEGF pathway inhibitor, e.g., bevacizumab, an antimetabolite (e.g., 5FU), leucovorin, a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin) and/or a topoisomerase inhibitor (e.g., irinotecan,

topotecan, etoposide, teniposide, lamellarin D, SN-38, camptothecin (e.g., CRLX101)). For example, in one embodiment, the CDP-taxane conjugate is administered with the following combination: a VEGF pathway inhibitor, e.g., bevacizumab, an antimetabolite (e.g., 5FU), leucovorin and a platinum-based agent (e.g., oxaliplatin); a VEGF pathway inhibitor, e.g., bevacizumab, an antimetabolite (e.g., 5FU), leucovorin, a platinum-based agent (e.g., oxaliplatin) and a topoisomerase inhibitor (e.g., irinotecan); or a VEGF pathway inhibitor, e.g., bevacizumab, an antimetabolite (e.g., 5FU), leucovorin and a topoisomerase inhibitor (e.g., irinotecan).

In another embodiment, the CDP-taxane conjugate is administered in combination with a VEGF pathway inhibitor, e.g., bevacizumab, and an antimetabolite wherein the antimetabolite is a pyrimidine analog, e.g., capecitabine. In one embodiment, the CDP-taxane conjugate is further administered in combination with a platinum-based agent (e.g., cisplatin, carboplatin, oxaliplatin) or a topoisomerase inhibitor (e.g., irinotecan, topotecan, etoposide, teniposide, lamellarin D, SN-38, camptothecin (e.g., CRLX101)). For example, in one embodiment, the CDP-taxane conjugate is administered with the following combination: a VEGF pathway inhibitor, e.g., bevacizumab, a pyrimidine analog, e.g., capecitabine, and a platinum-based agent (e.g., oxaliplatin); or a VEGF pathway inhibitor, e.g., bevacizumab, a pyrimidine analog, e.g., capecitabine, and a topoisomerase inhibitor (e.g., irinotecan).

In one embodiment, the CDP-taxane conjugate is administered in combination with an epidermal growth factor (EGF) pathway inhibitor, e.g., an EGF inhibitor or EGF receptor inhibitor. The EGF receptor inhibitor can be, e.g., cetuximab, erlotinib, gefitinib, panitumumab. In one embodiment, the CDP-taxane conjugate is administered in combination with an EGF pathway inhibitor, e.g., cetuximab or panitumumab, and a VEGF pathway inhibitor, e.g., bevacizumab.

In one embodiment, the CDP-taxane conjugate is administered in combination with a topoisomerase inhibitor (e.g., irinotecan, topotecan, etoposide, teniposide, lamellarin D, SN-38, camptothecin (e.g., CRLX101)). In one embodiment, the CDP-taxane conjugate is administered in combination with a topoisomerase inhibitor (e.g., irinotecan) and a VEGF pathway inhibitor, e.g., bevacizumab.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In yet another aspect, the invention features a method of identifying a subject, e.g., a human, having a proliferative disorder, e.g., cancer, for treatment with a CDP-taxane conjugate, e.g., a CDP-taxane conjugate described herein, the method comprising

identifying a subject having a proliferative disorder who has received an anticancer agent (e.g., a taxane) and has a neutrophil count less than a standard; and

identifying the subject as suitable for treatment with a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein.

In one embodiment, the method further comprising administering a CDP-taxane conjugate, e.g., a CDP-taxane conjugate described herein in an amount effective to treat the disorder.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an

embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the cancer is a cancer described herein. In one embodiment, the CDP-taxane conjugate is administered in combination with one or more additional chemotherapeutic agent, e.g., a chemotherapeutic agent or combination of chemotherapeutic agents described herein. In one embodiment, the CDP-taxane conjugate is administered in combination with a granulocyte colony stimulating factor, e.g., GCSF or GMCSF.

In one embodiment, the standard is a neutrophil count below or equal to 1500 cells/mm^3. In some embodiments, the standard is based on a neutrophil count prior to receiving an anticancer agent, e.g., mean neutrophil count decreased from the mean

neutrophil count prior to treatment with the anticancer agent, e.g., by at least 20%, 30%, 40 % or 50% after administration of the anticancer agent.

In another aspect, the invention features a method of treating a subject, e.g., a human, with a proliferative disorder, e.g., cancer, the method comprising

selecting a subject having a proliferative disease who has received an anticancer agent (e.g., a taxane) and has a neutrophil count less than a standard; and

administering a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to the subject in an amount effective to treat the proliferative disorder, to thereby treat the disorder.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the cancer is a cancer described herein. In one embodiment, the CDP-taxane conjugate is administered in combination with one or more additional chemotherapeutic agent, e.g., a chemotherapeutic agent or combination of chemotherapeutic agents described herein. In one embodiment, the CDP-taxane conjugate is administered in combination with a granulocyte colony stimulating factor, e.g., GCSF or GMCSF.

In one embodiment, the standard is a neutrophil count below or equal to 1500 cells/mm^3. In some embodiments, the standard is based on a neutrophil count prior to receiving an anticancer agent, e.g., mean neutrophil count decreased from the mean neutrophil count prior to treatment with the anticancer agent, e.g., by at least 20%, 30%, 40 % or 50% after administration of the anticancer agent.

In yet another aspect, the invention features a method for selecting a subject, e.g., a human, with a proliferative disorder, e.g., cancer, for treatment with a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, comprising:

determining whether a subject with a proliferative disorder has moderate to severe neutropenia; and

selecting a subject for treatment with a CDP-taxane conjugate on the basis that the subject has moderate to severe neutropenia.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein. In one embodiment, the dosing schedule is not changed between doses. For example, when the dosing schedule is every three weeks, an additional dose is administered in three weeks. In one embodiment, the dose does not change or is increased for an additional dose (or doses). For example, when a dose of the CDP-docetaxel conjugate is administered in an amount such that the conjugate includes 60 mg/m^2 of docetaxel, an additional dose is administered in an amount such that the conjugate includes 60 mg/m^2 or greater of docetaxel.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein. In one embodiment, the dosing schedule is not changed between doses. For example, when the dosing schedule is every three weeks, an additional dose is administered in three weeks. In one embodiment, the dose does not change or is increased for an additional dose (or doses). For example, when a dose of the CDP-paclitaxel conjugate is administered in an amount such that the conjugate includes 135 mg/m^2 or greater of paclitaxel, an additional dose is administered in an amount such that the conjugate includes 135 mg/m^2 or greater of paclitaxel.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein. In one embodiment, the dosing schedule is not changed between doses. For example, when the dosing schedule is every three weeks, an additional dose is administered in three weeks. In one embodiment, the dose does not change or is increased for an additional dose (or doses).

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker

shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein. In one embodiment, the dosing schedule is not changed between doses. For example, when the dosing schedule is every three weeks, an additional dose is administered in three weeks. In one embodiment, the dose does not change or is increased for an additional dose (or doses).

In one embodiment, the method further comprises administering a CDP-taxane conjugate, e.g., a CDP-taxane conjugate described herein, to the subject.

In one embodiment, the subject experienced moderate to severe neutropenia from treatment with an anticancer agent (e.g., a taxane). In one embodiment, the subject has one or more symptom of febrile neutropenia.

In one embodiment, the cancer is a cancer described herein. In one embodiment, the CDP-taxane conjugate is administered in combination with one or more additional chemotherapeutic agent, e.g., a chemotherapeutic agent or combination of chemotherapeutic agents described herein. In one embodiment, the CDP-taxane conjugate is administered in combination with a granulocyte colony stimulating factor, e.g., GCSF or GMCSF.

In one embodiment, the standard for moderate neutropenia is a neutrophil count of 1000 to 500 cells/mm^3. In one embodiment, the standard for severe neutropenia is a neutrophil count of less than 500 cells/mm^3.

In yet another aspect, the invention features a method for treating a subject, e.g., a human, with a proliferative disorder, e.g., cancer, comprising:

selecting a subject with a proliferative disorder, e.g., cancer, who has moderate to severe neutropenia; and

administering a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to the subject in an amount effective to treat the disorder, to thereby treat the proliferative disorder.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker

such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein. In one embodiment, the dosing schedule is not changed between doses. For example, when the dosing schedule is every three weeks, an additional dose is administered in three weeks. In one embodiment, the dose does not change or is increased for an additional dose (or doses). For example, when a dose of the CDP-docetaxel conjugate is administered in an amount such that the conjugate includes 60 mg/m^2 of docetaxel, an additional dose is administered in an amount such that the conjugate includes 60 mg/m^2 or greater of docetaxel.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein. In one embodiment, the dosing schedule is not changed between doses. For example, when the dosing schedule is every three weeks, an additional dose is administered in three weeks. In one embodiment, the dose does not change or is increased for an additional dose (or doses). For example, when a dose of the CDP-paclitaxel conjugate is administered in an amount such that the conjugate includes

135 mg/m^2 or greater of paclitaxel, an additional dose is administered in an amount such that the conjugate includes 135 mg/m^2 or greater of paclitaxel.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein. In one embodiment, the dosing schedule is not changed between doses. For example, when the dosing schedule is every three weeks, an additional dose is administered in three weeks. In one embodiment, the dose does not change or is increased for an additional dose (or doses).

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein. In one embodiment, the dosing schedule is not changed between doses. For example, when the dosing schedule is every three weeks, an additional dose is administered in three weeks. In one embodiment, the dose does not change or is increased for an additional dose (or doses).

In one embodiment, the method further comprises administering a CDP-taxane conjugate, e.g., a CDP-taxane conjugate described herein, to the subject.

In one embodiment, the subject experienced moderate to severe neutropenia from treatment with an anticancer agent (e.g., a taxane). In one embodiment, the subject has one or more symptom of febrile neutropenia.

In one embodiment, the cancer is a cancer described herein. In one embodiment, the CDP-taxane conjugate is administered in combination with one or more additional chemotherapeutic agent, e.g., a chemotherapeutic agent or combination of chemotherapeutic agents described herein. In one embodiment, the CDP-taxane conjugate is administered in combination with a granulocyte colony stimulating factor, e.g., GCSF or GMCSF.

In one embodiment, the standard for moderate neutropenia is a neutrophil count of 1000 to 500 cells/mm^3. In one embodiment, the standard for severe neutropenia is a neutrophil count of less than 500 cells/mm^3.

In yet another aspect, the invention features a method for selecting a subject, e.g., a human, with a proliferative disorder, e.g., cancer, for treatment with a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, comprising:

determining whether a subject with a proliferative disorder, e.g., cancer, has experienced neuropathy from treatment with an anticancer agent, e.g., a taxane, a vinca alkaloid, an alkylating agent, a platinum-based agent, a proteosome inhibitor or an epothilone; and

selecting a subject for treatment with a CDP-taxane conjugate, e.g., a CDP-taxane conjugate described herein, on the basis that the subject has experienced neuropathy from treatment with a chemotherapeutic agent, e.g., a taxane, a vinca alkaloid, an alkylating agent, a platinum-based agent, a proteosome inhibitor or an epothilone.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an

embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the dosing schedule is not changed between doses. For example, when the dosing schedule is every three weeks, an additional dose is administered in three weeks. In one embodiment, the dose does not change or is increased for an additional dose (or doses). For example, when a dose of the CDP-docetaxel conjugate is administered in an amount such that the conjugate includes 60 mg/m^2 of docetaxel, an additional dose is administered in an amount such that the conjugate includes 60 mg/m^2 or greater of docetaxel.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein. In one embodiment, the dosing schedule is not changed between doses. For example, when the dosing schedule is every three weeks, an additional dose is administered in three weeks. In one embodiment, the dose does not change or is increased for an additional dose (or doses). For example, when a dose of the CDP-paclitaxel conjugate is administered in an amount such that the conjugate includes 135 mg/m^2 or greater of paclitaxel, an additional dose is administered in an amount such that the conjugate includes 135 mg/m^2 or greater of paclitaxel.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a

CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein. In one embodiment, the dosing schedule is not changed between doses. For example, when the dosing schedule is every three weeks, an additional dose is administered in three weeks. In one embodiment, the dose does not change or is increased for an additional dose (or doses).

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein. In one embodiment, the dosing schedule is not changed between doses. For example, when the dosing schedule is every three weeks, an additional dose is administered in three weeks. In one embodiment, the dose does not change or is increased for an additional dose (or doses).

In one embodiment, the neuropathy is peripheral neuropathy. In one embodiment, the neuropathy is sensory neuropathy, motor neuropathy or both.

In one embodiment, the cancer is a cancer described herein. In one embodiment, the subject is selected for treatment with the CDP-taxane conjugate in combination with one or more additional chemotherapeutic agent, e.g., a chemotherapeutic agent or combination of chemotherapeutic agents described herein. In one embodiment, the CDP-taxane conjugate is administered in combination with a granulocyte colony stimulating factor, e.g., GCSF or GMCSF.

In yet another aspect, the invention features a method for treating a subject, e.g., a human, with a proliferative disorder, e.g., cancer, comprising:

selecting a subject with a proliferative disorder, e.g., cancer, who has experienced one or more symptom of neuropathy from treatment with a chemotherapeutic agent, e.g.,

a taxane (e.g., docetaxel or paclitaxel), a vinca alkaloid, an alkylating agent, a platinum-based agent, a proteosome inhibitor or an epothilone; and

administering a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to the subject in an amount effective to treat the disorder, to thereby treat the proliferative disorder.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein. In one embodiment, the dosing schedule is not changed between doses. For example, when the dosing schedule is every three weeks, an additional dose is administered in three weeks. In one embodiment, the dose does not change or is increased for an additional dose (or doses). For example, when a dose of the CDP-docetaxel conjugate is administered in an amount such that the conjugate includes 60 mg/m^2 of docetaxel, an additional dose is administered in an amount such that the conjugate includes 60 mg/m^2 or greater of docetaxel.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker

shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein. In one embodiment, the dosing schedule is not changed between doses. For example, when the dosing schedule is every three weeks, an additional dose is administered in three weeks. In one embodiment, the dose does not change or is increased for an additional dose (or doses). For example, when a dose of the CDP-paclitaxel conjugate is administered in an amount such that the conjugate includes 135 mg/m^2 or greater of paclitaxel, an additional dose is administered in an amount such that the conjugate includes 135 mg/m^2 or greater of paclitaxel.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein. In one embodiment, the dosing schedule is not changed between doses. For example, when the dosing schedule is every three weeks, an additional dose is administered in three weeks. In one embodiment, the dose does not change or is increased for an additional dose (or doses).

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein. In one embodiment, the dosing schedule is not changed between doses. For example, when the dosing schedule is every three weeks, an

additional dose is administered in three weeks. In one embodiment, the dose does not change or is increased for an additional dose (or doses).

In one embodiment, the subject experienced moderate to severe neuropathy from treatment with a chemotherapeutic agent. In one embodiment, the neuropathy is peripheral neuropathy. In one embodiment, the neuropathy is sensory neuropathy, motor neuropathy or both.

In one embodiment, the subject has experienced neuropathy after two, three, four, five cycles of treatment with an anticancer agent.

In one embodiment, the cancer is a cancer described herein. In one embodiment, the CDP-taxane conjugate is administered in combination with one or more additional chemotherapeutic agent, e.g., a chemotherapeutic agent or combination of chemotherapeutic agents described herein.

In another aspect, the invention features a method for selecting a subject, e.g., a human, with a proliferative disorder, e.g., cancer, for treatment with a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, comprising:

determining whether a subject with a proliferative disorder, e.g., cancer, has experienced an infusion site reaction (e.g., during or within 12 hours of infusion of an anticancer agent (e.g., a taxane, e.g., docetaxel or paclitaxel)) or has or is at risk for having hypersensitivity to treatment with an anticancer agent (e.g., a taxane, e.g., docetaxel or paclitaxel),

selecting a subject for treatment with a CDP-taxane conjugate on the basis that the subject is in need of a reduced infusion site reaction (e.g., reduced as compared to the reaction associated with or caused by the treatment with an anticancer agent (e.g., taxane)) or the subject has or is at risk for having hypersensitivity to treatment with an anticancer agent (e.g., a taxane, e.g., paclitaxel or docetaxel).

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g.,

a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein. In one embodiment, the dosing schedule is not changed between doses. For example, when the dosing schedule is every three weeks, an additional dose is administered in three weeks. In one embodiment, the dose does not change or is increased for an additional dose (or doses). For example, when a dose of the CDP-paclitaxel conjugate is administered in an amount such that the conjugate includes 135 mg/m^2 or greater of paclitaxel, an additional dose is administered in an amount such that the conjugate includes 135 mg/m^2 or greater of paclitaxel.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the subject has exhibited one or more symptom of infusion site reaction to a previous treatment with the anticancer agent (e.g., taxane). Symptoms of infusion site reaction include: phlebitis, cellulitis, induration, skin exfoliation, necrosis, fibrosis, hyperpigmentation, inflammation and extravasation.

In one embodiment, the subject has exhibited one or more symptom of hypersensitivity to a previous treatment with the anticancer agent (e.g., the taxane, e.g., a docetaxel or paclitaxel) or to a treatment formulated with Cremaphor and/or polysorbate. Symptoms hypersensitivity include: dyspnea, hypotension, angioedema, urticaria, bronchospasm and erythema.

In one embodiment, the cancer is a cancer described herein. In one embodiment, the CDP-taxane is selected for administration in combination with one or more additional chemotherapeutic agent, e.g., a chemotherapeutic agent or combination of chemotherapeutic agents described herein.

In one embodiment, the subject is further administered, e.g., prior to administration of the CDP-taxane conjugate, one or more of: an antihistamine (e.g., dexchloropheniramine and diphenhydramine), a steroid (e.g., a corticosteroid (e.g., dexamethasone), and an H_2 antagonist (e.g., ranitidine). In one embodiment, the subject is further administered one or more antiemetic (e.g., a 5HT3 receptor antagonist (dolasetron, granisetron, ondansetron, tropisetron, palonosetron, and mirtazapine), a dopamine antagonist (e.g., domperidone, droperidol, haloperidol, chloropromazine, promethazine, prochlorperazine, metoclopramide, alizapride and prochlorperazine), a

NK1 receptor antagonist (e.g., aprepitant and casopitant), a cannabinoid (e.g., cannabis, dronabinol, nabilone and sativex), benzodiazepine (e.g., midazolam and lorazepam), an anticholinergics (e.g., hyoscone) and other antiemetics (e.g., trimethobenzomide, emetrol, propofol and muscimol).

In yet another aspect, the invention features a method of treating a subject, e.g., a human, with a proliferative disorder, e.g., cancer, comprising:

selecting a subject with a proliferative disorder, e.g., cancer, who has experienced an infusion site reaction to treatment with an anticancer agent (e.g., a taxane, e.g., a docetaxel or paclitaxel) or has or is at risk for having hypersensitivity to an anticancer agent (e.g., a taxane, e.g., a docetaxel or paclitaxel)); and

administering a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to the subject in an amount effective to treat the disorder, to thereby treat the proliferative disorder.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate

comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the subject has exhibited one or more symptom of infusion site reaction to a previous treatment with the anticancer agent (e.g., taxane, e.g., a docetaxel or paclitaxel). Symptoms of infusion site reaction include: phlebitis, cellulitis, induration, skin exfoliation, necrosis, fibrosis, hyperpigmentation, inflammation and extravasation.

In one embodiment, the subject has exhibited one or more symptom of hypersensitivity to a previous treatment with the anticancer agent (e.g., the taxane) or a

treatment formulated with Cremaphor and/or polysorbate. Symptoms hypersensitivity include: dyspnea, hypotension, angioedema, urticaria, bronchospasm and erythema.

In one embodiment, the cancer is a cancer described herein. In one embodiment, the CDP-taxane conjugate is administered in combination with one or more additional chemotherapeutic agent, e.g., a chemotherapeutic agent or combination of chemotherapeutic agents described herein.

In one embodiment, the subject is further administered, e.g., prior to administration of the CDP-taxane conjugate, one or more of: an antihistamine (e.g., dexchloropheniramine and diphenhydramine), a steroid (e.g., a corticosteroid (e.g., dexamethasone), and an H_2 antagonist (e.g., ranitidine). In one embodiment, the subject is further administered one or more antiemetic (e.g., a 5HT3 receptor antagonist (dolasetron, granisetron, ondansetron, tropisetron, palonosetron, and mirtazapine), a dopamine antagonist (e.g., domperidone, droperidol, haloperidol, chloropromazine, promethazine, prochlorperazine, metoclopramide, alizapride and prochlorperazine), a NK1 receptor antagonist (e.g., aprepitant and casopitant), a cannabinoid (e.g., cannabis, dronabinol, nabilone and sativex), benzodiazepine (e.g., midazolam and lorazepam), an anticholinergics (e.g., hyoscone) and other antiemetics (e.g., trimethobenzomide, emetrol, propofol and muscimol).

In yet another aspect, the invention features a method of treating a subject, e.g., a human, with a proliferative disorder, e.g., cancer, comprising:

administering a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to a subject with a proliferative disorder, e.g., cancer, in an amount effective to treat the disorder and in the absence of administration of one or more of a corticosteroid, an antihistamine, an H1 antagonist, an H2 antagonist and an antiemetic, to thereby treat the proliferative disorder.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel,

larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an

embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is administered in the absence of administration of a corticosteroid (e.g., dexamethasone). In one embodiment, the CDP-taxane conjugate is administered in the absence of administration of diphenhydramine and/or dexchloropheniramine. In one embodiment, the CDP-taxane conjugate is administered in the absence of administration of cimetidine and/or ranitidine. In one embodiment, the CDP-taxane conjugate is administered in the absence of an H_2 antagonist (e.g., ranitidine). In one embodiment, the subject is further administered a CSP-taxane conjugate in the absence of an antiemetic (e.g., a 5HT3 receptor antagonist (dolasetron, granisetron, ondansetron, tropisetron, palonosetron, and mirtazapine), a dopamine antagonist (e.g., domperidone, droperidol, haloperidol, chloropromazine, promethazine, prochlorperazine, metoclopramide, alizapride and prochlorperazine), a NK1 receptor antagonist (e.g., aprepitant and casopitant), a cannabinoid (e.g., cannabis, dronabinol, nabilone and sativex), benzodiazepine (e.g., midazolam and lorazepam), an anticholinergics (e.g., hyoscone) or other antiemetics (e.g., trimethobenzomide, emetrol, propofol and muscimol).

In one embodiment, the cancer is a cancer described herein. In one embodiment, the CDP-taxane conjugate is administered in combination with one or more additional chemotherapeutic agent, e.g., a chemotherapeutic agent or combination of chemotherapeutic agents described herein.

In yet another aspect, the invention features a method of treating a subject, e.g., a human, with a proliferative disorder, e.g., cancer, comprising:

administering a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to a subject with a proliferative disorder, e.g., cancer, in an amount effective to treat the disorder and in combination with a corticosteroid (e.g.,

dexamethasone), e.g., wherein the corticosteroid (e.g., dexamethasone) is administered at a dose less than 60 mg, 55 mg, 50 mg, 45 mg, 40 mg, 35 mg, 30 mg or the corticosteroid is administered at a dose less than 10 mg, 8 mg, 6 mg or 4 mg, to thereby treat the disorder.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the

CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the cancer is a cancer described herein. In one embodiment, the CDP-taxane is administered in combination with one or more additional chemotherapeutic agent, e.g., a chemotherapeutic agent or combination of chemotherapeutic agents described herein.

In yet another aspect, the invention features a method of treating a subject, e.g., a human, with a proliferative disorder, e.g., cancer, comprising:

administering a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to a subject with a proliferative disorder, e.g., cancer, in an amount effective to treat the disorder and in combination with an antihistamine, a corticosteroid (e.g., dexamethasone), an antiemetic, an H1 antagonist (e.g., dexachlorapheniramine and/or diphenyhydramine) and/or an H2 antagonist (e.g., cimetidine and/or ranitidine), wherein the corticosteroid (e.g., dexamethasone) is administered at a dose less than 20 mg, 15 mg, 10 mg, 8 mg, or 5 mg; the H1 antagonist (e.g., diphenyhydramine) is administered at a dose of less than 50 mg, 45 mg, 30 mg, 20 mg, 15 mg, 10 mg, or 5 mg and/or the H1 antagonist (dexachlorapheniramine) is administered at a dose less than 10 mg, 8 mg, 5 mg, or 3 mg; and/or the H2 antagonist (e.g., cimetidine) is administered at a dose of less than 300 mg, 275 mg, 250 mg, 225 mg, 200 mg, 175 mg, 150 mg, 125 mg,

100 mg and/or the H2 antagonist (e.g., ranitidime) is administered at a dose less than 50 mg, 45 mg, 40 mg, 35 mg, 30 mg, 25 mg, 20 mg, to thereby treat the proliferative disorder.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a

CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the cancer is a cancer described herein. In one embodiment, the CDP-taxane conjugate is administered in combination with one or more additional chemotherapeutic agent, e.g., a chemotherapeutic agent or combination of chemotherapeutic agents described herein.

In yet another aspect, the invention features a method of selecting a subject, e.g., a human, with a proliferative disorder, e.g., cancer, for treatment with a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, comprising:

determining if a subject has hepatic impairment, e.g., if the subject has alanine aminotransferase (ALT), aspartate aminotransferase (AST) and/or bilirubin levels in a subject having a proliferative disorder; and

selecting a subject having hepatic impairment, e.g., a subject having ALT and/or AST levels greater than 1.5 times the upper limit of normal (ULN) (e.g., 2.5 times greater than the ULN) and/or bilirubin levels greater than 1.5 or 2 times the ULN for treatment with a CDP-taxane conjugate, e.g., a CDP-taxane conjugate described herein.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel,

larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an

embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the cancer is a cancer described herein. In one embodiment, the subject is selected for treatment with the CDP-taxane conjugate in combination with one or more additional chemotherapeutic agent, e.g., a chemotherapeutic agent or combination of chemotherapeutic agents described herein.

In yet another aspect, the invention features a method of treating a subject, e.g., a human, having a proliferative disorder, e.g., cancer, comprising:

selecting a subject with a proliferative disorder who has hepatic impairment, e.g., a subject who has alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels greater than 1.5 times the upper limit of normal (ULN) (e.g., 2.5 times the ULN) and/or bilirubin levels greater than 1.5 or 2 times the ULN; and

administering a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to the subject in an amount effective to treat the disorder, to thereby treat the proliferative disorder.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker

shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the cancer is a cancer described herein. In one embodiment, the subject is selected for treatment with the CDP-taxane conjugate in combination with

one or more additional chemotherapeutic agent, e.g., a chemotherapeutic agent or combination of chemotherapeutic agents described herein.

In yet another aspect, the invention features a method of selecting a subject, e.g., a human, with a proliferative disorder, e.g., cancer, for treatment with a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate, and/or a CDP-cabazitaxel conjugate described herein, comprising:

determining if a subject has hepatic impairment, e.g., the subject has alkaline phosphatase (ALP), serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT) and/or bilirubin levels in a subject having a proliferative disorder; and

selecting a subject having hepatic impairment, e.g., a subject having ALP levels greater than 2.5 times the upper limit of normal (ULN), SGOT and/or SGPT levels greater than 1.5 times the upper limit of normal (ULN) and/or bilirubin levels greater than the ULN for treatment with a CDP-taxane conjugate, e.g., a CDP-taxane conjugate described herein.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the cancer is a cancer described herein. In one embodiment, the subject is selected for treatment with the CDP-taxane conjugate in combination with one or more additional chemotherapeutic agent, e.g., a chemotherapeutic agent or combination of chemotherapeutic agents described herein.

In yet another aspect, the invention features a method of treating a subject, e.g., a human, having a proliferative disorder, e.g., cancer, comprising:

selecting a subject with a proliferative disorder who has hepatic impairment, e.g., a subject who has alkaline phosphatase (ALP) levels greater than 2.5 times the upper limit of normal (ULN), serum glutamate oxaloacetate transaminase (SGOT) and/or serum glutamate pyruvate transaminase (SGPT) levels greater than 1.5 times the ULN and/or bilirubin levels greater than the ULN; and

administering a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, to the subject in an amount effective to treat the disorder, to thereby treat the proliferative disorder.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the cancer is a cancer described herein. In one embodiment, the subject is selected for treatment with the CDP-taxane conjugate in combination with one or more additional chemotherapeutic agent, e.g., a chemotherapeutic agent or combination of chemotherapeutic agents described herein.

In yet another aspect, the invention features a method of selecting a subject, e.g., a human, with a proliferative disorder, e.g., cancer, for treatment with a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, comprising:

determining if a subject having a proliferative disorder is currently being administered (e.g., the subject has been administered a cytochrome P450 isoenzyme inhibitor, e.g., a CYP3A4 inhibitor or a CYP2C8 inhibitor, the same day as chemotherapy treatment or within 1, 2, 3, 4, 5, 6, or 7 days before chemotherapy treatment) or will be

administered (e.g., will be administered on the same day as the chemotherapy treatment or within 1, 2, 3, 4, 5, 6, or 7 days after chemotherapy treatment) a cytochrome P450 isoenzyme inhibitor, e.g., CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, amprenavir, indinavir, nelfinavir, delavirdine or voriconazole) and/or a CYP2C8 inhibitor (e.g., quercetin); and

selecting a subject with a proliferative disorder, e.g., cancer, who is currently being administered or will be administered a cytochrome P450 isoenzyme, e.g., a CYP3A4 inhibitor and/or a CYP2C8 inhibitor, for treatment with a CDP-taxane conjugate, e.g., a CDP-taxane conjugate described herein, at a dose described herein.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the cancer is a cancer described herein. In one embodiment, the CDP-taxane conjugate is administered in combination with one or more additional chemotherapeutic agent, e.g., a chemotherapeutic agent or combination of chemotherapeutic agents described herein.

In another aspect, the invention features a method of treating a subject, e.g., a human, having a proliferative disorder, e.g., cancer, comprising:

selecting a subject with a proliferative disorder, e.g., cancer, who is currently being administered or will be, administered a cytochrome P450 isoenzyme, e.g., a CYP3A4 inhibitor and/or a CYP2C8 inhibitor;

administering a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate, described herein, to the subject at a dose described herein, to thereby treat the disorder.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-paclitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the cancer is a cancer described herein. In one embodiment, the CDP-taxane conjugate is administered in combination with one or more additional chemotherapeutic agent, e.g., a chemotherapeutic agent or combination of chemotherapeutic agents described herein.

In yet another aspect, the invention features a method of selecting a subject, e.g., a human, with a proliferative disorder, e.g., cancer, for treatment with a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate described herein, comprising:

determining if a subject having a proliferative disorder has or is at risk for having fluid retention and/or effusion and

selecting a subject with a proliferative disorder, e.g., cancer, who has or is at risk for having fluid retention, for treatment with a CDP-taxane conjugate, e.g., a CDP-taxane conjugate described herein, at a dose described herein.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an

embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the subject has one or more of the following symptoms of fluid retention: edema (e.g., peripheral, localized, generalized, lymphedema, pulmonary edema, or unspecified edema) and effusion (e.g., pleural, pericardial and ascites).

In one embodiment, the cancer is a cancer described herein. In one embodiment, the CDP-taxane conjugate is administered in combination with one or more additional chemotherapeutic agent, e.g., a chemotherapeutic agent or combination of chemotherapeutic agents described herein.

In another aspect, the invention features a method of treating a subject, e.g., a human, having a proliferative disorder, e.g., cancer, comprising:

selecting a subject with a proliferative disorder, e.g., cancer, who has or is at risk for having fluid retention;

administering a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate, described herein, to the subject at a dose described herein, to thereby treat the disorder.

In an embodiment, the CDP-taxane conjugate comprises taxane molecules (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel molecules), coupled, e.g., via a linker such as a linker described herein, to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate comprises a taxane (e.g., docetaxel, paclitaxel, larotaxel and/or cabazitaxel), coupled via a linker shown in Fig. 2 to a CDP moiety, e.g., a CDP described herein. In an embodiment, the CDP-taxane conjugate is a CDP-taxane conjugate shown in Fig. 2.

In one embodiment, the CDP-taxane conjugate is a CDP-docetaxel conjugate, e.g., a CDP-docetaxel conjugate described herein, e.g., a CDP-docetaxel conjugate comprising docetaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate comprises docetaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-docetaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-docetaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-larotaxel conjugate, e.g., a CDP-larotaxel conjugate described herein, e.g., a CDP-larotaxel conjugate comprising

larotaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate comprises larotaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-larotaxel conjugate is a CDP-larotaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-larotaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate comprises cabazitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-cabazitaxel conjugate is a CDP-cabazitaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate is a CDP-paclitaxel conjugate, e.g., a CDP-paclitaxel conjugate described herein, e.g., a CDP-paclitaxel conjugate comprising paclitaxel, coupled, e.g., via linkers, to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate comprises paclitaxel, coupled via a linker shown in Fig. 2 to a CDP described herein. In an embodiment, the CDP-paclitaxel conjugate is a CDP-docetaxel conjugate shown in Fig. 2.

In one embodiment, the CDP-paclitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the subject has one or more of the following symptoms of fluid retention: edema (e.g., peripheral, localized, generalized, lymphedema, pulmonary edema, or unspecified edema) and effusion (e.g., pleural, pericardial and ascites).

In one embodiment, the cancer is a cancer described herein. In one embodiment, the CDP-taxane conjugate is administered in combination with one or more additional chemotherapeutic agent, e.g., a chemotherapeutic agent or combination of chemotherapeutic agents described herein.

In another aspect, the disclosure features a method of selecting a subject, e.g., a human, with a proliferative disorder, e.g., cancer, for treatment treating the subject with a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate, described herein, comprising:

determining if a subject with a proliferative disorder, e.g., a cancer, is at risk for or has a gastrointestinal disorder, e.g., diarrhea, nausea and/or vomiting, or has experienced a gastrointestinal disorder (e.g., diarrhea, nausea and/or vomiting) from treatment with an anticancer agent, e.g., cabazitaxel, and

selecting a subject who is at risk for or has a gastrointestinal disorder (e.g., diarrhea, nausea and/or vomiting) or has experienced a gastrointestinal disorder (e.g., diarrhea, nausea and/or vomiting) from treatment with an anticancer agent (e.g., cabazitaxel) for treatment with a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate, described herein.

In one embodiment, the method further comprises administering a CDP-taxane conjugate to the subject.

In one embodiment, the polymer-anticancer agent conjugate, particle or composition is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., directly or via linkers, to a CDP described herein. In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate described herein e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate, described herein, is administered in combination with one or more of: an anti-diarrheal agent and an antiemetic. The anti-diarrheal agent can be, e.g., an opioid (e.g., codeine, oxicodeine, Percocet, paregoric, tincture of opium, diphenoxylate, or diflenoxin), loperamide, bismuth subsalicylate, lanreotide, vapreotide, motilin antagonists, COX2 inhibitors (e.g., celecoxib), glutamine, thalidomide, a kaolin agent, a pectin agent, a berberine agent, a muscarinic agent, octreotide or a DPP-IV inhibitor. The antiemetic can be, e.g., a 5HT3 receptor antagonist (dolasetron,

granisetron, ondansetron, tropisetron, palonosetron, and mirtazapine), a dopamine antagonist (e.g., domperidone, droperidol, haloperidol, chloropromazine, promethazine, prochlorperazine, metoclopramide, alizapride and prochlorperazine), a NK1 receptor antagonist (e.g., aprepitant and casopitant), a cannabinoid (e.g., cannabis, dronabinol, nabilone and sativex), benzodiazepine (e.g., midazolam and lorazepam), an anticholinergics (e.g., hyoscone) and other antiemetics (e.g., trimethobenzomide, emetrol, propofol and muscimol).

In another aspect, the disclosure features a method of selecting a subject, e.g., a human, with a proliferative disorder, e.g., cancer, for treatment treating the subject with a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate, described herein, comprising:

determining if a subject with a proliferative disorder, e.g., a cancer, is at risk for or has experienced renal failure, e.g., has one or more of sepsis, dehydration and obstructive uropathy, and

selecting a subject who is at risk for or has experienced renal failure for treatment with a CDP-taxane conjugate, e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate, described herein.

In one embodiment, the method further comprises administering a CDP-taxane conjugate to the subject.

In one embodiment, the CDP-taxane conjugate is a CDP-cabazitaxel conjugate, e.g., a CDP-cabazitaxel conjugate described herein, e.g., a CDP-cabazitaxel conjugate comprising cabazitaxel, coupled, e.g., directly or via linkers, to a CDP described herein. In one embodiment, the CDP-cabazitaxel conjugate is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-taxane conjugate described herein e.g., a CDP-docetaxel conjugate, a CDP-paclitaxel conjugate, a CDP-larotaxel conjugate and/or a CDP-cabazitaxel conjugate, described herein, is administered in combination with one or more of: an anti-diarrheal agent and an antiemetic. The anti-diarrheal agent can be, e.g., an opioid (e.g., codeine, oxicodeine, Percocet, paregoric, tincture of opium,

diphenoxylate, or diflenoxin), loperamide, bismuth subsalicylate, lanreotide, vapreotide, motilin antagonists, COX2 inhibitors (e.g., celecoxib), glutamine, thalidomide, a kaolin agent, a pectin agent, a berberine agent, a muscarinic agent, octreotide or a DPP-IV inhibitor. The antiemetic can be, e.g., one or more of a 5HT3 receptor antagonist (dolasetron, granisetron, ondansetron, tropisetron, palonosetron, and mirtazapine), a dopamine antagonist (e.g., domperidone, droperidol, haloperidol, chloropromazine, promethazine, prochlorperazine, metoclopramide, alizapride and prochlorperazine), a NK1 receptor antagonist (e.g., aprepitant and casopitant), a cannabinoid (e.g., cannabis, dronabinol, nabilone and sativex), benzodiazepine (e.g., midazolam and lorazepam), an anticholinergics (e.g., hyoscone) and other antiemetics (e.g., trimethobenzomide, emetrol, propofol and muscimol).

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and the drawings, and from the claims.

Brief Description of the Figures

Fig. 1 depicts a cyclodextrin containing polymer (CDP).

Fig. 2 depicts a table which shows exemplary CDP-taxane conjugates.

Detailed Description of the Invention

The present invention relates to novel compositions of therapeutic cyclodextrin-containing polymers conjugated to a taxane, particles containing therapeutic cyclodextrin-containing polymers conjugated to a taxane, compositions and mixtures comprising cyclodextran-containing polymers, and methods of use thereof. In certain embodiments, these cyclodextrin-containing polymers improve taxane stability and/or taxane solubility, and/or reduce taxane toxicity, and/or improve efficacy of the taxane when used *in vivo*.

By selecting from a variety of linker groups used to link a taxane to a CDP, the rate of taxane release from the CDP can be attenuated for controlled delivery. The

invention also relates to methods of treating subjects, e.g., humans, with a CDP-taxane conjugate described herein. The invention further relates to methods for conducting a pharmaceutical business comprising manufacturing, licensing, or distributing kits containing or relating to the CDP-taxane conjugates described herein.

More generally, the present invention provides water-soluble, biocompatible polymer conjugates comprising a water-soluble, biocompatible cyclodextrin containing polymer covalently attached to a taxane through attachments that are cleaved under biological conditions to release the taxane.

Polymeric conjugates featured in the present invention may be useful to improve solubility and/or stability of a bioactive/therapeutic agent, such as taxane, reduce drug-drug interactions, reduce interactions with blood elements including plasma proteins, reduce or eliminate immunogenicity, protect the agent from metabolism, modulate drug-release kinetics, improve circulation time, improve drug half-life (e.g., in the serum, or in selected tissues, such as tumors), attenuate toxicity, improve efficacy, normalize drug metabolism across subjects of different species, ethnicities, and/or races, and/or provide for targeted delivery into specific cells or tissues. Poorly soluble and/or toxic compounds may benefit particularly from incorporation into polymeric compounds of the invention.

An "effective amount" or "an amount effective" refers to an amount of the CDP-taxane conjugate which is effective, upon single or multiple dose administrations to a subject, in treating a cell, or curing, alleviating, relieving or improving a symptom of a disorder. An effective amount of the composition may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the compound to elicit a desired response in the individual. An effective amount is also one in which any toxic or detrimental effects of the composition is outweighed by the therapeutically beneficial effects.

"Pharmaceutically acceptable carrier or adjuvant," as used herein, refers to a carrier or adjuvant that may be administered to a patient, together with a CDP-taxane conjugate described herein, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the particle. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose, mannitol and sucrose;

(2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical compositions.

As used herein the term "low aqueous solubility" refers to water insoluble compounds having poor solubility in water, that is <5 mg/ml at physiological pH (6.5-7.4). Preferably, their water solubility is <1 mg/ml, more preferably <0.1 mg/ml. It is desirable that the drug is stable in water as a dispersion; otherwise a lyophilized or spray-dried solid form may be desirable.

As used herein, the term "prevent" or "preventing" as used in the context of the administration of an agent to a subject, refers to subjecting the subject to a regimen, e.g., the administration of a CDP-taxane conjugate such that the onset of at least one symptom of the disorder is delayed as compared to what would be seen in the absence of the regimen.

As used herein, the term "subject" is intended to include human and non-human animals. Exemplary human subjects include a human patient having a disorder, e.g., a disorder described herein, or a normal subject. The term "non-human animals" includes all vertebrates, e.g., non-mammals (such as chickens, amphibians, reptiles) and mammals, such as non-human primates, domesticated and/or agriculturally useful animals, e.g., sheep, dog, cat, cow, pig, etc.

As used herein, the term "treat" or "treating" a subject having a disorder refers to subjecting the subject to a regimen, e.g., the administration of a CDP-taxane conjugate such that at least one symptom of the disorder is cured, healed, alleviated, relieved, altered, remedied, ameliorated, or improved. Treating includes administering an amount effective to alleviate, relieve, alter, remedy, ameliorate, improve or affect the disorder or

the symptoms of the disorder. The treatment may inhibit deterioration or worsening of a symptom of a disorder.

The term “alkenyl” refers to an aliphatic group containing at least one double bond.

The terms "alkoxyl" or "alkoxy" refers to an alkyl group, as defined below, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. An "ether" is two hydrocarbons covalently linked by an oxygen.

The term "alkyl" refers to the radical of saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl-substituted cycloalkyl groups, and cycloalkyl-substituted alkyl groups. In preferred embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C_1-C_{30} for straight chains, C_3-C_{30} for branched chains), and more preferably 20 or fewer, and most preferably 10 or fewer. Likewise, preferred cycloalkyls have from 3-10 carbon atoms in their ring structure, and more preferably have 5, 6 or 7 carbons in the ring structure.

The term “alkynyl” refers to an aliphatic group containing at least one triple bond.

The term "aralkyl" or “arylalkyl” refers to an alkyl group substituted with an aryl group (e.g., a phenyl or naphthyl).

The term "aryl" includes 5-14 membered single-ring or bicyclic aromatic groups, for example, benzene, naphthalene, and the like. The aromatic ring can be substituted at one or more ring positions with such substituents as described above, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, polycyclyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphate, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, -CF_3, -CN, or the like. The term “aryl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls,

cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls. Each ring can contain, e.g., 5-7 members. The term "arylene" refers to a divalent aryl, as defined herein.

The term "arylalkenyl" refers to an alkenyl group substituted with an aryl group.

The terms "halo" and "halogen" means halogen and includes chloro, fluoro, bromo, and iodo.

The terms "hetaralkyl", "heteroaralkyl" or "heteroarylalkyl" refers to an alkyl group substituted with a heteroaryl group.

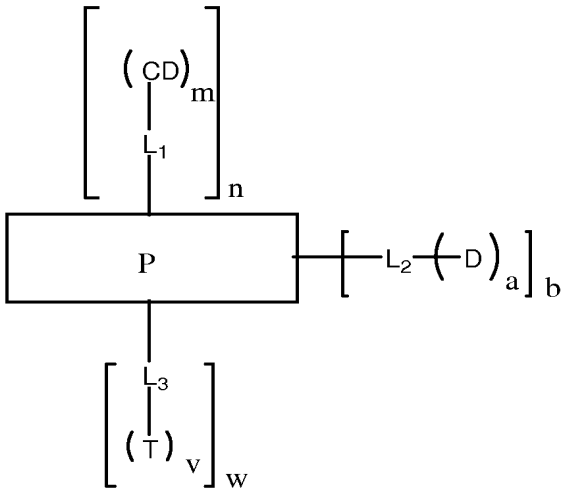
The term "heteroaryl" refers to an aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2, 3, or 4 atoms of each ring may be substituted by a substituent. Examples of heteroaryl groups include pyridyl, furyl or furanyl, imidazolyl, benzimidazolyl, pyrimidinyl, thiophenyl or thienyl, quinolinyl, indolyl, thiazolyl, and the like. The term "heteroarylene" refers to a divalent heteroaryl, as defined herein.

The term "heteroarylalkenyl" refers to an alkenyl group substituted with a heteroaryl group.

CDP-Taxane conjugates

Described herein are cyclodextrin containing polymer ("CDP")-taxane conjugates, wherein one or more taxane are covalently attached to the CDP (e.g., either directly or through a linker). The CDP-taxane conjugates include linear or branched cyclodextrin-containing polymers and polymers grafted with cyclodextrin. Exemplary cyclodextrin-containing polymers that may be modified as described herein are taught in U.S. Patent Nos. 7,270,808, 6,509,323, 7,091,192, 6,884,789, U.S. Publication Nos. 20040087024, 20040109888 and 20070025952.

Accordingly, in one embodiment the CDP-taxane conjugate is represented by Formula I:



(I)

wherein

P represents a linear or branched polymer chain;

CD represents a cyclic moiety such as a cyclodextrin moiety;

L_1, L_2 and L_3, independently for each occurrence, may be absent or represent a linker group;

D, independently for each occurrence, represents a taxane or a prodrug thereof;

T, independently for each occurrence, represents a targeting ligand or precursor thereof;

a, m, and v, independently for each occurrence, represent integers in the range of 1 to 10 (preferably 1 to 8, 1 to 5, or even 1 to 3);

n and w, independently for each occurrence, represent an integer in the range of 0 to about 30,000 (preferably <25,000, <20,000, <15,000, <10,000, <5,000, <1,000, <500, <100, <50, <25, <10, or even <5); and

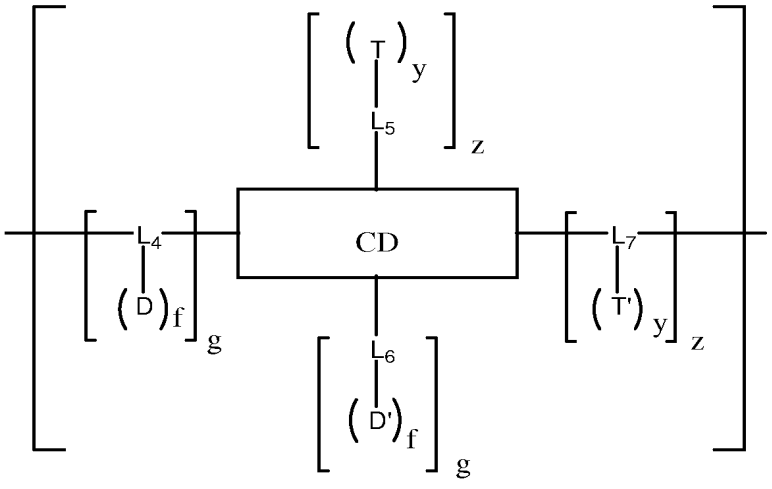
b represents an integer in the range of 1 to about 30,000 (preferably <25,000, <20,000, <15,000, <10,000, <5,000, <1,000, <500, <100, <50, <25, <10, or even <5),

wherein either P comprises cyclodextrin moieties or n is at least 1.

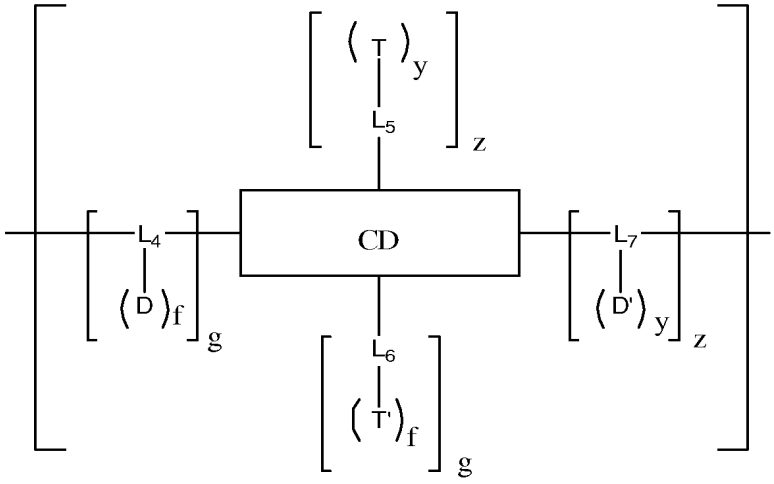
In some embodiments, one or more of the taxane moieties in the CDP-taxane conjugate can be replaced with another therapeutic agent, e.g., another anticancer agent

or anti-inflammatory agent. Examples of other anticancer agents are described herein. Examples of anti-inflammatory agents include a steroid, e.g., prednisone, and a NSAID.

In certain embodiments, P contains a plurality of cyclodextrin moieties within the polymer chain as opposed to the cyclodextrin moieties being grafted on to pendant groups off of the polymeric chain. Thus in certain embodiments, the polymer chain of formula I further comprises n' units of U, wherein n' represents an integer in the range of 1 to about 30,000, e.g., from 4-100, 4-50, 4-25, 4-15, 6-100, 6-50, 6-25, and 6-15 (preferably <25,000, <20,000, <15,000, <10,000, <5,000, <1,000, <500, <100, <50, <25, <20, <15, <10, or even <5); and U is represented by one of the general formulae below:



or



wherein

CD represents a cyclic moiety, such as a cyclodextrin moiety, or derivative thereof;

L_4, L_5, L_6, and L_7, independently for each occurrence, may be absent or represent a linker group;

D and D', independently for each occurrence, represent the same or different taxane or prodrug forms thereof;

T and T', independently for each occurrence, represent the same or different targeting ligand or precursor thereof;

f and y, independently for each occurrence, represent an integer in the range of 1 and 10; and

g and z, independently for each occurrence, represent an integer in the range of 0 and 10.

Preferably the polymer has a plurality of D or D' moieties. In some embodiments, at least 50% of the U units have at least one D or D'. In some embodiments, one or more of the taxane moieties in the CDP-taxane conjugate can be replaced with another therapeutic agent, e.g., another anticancer agent or anti-inflammatory agent.

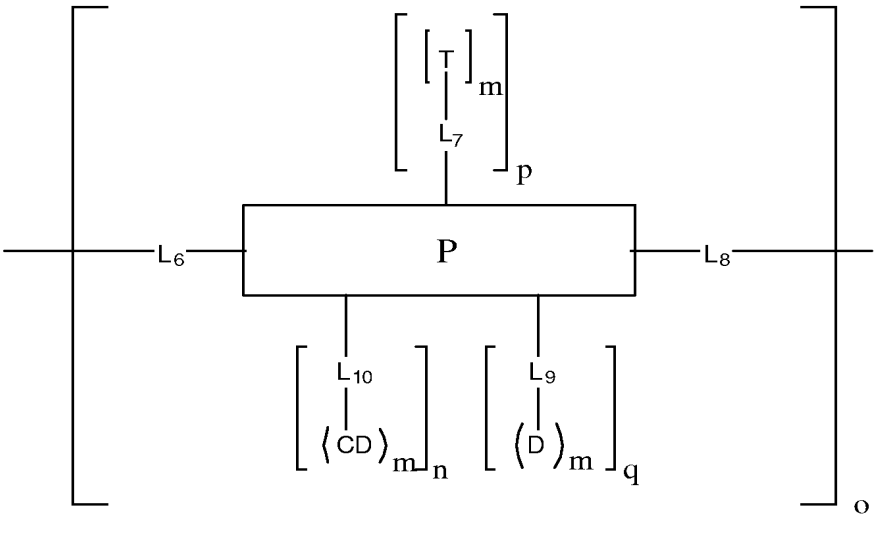
In preferred embodiments, L_4 and L_7 represent linker groups.

The CDP may include a polycation, polyanion, or non-ionic polymer. A polycationic or polyanionic polymer has at least one site that bears a positive or negative charge, respectively. In certain such embodiments, at least one of the linker moiety and the cyclic moiety comprises such a charged site, so that every occurrence of that moiety includes a charged site. In some embodiments, the CDP is biocompatible.

In certain embodiments, the CDP may include polysaccharides, and other non-protein biocompatible polymers, and combinations thereof, that contain at least one terminal hydroxyl group, such as polyvinylpyrrollidone, poly(oxyethylene)glycol (PEG), polysuccinic anhydride, polysebacic acid, PEG-phosphate, polyglutamate, polyethylenimine, maleic anhydride divinylether (DIVMA), cellulose, pullulans, inulin, polyvinyl alcohol (PVA), N-(2-hydroxypropyl)methacrylamide (HPMA), dextran and hydroxyethyl starch (HES), and have optional pendant groups for grafting therapeutic

agents, targeting ligands and/or cyclodextrin moieties. In certain embodiments, the polymer may be biodegradable such as poly(lactic acid), poly(glycolic acid), poly(alkyl 2-cyanoacrylates), polyanhydrides, and polyorthoesters, or bioerodible such as polylactide-glycolide copolymers, and derivatives thereof, non-peptide polyaminoacids, polyiminocarbonates, poly alpha-amino acids, polyalkyl-cyano-acrylate, polyphosphazenes or acyloxymethyl poly aspartate and polyglutamate *c*opolymers and mixtures thereof.

In another embodiment the CDP-taxane conjugate is represented by Formula II:



(II)

wherein

P represents a monomer unit of a polymer that comprises cyclodextrin moieties;

T, independently for each occurrence, represents a targeting ligand or a precursor thereof;

L_6, L_7, L_8, L_9, and L_{10}, independently for each occurrence, may be absent or represent a linker group;

CD, independently for each occurrence, represents a cyclodextrin moiety or a derivative thereof;

D, independently for each occurrence, represents a taxane or a prodrug form thereof;

m, independently for each occurrence, represents an integer in the range of 1 to 10 (preferably 1 to 8, 1 to 5, or even 1 to 3);

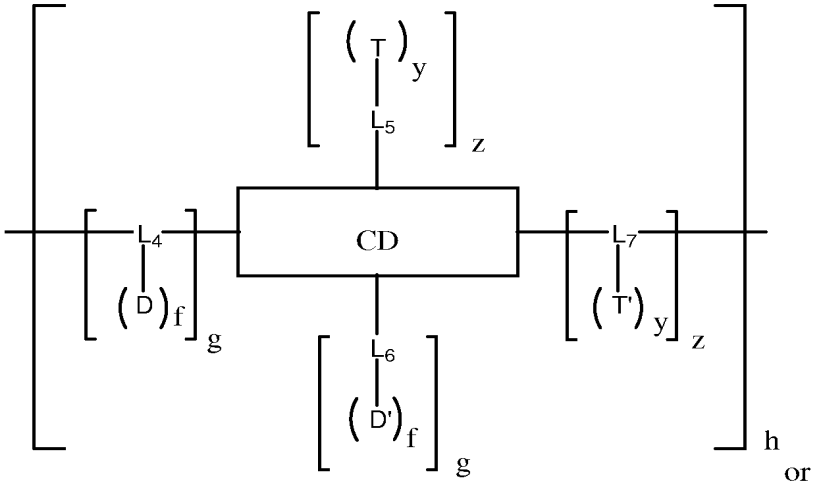
o represents an integer in the range of 1 to about 30,000 (preferably <25,000, <20,000, <15,000, <10,000, <5,000, <1,000, <500, <100, <50, <25, <10, or even <5); and

p, n, and q, independently for each occurrence, represent an integer in the range of 0 to 10 (preferably 0 to 8, 0 to 5, 0 to 3, or even 0 to about 2),

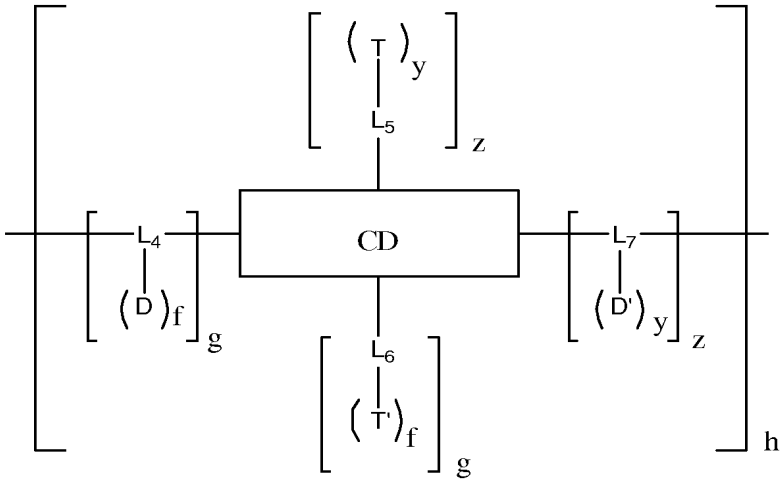
wherein CD and D are preferably each present at least 1 location (preferably at least 5, 10, 25, or even 50 or 100 locations) in the compound.

In some embodiments, one or more of the taxane moieties in the CDP-taxane conjugate can be replaced with another therapeutic agent, e.g., another anticancer agent or anti-inflammatory agent. Examples of an anticancer agent are described herein. Examples of anti-inflammatory agents include a steroid, e.g., prednisone, or a NSAID.

In another embodiment the CDP-taxane conjugate is represented either of the formulae below:



or



wherein

CD represents a cyclic moiety, such as a cyclodextrin moiety, or derivative thereof;

L_4, L_5, L_6, and L_7, independently for each occurrence, may be absent or represent a linker group;

D and D', independently for each occurrence, represent the same or different taxane or prodrug thereof;

T and T', independently for each occurrence, represent the same or different targeting ligand or precursor thereof;

f and y, independently for each occurrence, represent an integer in the range of 1 and 10 (preferably 1 to 8, 1 to 5, or even 1 to 3);

g and z, independently for each occurrence, represent an integer in the range of 0 and 10 (preferably 0 to 8, 0 to 5, 0 to 3, or even 0 to about 2); and

h represents an integer in the range of 1 and 30,000 , e.g., from 4-100, 4-50, 4-25, 4-15, 6-100, 6-50, 6-25, and 6-15 (preferably <25,000, <20,000, <15,000, <10,000, <5,000, <1,000, <500, <100, <50, <25, <20, <15, <10, or even <5),

wherein at least one occurrence (and preferably at least 5, 10, or even at least 20, 50, or 100 occurrences) of g represents an integer greater than 0.

Preferably the polymer has a plurality of D or D' moieties. In some embodiments, at least 50% of the polymer repeating units have at least one D or D'. In some embodiments, one or more of the taxane moieties in the CDP-taxane conjugate can

be replaced with another therapeutic agent, e.g., another anticancer agent or anti-inflammatory agent.

In preferred embodiments, L4 and L7 represent linker groups.

In certain such embodiments, the CDP comprises cyclic moieties alternating with linker moieties that connect the cyclic structures, e.g., into linear or branched polymers, preferably linear polymers. The cyclic moieties may be any suitable cyclic structures, such as cyclodextrins, crown ethers (e.g., 18-crown-6, 15-crown-5, 12-crown-4, etc.), cyclic oligopeptides (e.g., comprising from 5 to 10 amino acid residues), cryptands or cryptates (e.g., cryptand [2.2.2], cryptand-2,1,1, and complexes thereof), calixarenes, or cavitands, or any combination thereof. Preferably, the cyclic structure is (or is modified to be) water-soluble. In certain embodiments, e.g., for the preparation of a linear polymer, the cyclic structure is selected such that under polymerization conditions, exactly two moieties of each cyclic structure are reactive with the linker moieties, such that the resulting polymer comprises (or consists essentially of) an alternating series of cyclic moieties and linker moieties, such as at least four of each type of moiety. Suitable difunctionalized cyclic moieties include many that are commercially available and/or amenable to preparation using published protocols. In certain embodiments, conjugates are soluble in water to a concentration of at least 0.1 g/mL, preferably at least 0.25 g/mL.

Thus, in certain embodiments, the invention relates to novel compositions of therapeutic cyclodextrin-containing polymeric compounds designed for drug delivery of a taxane. In certain embodiments, these CDPs improve drug stability and/or solubility, and/or reduce toxicity, and/or improve efficacy of the taxane when used *in vivo*. Furthermore, by selecting from a variety of linker groups, and/or targeting ligands, the rate of taxane release from the CDP can be attenuated for controlled delivery.

In certain embodiments, the CDP comprises a linear cyclodextrin-containing polymer, e.g., the polymer backbone includes cyclodextrin moieties. For example, the polymer may be a water-soluble, linear cyclodextrin polymer produced by providing at least one cyclodextrin derivative modified to bear one reactive site at each of exactly two positions, and reacting the cyclodextrin derivative with a linker having exactly two reactive moieties capable of forming a covalent bond with the reactive sites under polymerization conditions that promote reaction of the reactive sites with the reactive

moieties to form covalent bonds between the linker and the cyclodextrin derivative, whereby a linear polymer comprising alternating units of cyclodextrin derivatives and linkers is produced. Alternatively the polymer may be a water-soluble, linear cyclodextrin polymer having a linear polymer backbone, which polymer comprises a plurality of substituted or unsubstituted cyclodextrin moieties and linker moieties in the linear polymer backbone, wherein each of the cyclodextrin moieties, other than a cyclodextrin moiety at the terminus of a polymer chain, is attached to two of said linker moieties, each linker moiety covalently linking two cyclodextrin moieties. In yet another embodiment, the polymer is a water-soluble, linear cyclodextrin polymer comprising a plurality of cyclodextrin moieties covalently linked together by a plurality of linker moieties, wherein each cyclodextrin moiety, other than a cyclodextrin moiety at the terminus of a polymer chain, is attached to two linker moieties to form a linear cyclodextrin polymer.

Described herein are CDP-taxane conjugates, wherein one or more taxane is covalently attached to the CDP. The CDP can include linear or branched cyclodextrin-containing polymers and/or polymers grafted with cyclodextrin. Exemplary cyclodextrin-containing polymers that may be modified as described herein are taught in U.S. Patent Nos. 7,270,808, 6,509,323, 7,091,192, 6,884,789, U.S. Publication Nos. 20040087024, 20040109888 and 20070025952, which are incorporated herein by reference in their entirety.

In some embodiments, the CDP-taxane conjugate comprises a water soluble linear polymer conjugate comprising: cyclodextrin moieties; comonomers which do not contain cyclodextrin moieties (comonomers); and a plurality of taxanes; wherein the CDP-taxane conjugate comprises at least four, five six, seven, eight, etc., cyclodextrin moieties and at least four, five six, seven, eight, or more, comonomers. In some embodiments, the taxane is a taxane described herein, for example, the taxane is docetaxel, paclitaxel, larotaxel and/or cabazitaxel. The taxane can be attached to the CDP via a functional group such as a hydroxyl group, or where appropriate, an amino group.

In some embodiments, one or more of the taxane moieties in the CDP-taxane conjugate can be replaced with another therapeutic agent, e.g., another anticancer agent or anti-inflammatory agent.

In some embodiments, the least four cyclodextrin moieties and at least four comonomers alternate in the CDP-taxane conjugate. In some embodiments, said taxanes are cleaved from said CDP-taxane conjugate under biological conditions to release taxane. In some embodiments, the cyclodextrin moieties comprise linkers to which taxanes are linked. In some embodiments, the taxanes are attached via linkers.

In some embodiments, the comonomer comprises residues of at least two functional groups through which reaction and linkage of the cyclodextrin monomers was achieved. In some embodiments, the functional groups, which may be the same or different, terminal or internal, of each comonomer comprise an amino, acid, imidazole, hydroxyl, thio, acyl halide, -HC=CH-, —C≡C— group, or derivative thereof. In some embodiments, the two functional groups are the same and are located at termini of the comonomer precursor. In some embodiments, a comonomer contains one or more pendant groups with at least one functional group through which reaction and thus linkage of a taxane was achieved. In some embodiments, the functional groups, which may be the same or different, terminal or internal, of each comonomer pendant group comprise an amino, acid, imidazole, hydroxyl, thiol, acyl halide, ethylene, ethyne group, or derivative thereof. In some embodiments, the pendant group is a substituted or unsubstituted branched, cyclic or straight chain C_1-C_{10} alkyl, or arylalkyl optionally containing one or more heteroatoms within the chain or ring. In some embodiments, the cyclodextrin moiety comprises an alpha, beta, or gamma cyclodextrin moiety. In some embodiments, at least about 50% of available positions on the CDP are reacted with a taxane and/or a linker taxane (e.g., at least about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%). In some embodiments, the taxane is at least 5%, 10%, 15%, 20%, 25%, 30%, or 35% by weight of CDP-taxane conjugate.

In some embodiments, the comonomer comprises polyethylene glycol of molecular weight 3,400 Da, the cyclodextrin moiety comprises beta-cyclodextrin, the theoretical maximum loading of the taxane on the CDP-taxane conjugate is about 25% by weight, and the taxane is about 17-21% by weight of CDP-taxane conjugate. In some embodiments, the taxane is poorly soluble in water. In some embodiments, the solubility of the taxane is <5 mg/ml at physiological pH. In some embodiments, the taxane is a hydrophobic compound with a log P>0.4, >0.6, >0.8, >1, >2, >3, >4, or >5.

In some embodiments, the taxane is attached to the CDP via a second compound.

In some embodiments, administration of the CDP-taxane conjugate to a subject results in release of the taxane over a period of at least 6 hours. In some embodiments, administration of the CDP-taxane conjugate to a subject results in release of the taxane over a period of 2 hours, 3 hours, 5 hours, 6 hours, 8 hours, 10 hours, 15 hours, 20 hours, 1 day, 2 days, 3 days, 4 days, 7 days, 10 days, 14 days, 17 days, 20 days, 24 days, 27 days up to a month. In some embodiments, upon administration of the CDP-taxane conjugate to a subject the rate of taxane release is dependent primarily upon the rate of hydrolysis as opposed to enzymatic cleavage.

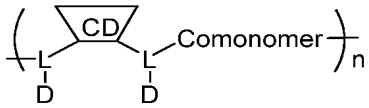
In some embodiments, the CDP-taxane conjugate has a molecular weight of 10,000-500,000. In some embodiments, the cyclodextrin moieties make up at least about 2%, 5%, 10%, 20%, 30%, 50% or 80% of the CDP-taxane conjugate by weight.

In some embodiments, the CDP-taxane conjugate is made by a method comprising providing cyclodextrin moiety precursors modified to bear one reactive site at each of exactly two positions, and reacting the cyclodextrin moiety precursors with comonomer precursors having exactly two reactive moieties capable of forming a covalent bond with the reactive sites under polymerization conditions that promote reaction of the reactive sites with the reactive moieties to form covalent bonds between the comonomers and the cyclodextrin moieties, whereby a CDP comprising alternating units of a cyclodextrin moiety and a comonomer is produced. In some embodiments, the cyclodextrin moiety precursors are in a composition, the composition being substantially free of cyclodextrin moieties having other than two positions modified to bear a reactive site (e.g., cyclodextrin moieties having 1, 3, 4, 5, 6, or 7 positions modified to bear a reactive site).

In some embodiments, a comonomer of the CDP-taxane conjugate comprises a moiety selected from the group consisting of: an alkylene chain, polysuccinic anhydride, poly-L-glutamic acid, poly(ethyleneimine), an oligosaccharide, and an amino acid chain. In some embodiments, a CDP-taxane conjugate comonomer comprises a polyethylene glycol chain. In some embodiments, a comonomer comprises a moiety selected from: polyglycolic acid and polylactic acid chain. In some embodiments, a comonomer comprises a hydrocarbylene group wherein one or more methylene groups is optionally

replaced by a group Y (provided that none of the Y groups are adjacent to each other), wherein each Y, independently for each occurrence, is selected from, substituted or unsubstituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, or -O-, C(=X) (wherein X is NR_1, O or S), -OC(O)-, -C(=O)O, -NR_1-, -NR_1CO-, -C(O)NR_1-, -$S(O)_n$- (wherein n is 0, 1, or 2), -OC(O)-NR_1, -NR_1-C(O)-NR_1-, -$NR_1$1-C(NR_1)-NR_1-, and -$B(OR_1)$-; and R_1, independently for each occurrence, represents H or a lower alkyl.

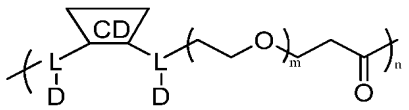
In some embodiments, the CDP-taxane conjugate is a polymer having attached thereto a plurality of D moieties of the following formula:



wherein each L is independently a linker, and each D is independently a taxane, a prodrug derivative thereof, or absent; and each comonomer is independently a comonomer described herein, and n is at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20, provided that the polymer comprises at least one taxane and in some embodiments, at least two taxane moieties. In some embodiments, the molecular weight of the comonomer is from about 2000 to about 5000 Da (e.g., from about 2000 to about 4500, from about 3000 to about 4000 Da, or less than about 4000, (e.g., about 3400 Da)).

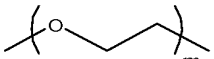
In some embodiments, the taxane is a taxane described herein, for example, the taxane is docetaxel, paclitaxel, larotaxel or cabazitaxel. The taxane can be attached to the CDP via a functional group such as a hydroxyl group, or where appropriate, an amino group. In some embodiments, one or more of the taxane moieties in the CDP-taxane conjugate can be replaced with another therapeutic agent, e.g., another anticancer agent or anti-inflammatory agent.

In some embodiments, the CDP-taxane conjugate is a polymer having attached thereto a plurality of D moieties of the following formula:



wherein each L is independently a linker, and each D is independently a taxane, a prodrug derivative thereof, or absent, provided that the polymer comprises at least one

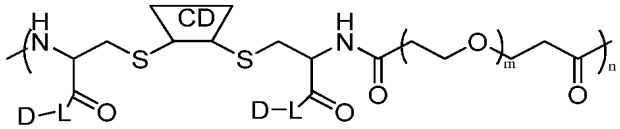
taxane and in some embodiments, at least two taxane moieties (e.g., at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more); and

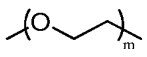
wherein the group  has a Mw of 4.0 kDa or less, e.g., 3.2 to 3.8 kDa, e.g., 3.4 kDa and n is at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

In some embodiments, the taxane is a taxane described herein, for example, the taxane is docetaxel, paclitaxel, larotaxel or cabazitaxel. The taxane can be attached to the CDP via a functional group such as a hydroxyl group, or where appropriate, an amino group. In some embodiments, one or more of the taxane moieties in the CDP-taxane conjugate can be replaced with another therapeutic agent, e.g., another anticancer agent or anti-inflammatory agent.

In some embodiments, less than all of the L moieties are attached to D moieties, meaning in some embodiments, at least one D is absent. In some embodiments, the loading of the D moieties on the CDP-taxane conjugate is from about 1 to about 50% (e.g., from about 1 to about 25%, from about 5 to about 20% or from about 5 to about 15%). In some embodiments, each L independently comprises an amino acid or a derivative thereof. In some embodiments, each L independently comprises a plurality of amino acids or derivatives thereof. In some embodiments, each L is independently a dipeptide or derivative thereof.

In some embodiments, the CDP-taxane conjugate is a polymer having attached thereto a plurality of L-D moieties of the following formula:



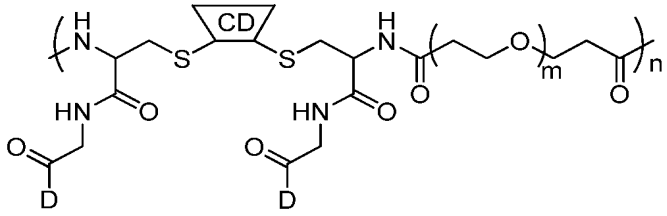
wherein each L is independently a linker or absent and each D is independently a taxane, a prodrug derivative thereof, or absent and wherein the group  has a Mw of 4.0 kDa or less, e.g., 3.2 to 3.8 kDa, e.g., 3.4 kDa and n is at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20, provided that the polymer comprises at least one taxane and in some embodiments, at least two taxane moieties (e.g., at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more).

In some embodiments, the taxane is a taxane described herein, for example, the taxane is docetaxel, paclitaxel, larotaxel or cabazitaxel.

In some embodiments, less than all of the C(=O) moieties are attached to L-D moieties, meaning in some embodiments, at least one L and/or D is absent. In some embodiments, the loading of the L, D and/or L-D moieties on the CDP-taxane conjugate is from about 1 to about 50% (e.g., from about 1 to about 25%, from about 5 to about 20% or from about 5 to about 15%). In some embodiments, each L is independently an amino acid or derivative thereof. In some embodiments, each L is glycine or a derivative thereof.

In some embodiments, one or more of the taxane moieties in the CDP-taxane conjugate can be replaced with another therapeutic agent, e.g., another anticancer agent or anti-inflammatory agent.

In some embodiments, the CDP-taxane conjugate is a polymer having the following formula:



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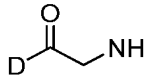
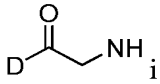
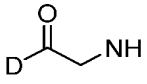
In some embodiments, less than all of the C(=O) moieties are attached to  moieties, meaning in some embodiments,  is absent, provided that the polymer comprises at least one taxane and in some embodiments, at least two taxane moieties (e.g., at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more).

In some embodiments, the loading of the  moieties on the CDP-taxane conjugate is from about 1 to about 50% (e.g., from about 1 to about 25%, from about 5 to about 25% or from about 15 to about 15%).

In some embodiments, the taxane is a taxane described herein, for example, the taxane is docetaxel, paclitaxel, larotaxel or cabazitaxel.

In some embodiments, one or more of the taxane moieties in the CDP-taxane conjugate can be replaced with another therapeutic agent, e.g., another anticancer agent or anti-inflammatory agent.

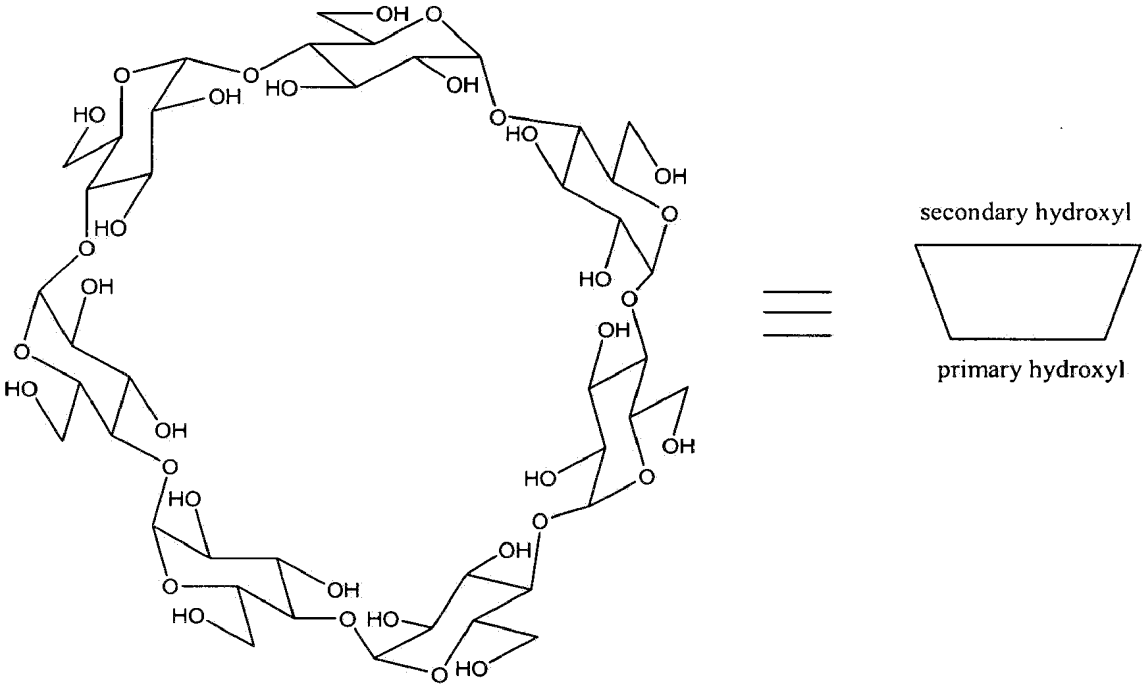
In some embodiments, the CDP-taxane conjugate will contain a taxane and at least one additional therapeutic agent. For instance, a taxane and one more different cancer drugs, an immunosuppressant, an antibiotic or an anti-inflammatory agent may be grafted on to the polymer via optional linkers. By selecting different linkers for different drugs, the release of each drug may be attenuated to achieve maximal dosage and efficacy.

Cyclodextrins

In certain embodiments, the cyclodextrin moieties make up at least about 2%, 5% or 10% by weight, up to 20%, 30%, 50% or even 80% of the CDP by weight. In certain embodiments, the taxanes, or targeting ligands make up at least about 1%, 5%, 10% or 15%, 20%, 25%, 30% or even 35% of the CDP by weight. Number-average molecular weight (M_n) may also vary widely, but generally fall in the range of about 1,000 to about 500,000 daltons, preferably from about 5000 to about 200,000 daltons and, even more preferably, from about 10,000 to about 100,000. Most preferably, M_n varies between about 12,000 and 65,000 daltons. In certain other embodiments, M_n varies between about 3000 and 150,000 daltons. Within a given sample of a subject polymer, a wide range of molecular weights may be present. For example, molecules within the sample may have molecular weights that differ by a factor of 2, 5, 10, 20, 50, 100, or more, or that differ from the average molecular weight by a factor of 2, 5, 10, 20, 50, 100, or more. Exemplary cyclodextrin moieties include cyclic structures consisting essentially of from 7 to 9 saccharide moieties, such as cyclodextrin and oxidized cyclodextrin. A cyclodextrin moiety optionally comprises a linker moiety that forms a covalent linkage between the cyclic structure and the polymer backbone, preferably having from 1 to 20 atoms in the chain, such as alkyl chains, including dicarboxylic acid derivatives (such as glutaric acid derivatives, succinic acid derivatives, and the like), and heteroalkyl chains, such as oligoethylene glycol chains.

Cyclodextrins are cyclic polysaccharides containing naturally occurring D-(+)-glucopyranose units in an α-(1,4) linkage. The most common cyclodextrins are alpha

((α)-cyclodextrins, beta (β)-cyclodextrins and gamma (γ)-cyclodextrins which contain, respectively six, seven, or eight glucopyranose units. Structurally, the cyclic nature of a cyclodextrin forms a torus or donut-like shape having an inner apolar or hydrophobic cavity, the secondary hydroxyl groups situated on one side of the cyclodextrin torus and the primary hydroxyl groups situated on the other. Thus, using (β)-cyclodextrin as an example, a cyclodextrin is often represented schematically as follows.



The side on which the secondary hydroxyl groups are located has a wider diameter than the side on which the primary hydroxyl groups are located. The present invention contemplates covalent linkages to cyclodextrin moieties on the primary and/or secondary hydroxyl groups. The hydrophobic nature of the cyclodextrin inner cavity allows for host-guest inclusion complexes of a variety of compounds, e.g., adamantane. (Comprehensive Supramolecular Chemistry, Volume 3, J.L. Atwood et al., eds., Pergamon Press (1996); T. Cserhati, Analytical Biochemistry, 225:328-332(1995); Husain et al., Applied Spectroscopy, 46:652-658 (1992); FR 2 665 169). Additional

methods for modifying polymers are disclosed in Suh, J. and Noh, Y., *Bioorg. Med. Chem. Lett.* 1998, *8*, 1327-1330.

In certain embodiments, the compounds comprise cyclodextrin moieties and wherein at least one or a plurality of the cyclodextrin moieties of the CDP-taxane conjugate is oxidized. In certain embodiments, the cyclodextrin moieties of P alternate with linker moieties in the polymer chain.

Comonomers

In addition to a cyclodextrin moiety, the CDP can also include a comonomer, for example, a comonomer described herein. In some embodiments, a comonomer of the CDP-taxane conjugate comprises a moiety selected from the group consisting of: an alkylene chain, polysuccinic anhydride, poly-L-glutamic acid, poly(ethyleneimine), an oligosaccharide, and an amino acid chain. In some embodiments, a CDP-taxane conjugate comonomer comprises a polyethylene glycol chain. In some embodiments, a comonomer comprises a moiety selected from: polyglycolic acid and polylactic acid chain. In some embodiments, a comonomer comprises a hydrocarbylene group wherein one or more methylene groups is optionally replaced by a group Y (provided that none of the Y groups are adjacent to each other), wherein each Y, independently for each occurrence, is selected from, substituted or unsubstituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, or -O-, C(=X) (wherein X is NR_1, O or S), -OC(O)-, -C(=O)O, -NR_1-, -NR_1CO-, -C(O)NR_1-, -$S(O)_n$- (wherein n is 0, 1, or 2), -OC(O)-NR_1, -NR_1-C(O)-NR_1-, -$NR_1$1-C(NR_1)-NR_1-, and -B(OR_1)-; and R_1, independently for each occurrence, represents H or a lower alkyl.

In some embodiments, a comonomer can be and/or can comprise a linker such as a linker described herein.

Linkers/tethers

The CDPs described herein can include one or more linkers. In some embodiments, a linker, such as a linker described herein, can link a cyclodextrin moiety to a comonomer. In some embodiments, a linker can link a taxane to a CDP. In some embodiments, for example, when referring to a linker that links a taxane to the CDP, the linker can be referred to as a tether.

In certain embodiments, a plurality of the linker moieties are attached to a taxane or prodrug thereof and are cleaved under biological conditions.

Described herein are CDP-taxane conjugates that comprise a CDP covalently attached to taxanes through attachments that are cleaved under biological conditions to release the taxane. In certain embodiments, a CDP-taxane conjugate comprises a taxane covalently attached to a polymer, preferably a biocompatible polymer, through a tether, e.g., a linker, wherein the tether comprises a selectivity-determining moiety and a self-cyclizing moiety which are covalently attached to one another in the tether, e.g., between the polymer and the taxane.

In some embodiments, such taxanes are covalently attached to CDPs through functional groups comprising one or more heteroatoms, for example, hydroxy, thiol, carboxy, amino, and amide groups. Such groups may be covalently attached to the subject polymers through linker groups as described herein, for example, biocleavable linker groups, and/or through tethers, such as a tether comprising a selectivity-determining moiety and a self-cyclizing moiety which are covalently attached to one another.

In certain embodiments, the CDP-taxane conjugate comprises a taxane covalently attached to the CDP through a tether, wherein the tether comprises a self-cyclizing moiety. In some embodiments, the tether further comprises a selectivity-determining moiety. Thus, one aspect of the invention relates to a polymer conjugate comprising a therapeutic agent covalently attached to a polymer, preferably a biocompatible polymer, through a tether, wherein the tether comprises a selectivity-determining moiety and a self-cyclizing moiety which are covalently attached to one another.

In some embodiments, the selectivity-determining moiety is bonded to the self-cyclizing moiety between the self-cyclizing moiety and the CDP.

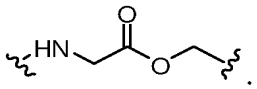
In certain embodiments, the selectivity-determining moiety is a moiety that promotes selectivity in the cleavage of the bond between the selectivity-determining moiety and the self-cyclizing moiety. Such a moiety may, for example, promote enzymatic cleavage between the selectivity-determining moiety and the self-cyclizing moiety. Alternatively, such a moiety may promote cleavage between the selectivity-

determining moiety and the self-cyclizing moiety under acidic conditions or basic conditions.

In certain embodiments, the invention contemplates any combination of the foregoing. Those skilled in the art will recognize that, for example, any CDP of the invention in combination with any linker (e.g., a linker described herein such as a self-cyclizing moiety, any selectivity-determining moiety, and/or any taxane) are within the scope of the invention.

In certain embodiments, the selectivity-determining moiety is selected such that the bond is cleaved under acidic conditions.

In certain embodiments where the selectivity-determining moiety is selected such that the bond is cleaved under basic conditions, the selectivity-determining moiety is an aminoalkylcarbonyloxyalkyl moiety. In certain embodiments, the selectivity-determining moiety has a structure

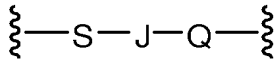


In certain embodiments where the selectivity-determining moiety is selected such that the bond is cleaved enzymatically, it may be selected such that a particular enzyme or class of enzymes cleaves the bond. In certain preferred such embodiments, the selectivity-determining moiety may be selected such that the bond is cleaved by a cathepsin, preferably cathepsin B.

In certain embodiments the selectivity-determining moiety comprises a peptide, preferably a dipeptide, tripeptide, or tetrapeptide. In certain such embodiments, the peptide is a dipeptide is selected from KF and FK, In certain embodiments, the peptide is a tripeptide is selected from GFA, GLA, AVA, GVA, GIA, GVL, GVF, and AVF. In certain embodiments, the peptide is a tetrapeptide selected from GFYA and GFLG, preferably GFLG.

In certain such embodiments, a peptide, such as GFLG, is selected such that the bond between the selectivity-determining moiety and the self-cyclizing moiety is cleaved by a cathepsin, preferably cathepsin B.

In certain embodiments, the selectivity-determining moiety is represented by Formula A:

 (A),

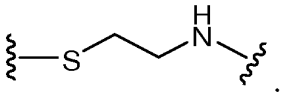
wherein

S a sulfur atom that is part of a disulfide bond;

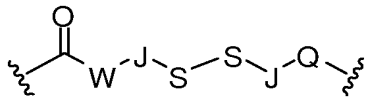
J is optionally substituted hydrocarbyl; and

Q is O or NR^{13}, wherein R^{13} is hydrogen or alkyl.

In certain embodiments, J may be polyethylene glycol, polyethylene, polyester, alkenyl, or alkyl. In certain embodiments, J may represent a hydrocarbylene group comprising one or more methylene groups, wherein one or more methylene groups is optionally replaced by a group Y (provided that none of the Y groups are adjacent to each other), wherein each Y, independently for each occurrence, is selected from, substituted or unsubstituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, or -O-, C(=X) (wherein X is NR^{30}, O or S), -OC(O)-, -C(=O)O, -NR^{30}-, -NR_1CO-, -$C(O)NR^{30}$-, -$S(O)_n$- (wherein n is 0, 1, or 2), -OC(O)-NR^{30}, -NR^{30}-C(O)-NR^{30}-, -NR^{30}-$C(NR^{30})$-NR^{30}-, and -$B(OR^{30})$-; and R^{30}, independently for each occurrence, represents H or a lower alkyl. In certain embodiments, J may be substituted or unsubstituted lower alkylene, such as ethylene.

For example, the selectivity-determining moiety may be  .

In certain embodiments, the selectivity-determining moiety is represented by Formula B:

 (B),

wherein

W is either a direct bond or selected from lower alkyl, NR^{14}, S, O;

S is sulfur;

J, independently and for each occurrence, is hydrocarbyl or polyethylene glycol;

Q is O or NR^{13}, wherein R^{13} is hydrogen or alkyl; and

R^{14} is selected from hydrogen and alkyl.

In certain such embodiments, J may be substituted or unsubstituted lower alkyl, such as methylene. In certain such embodiments, J may be an aryl ring. In certain embodiments, the aryl ring is a benzo ring. In certain embodiments W and S are in a 1,2-relationship on the aryl ring. In certain embodiments, the aryl ring may be optionally substituted with alkyl, alkenyl, alkoxy, aralkyl, aryl, heteroaryl, halogen, -CN, azido, -NR^xR^x, -CO_2OR^x, -C(O)-NR^xR^x, -C(O)-R^x, -NR^x-C(O)-R^x, -$NR^xSO_2R^x$, -SR^x, -S(O)R^x, -SO_2R^x, -$SO_2NR^xR^x$, -$(C(R^x)_2)_n$-OR^x, -$(C(R^x)_2)_n$-NR^xR^x, and -$(C(R^x)_2)_n$-SO_2R^x; wherein R^x is, independently for each occurrence, H or lower alkyl; and n is, independently for each occurrence, an integer from 0 to 2.

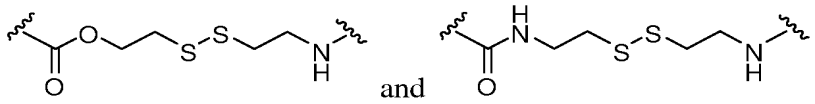
In certain embodiments, the aryl ring is optionally substituted with alkyl, alkenyl, alkoxy, aralkyl, aryl, heteroaryl, halogen, -CN, azido, -NR^xR^x, -CO_2OR^x, -C(O)-NR^xR^x, -C(O)-R^x, -NR^x-C(O)-R^x, -$NR^xSO_2R^x$, -SR^x, -S(O)R^x, -SO_2R^x, -$SO_2NR^xR^x$, -$(C(R^x)_2)_n$-OR^x, -$(C(R^x)_2)_n$-NR^xR^x, and -$(C(R^x)_2)_n$-SO_2R^x; wherein R^x is, independently for each occurrence, H or lower alkyl; and n is, independently for each occurrence, an integer from 0 to 2.

In certain embodiments, J, independently and for each occurrence, is polyethylene glycol, polyethylene, polyester, alkenyl, or alkyl.

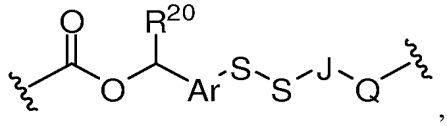
In certain embodiments, independently and for each occurrence, the linker comprises a hydrocarbylene group comprising one or more methylene groups, wherein one or more methylene groups is optionally replaced by a group Y (provided that none of the Y groups are adjacent to each other), wherein each Y, independently for each occurrence, is selected from, substituted or unsubstituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, or -O-, C(=X) (wherein X is NR^{30}, O or S), -OC(O)-, -C(=O)O, -NR^{30}-, -NR_1CO-, -C(O)NR^{30}-, -$S(O)_n$- (wherein n is 0, 1, or 2), -OC(O)-NR^{30}, -NR^{30}-C(O)-NR^{30}-, -NR^{30}-$C(NR^{30})$-NR^{30}-, and -$B(OR^{30})$-; and R^{30}, independently for each occurrence, represents H or a lower alkyl.

In certain embodiments, J, independently and for each occurrence, is substituted or unsubstituted lower alkylene. In certain embodiments, J, independently and for each occurrence, is substituted or unsubstituted ethylene.

In certain embodiments, the selectivity-determining moiety is selected from

 and .

The selectivity-determining moiety may include groups with bonds that are cleavable under certain conditions, such as disulfide groups. In certain embodiments, the selectivity-determining moiety comprises a disulfide-containing moiety, for example, comprising aryl and/or alkyl group(s) bonded to a disulfide group. In certain embodiments, the selectivity-determining moiety has a structure

 ,

wherein

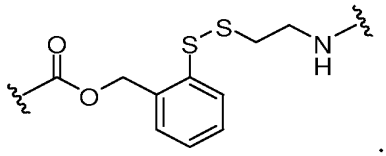
Ar is a substituted or unsubstituted benzo ring;

J is optionally substituted hydrocarbyl; and

Q is O or NR^{13},

wherein R^{13} is hydrogen or alkyl.

In certain embodiments, Ar is unsubstituted. In certain embodiments, Ar is a 1,2-benzo ring. For example, suitable moieties within Formula B include

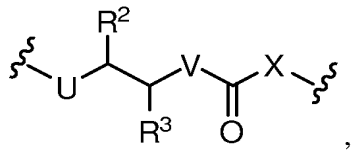
 .

In certain embodiments, the self-cyclizing moiety is selected such that upon cleavage of the bond between the selectivity-determining moiety and the self-cyclizing moiety, cyclization occurs thereby releasing the therapeutic agent. Such a cleavage-cyclization-release cascade may occur sequentially in discrete steps or substantially simultaneously. Thus, in certain embodiments, there may be a temporal and/or spatial difference between the cleavage and the self-cyclization. The rate of the self-cyclization cascade may depend on pH, e.g., a basic pH may increase the rate of self-cyclization after cleavage. Self-cyclization may have a half-life after introduction *in vivo* of 24 hours, 18

hours, 14 hours, 10 hours, 6 hours, 3 hours, 2 hours, 1 hour, 30 minutes, 10 minutes, 5 minutes, or 1 minute.

In certain such embodiments, the self-cyclizing moiety may be selected such that, upon cyclization, a five- or six-membered ring is formed, preferably a five-membered ring. In certain such embodiments, the five- or six-membered ring comprises at least one heteroatom selected from oxygen, nitrogen, or sulfur, preferably at least two, wherein the heteroatoms may be the same or different. In certain such embodiments, the heterocyclic ring contains at least one nitrogen, preferably two. In certain such embodiments, the self-cyclizing moiety cyclizes to form an imidazolidone.

In certain embodiments, the self-cyclizing moiety has a structure



,

wherein

U is selected from NR^1 and S;

X is selected from O, NR^5, and S, preferably O or S;

V is selected from O, S and NR^4, preferably O or NR^4;

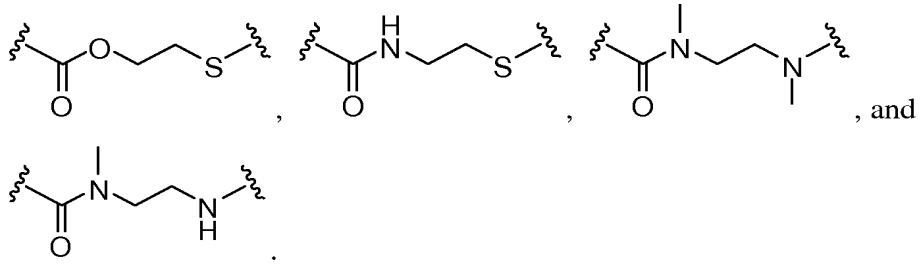
R^2 and R^3 are independently selected from hydrogen, alkyl, and alkoxy; or R^2 and R^3 together with the carbon atoms to which they are attached form a ring; and

R^1, R^4, and R^5 are independently selected from hydrogen and alkyl.

In certain embodiments, U is NR^1 and/or V is NR^4, and R^1 and R^4 are independently selected from methyl, ethyl, propyl, and isopropyl. In certain embodiments, both R^1 and R^4 are methyl. On certain embodiments, both R^2 and R^3 are hydrogen. In certain embodiments R^2 and R^3 are independently alkyl, preferably lower alkyl. In certain embodiments, R^2 and R^3 together are $-(CH_2)_n-$ wherein n is 3 or 4, thereby forming a cyclopentyl or cyclohexyl ring. In certain embodiments, the nature of R^2 and R^3 may affect the rate of cyclization of the self-cyclizing moiety. In certain such embodiments, it would be expected that the rate of cyclization would be greater when R^2 and R^3 together with the carbon atoms to which they are attached form a ring than the

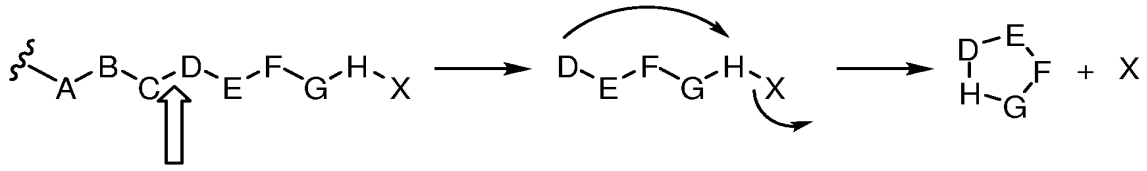
rate when R^2 and R^3 are independently selected from hydrogen, alkyl, and alkoxy. In certain embodiments, U is bonded to the self-cyclizing moiety.

In certain embodiments, the self-cyclizing moiety is selected from



In certain embodiments, the selectivity-determining moiety may connect to the self-cyclizing moiety through carbonyl-heteroatom bonds, e.g., amide, carbamate, carbonate, ester, thioester, and urea bonds.

In certain embodiments, a taxane is covalently attached to a polymer through a tether, wherein the tether comprises a selectivity-determining moiety and a self-cyclizing moiety which are covalently attached to one another. In certain embodiments, the self-cyclizing moiety is selected such that after cleavage of the bond between the selectivity-determining moiety and the self-cyclizing moiety, cyclization of the self-cyclizing moiety occurs, thereby releasing the therapeutic agent. As an illustration, ABC may be a selectivity-determining moiety, and DEFGH maybe be a self-cyclizing moiety, and ABC may be selected such that enzyme Y cleaves between C and D. Once cleavage of the bond between C and D progresses to a certain point, D will cyclize onto H, thereby releasing therapeutic agent X, or a prodrug thereof.



In certain embodiments, taxane X may further comprise additional intervening components, including, but not limited to another self-cyclizing moiety or a leaving group linker, such as CO_2 or methoxymethyl, that spontaneously dissociates from the remainder of the molecule after cleavage occurs.

In some embodiments, a linker may be and/or comprise an alkylene chain, a polyethylene glycol (PEG) chain, polysuccinic anhydride, poly-L-glutamic acid,

poly(ethyleneimine), an oligosaccharide, an amino acid (e.g., glycine or cysteine), an amino acid chain, or any other suitable linkage. In certain embodiments, the linker group itself can be stable under physiological conditions, such as an alkylene chain, or it can be cleavable under physiological conditions, such as by an enzyme (e.g., the linkage contains a peptide sequence that is a substrate for a peptidase), or by hydrolysis (e.g., the linkage contains a hydrolyzable group, such as an ester or thioester). The linker groups can be biologically inactive, such as a PEG, polyglycolic acid, or polylactic acid chain, or can be biologically active, such as an oligo- or polypeptide that, when cleaved from the moieties, binds a receptor, deactivates an enzyme, etc. Various oligomeric linker groups that are biologically compatible and/or bioerodible are known in the art, and the selection of the linkage may influence the ultimate properties of the material, such as whether it is durable when implanted, whether it gradually deforms or shrinks after implantation, or whether it gradually degrades and is absorbed by the body. The linker group may be attached to the moieties by any suitable bond or functional group, including carbon-carbon bonds, esters, ethers, amides, amines, carbonates, carbamates, sulfonamides, etc.

In certain embodiments the linker group(s) of the present invention represent a hydrocarbylene group wherein one or more methylene groups is optionally replaced by a group Y (provided that none of the Y groups are adjacent to each other), wherein each Y, independently for each occurrence, is selected from, substituted or unsubstituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, or -O-, C(=X) (wherein X is NR_1, O or S), -OC(O)-, -C(=O)O, -NR_1-, -NR_1CO-, -C(O)NR_1-, -$S(O)_n$- (wherein n is 0, 1, or 2), -OC(O)-NR_1, -NR_1-C(O)-NR_1-, -NR_1-C(NR_1)-NR_1-, and -B(OR_1)-; and R_1, independently for each occurrence, represents H or a lower alkyl.

In certain embodiments, the linker group represents a derivatized or non-derivatized amino acid (e.g., glycine or cysteine). In certain embodiments, linker groups with one or more terminal carboxyl groups may be conjugated to the polymer. In certain embodiments, one or more of these terminal carboxyl groups may be capped by covalently attaching them to a therapeutic agent, a targeting moiety, or a cyclodextrin moiety via an (thio)ester or amide bond. In still other embodiments, linker groups with one or more terminal hydroxyl, thiol, or amino groups may be incorporated into the polymer. In preferred embodiments, one or more of these terminal hydroxyl groups may

be capped by covalently attaching them to a therapeutic agent, a targeting moiety, or a cyclodextrin moiety via an (thio)ester, amide, carbonate, carbamate, thiocarbonate, or thiocarbamate bond. In certain embodiments, these (thio)ester, amide, (thio)carbonate or (thio)carbamates bonds may be biohydrolyzable, i.e., capable of being hydrolyzed under biological conditions.

In certain embodiments, a linker group represents a hydrocarbylene group wherein one or more methylene groups is optionally replaced by a group Y (provided that none of the Y groups are adjacent to each other), wherein each Y, independently for each occurrence, is selected from, substituted or unsubstituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, or -O-, C(=X) (wherein X is NR_1, O or S), -OC(O)-, -C(=O)O, -NR_1-, -NR_1CO-, -C(O)NR_1-, -$S(O)_n$- (wherein n is 0, 1, or 2), -OC(O)-NR_1, -NR_1-C(O)-NR_1-, -NR_1-C(NR_1)-NR_1-, and -B(OR_1)-; and R_1, independently for each occurrence, represents H or a lower alkyl.

In certain embodiments, a linker group, e.g., between a taxane and the CDP, comprises a self-cyclizing moiety. In certain embodiments, a linker group, e.g., between a taxane and the CDP, comprises a selectivity-determining moiety.

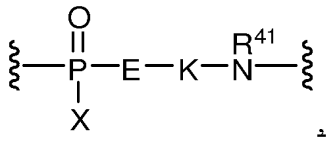
In certain embodiments as disclosed herein, a linker group, e.g., between a taxane and the CDP, comprises a self-cyclizing moiety and a selectivity-determining moiety.

In certain embodiments as disclosed herein, the taxane or targeting ligand is covalently bonded to the linker group via a biohydrolyzable bond (e.g., an ester, amide, carbonate, carbamate, or a phosphate).

In certain embodiments as disclosed herein, the CDP comprises cyclodextrin moieties that alternate with linker moieties in the polymer chain.

In certain embodiments, the linker moieties are attached to taxanes or prodrugs thereof that are cleaved under biological conditions.

In certain embodiments, at least one linker that connects the taxane or prodrug thereof to the polymer comprises a group represented by the formula



wherein

P is phosphorus;

O is oxygen;

E represents oxygen or NR^{40};

K represents hydrocarbyl;

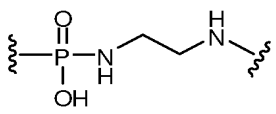
X is selected from OR^{42} or $NR^{43}R^{44}$; and

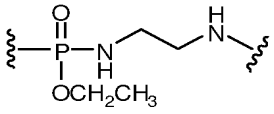
R^{40}, R^{41}, R^{42}, R^{43}, and R^{44} independently represent hydrogen or optionally substituted alkyl.

In certain embodiments, E is NR^{40} and R^{40} is hydrogen.

In certain embodiments, K is lower alkylene (e.g., ethylene).

In certain embodiments, at least one linker comprises a group selected from



and


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In certain embodiments, X is OR^{42}.

In certain embodiments, the linker group comprises an amino acid or peptide, or derivative thereof (e.g., a glycine or cysteine).

In certain embodiments as disclosed herein, the linker is connected to the taxane through a hydroxyl group (e.g., forming an ester bond). In certain embodiments as disclosed herein, the linker is connected to the taxane through an amino group (e.g., forming an amide bond).

In certain embodiments, the linker group that connects to the taxane may comprise a self-cyclizing moiety, or a selectivity-determining moiety, or both. In certain embodiments, the selectivity-determining moiety is a moiety that promotes selectivity in the cleavage of the bond between the selectivity-determining moiety and the self-cyclizing moiety. Such a moiety may, for example, promote enzymatic cleavage between the selectivity-determining moiety and the self-cyclizing moiety. Alternatively, such a moiety may promote cleavage between the selectivity-determining moiety and the self-cyclizing moiety under acidic conditions or basic conditions.

In certain embodiments, any of the linker groups may comprise a self-cyclizing moiety or a selectivity-determining moiety, or both. In certain embodiments, the

selectivity-determining moiety may be bonded to the self-cyclizing moiety between the self-cyclizing moiety and the polymer.

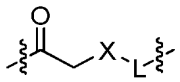
In certain embodiments, any of the linker groups may independently be or include an alkyl chain, a polyethylene glycol (PEG) chain, polysuccinic anhydride, poly-L-glutamic acid, poly(ethyleneimine), an oligosaccharide, an amino acid chain, or any other suitable linkage. In certain embodiments, the linker group itself can be stable under physiological conditions, such as an alkyl chain, or it can be cleavable under physiological conditions, such as by an enzyme (e.g., the linkage contains a peptide sequence that is a substrate for a peptidase), or by hydrolysis (e.g., the linkage contains a hydrolyzable group, such as an ester or thioester). The linker groups can be biologically inactive, such as a PEG, polyglycolic acid, or polylactic acid chain, or can be biologically active, such as an oligo- or polypeptide that, when cleaved from the moieties, binds a receptor, deactivates an enzyme, etc. Various oligomeric linker groups that are biologically compatible and/or bioerodible are known in the art, and the selection of the linkage may influence the ultimate properties of the material, such as whether it is durable when implanted, whether it gradually deforms or shrinks after implantation, or whether it gradually degrades and is absorbed by the body. The linker group may be attached to the moieties by any suitable bond or functional group, including carbon-carbon bonds, esters, ethers, amides, amines, carbonates, carbamates, sulfonamides, etc.

In certain embodiments, any of the linker groups may independently be an alkyl group wherein one or more methylene groups is optionally replaced by a group Y (provided that none of the Y groups are adjacent to each other), wherein each Y, independently for each occurrence, is selected from aryl, heteroaryl, carbocyclyl, heterocyclyl, or -O-, C(=X) (wherein X is NR^1, O or S), -OC(O)-, -C(=O)O-, -NR^1-, -NR^1CO-, -C(O)NR^1-, -$S(O)_n$- (wherein n is 0, 1, or 2), -OC(O)-NR^1-, -NR^1-C(O)-NR^1-, -NR^1-C(NR^1)-NR^1-, and -B(OR^1)-; and R^1, independently for each occurrence, is H or lower alkyl.

In one embodiment, the linker used to link taxane to a CDP controls the rate of taxane release from the CDP. For example, the linker can be a linker which in the PBS protocol described herein, releases within 24 hours as free taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel, 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%,

92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or all of the taxane in the CDP-conjugated taxane initially present in the assay. In some embodiments, in the PBS protocol described herein, the linker releases 71± 10 % of the taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel from the CDP-conjugated taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel within 24 hours, wherein 71 is the % of taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel released from the CDP- conjugate taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel at 24 hours by a reference structure, e.g., a taxane such as docetaxel paclitaxel and/or cabazitaxel coupled via 2-(2-(2-aminoethoxy)ethoxy)acetic acetate (i.e., aminoethoxyethoxy)to the same CDP in the PBS protocol described herein. In other embodiments, the linker releases 88± 10 % of the taxane from the CDP-conjugated taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel, within 24 hours, wherein 88 is the % of taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel, released from the CDP-conjugate taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel, at 24 hours by a reference structure, e.g., taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel, coupled via glycine to the same CDP in the PBS protocol described herein or the linker releases 95± 5 % of the taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel, from the CDP-conjugated taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel, within 24 hours, wherein 95 is the % of taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel, released from the CDP-conjugate taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel, at 24 hours by a reference structure, e.g., taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel coupled via alanine glycolate to the same CDP in the PBS protocol described herein. Such linkers include linkers which are released by hydrolysis of an ester bond, which hydrolysis releases taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel conjugated to CDP from CDP. In one embodiment, the linker is selected from glycine, alanine glycolate and 2-(2-(2-aminoethoxy)ethoxy)acetic acetate (i.e., aminoethoxyethoxy). In one embodiment, the linker used to link taxane to a CDP attaches to the taxane via an ester linkage and the CDP via an amide linkage. In some preferred embodiments, the linker includes a heteroatom attached to the carbon positioned alpha to the carbonyl carbon that forms the ester linkage with the taxane.

In one embodiment, the linker used to link taxane to a CDP has the following formula



wherein

X is O, NH, or Nalkyl; and

L is an alkylenyl or heteroalkylenyl chain, wherein one or more of the carbons of the alkylenyl or heteroalkylenyl are optionally substituted (e.g., with an oxo moiety), or wherein L is absent;

wherein the carbonyl portion of the linker attaches to the taxane to form an ester linkage; and

wherein the X-L portion of the linker attaches to the CDP to form an amide bond.

In one embodiment, X is NH. In one embodiment, X is NH and L is absent.

In one embodiment, X is O. In one embodiment, X is O and L is an alkylenyl or heteroalkylenyl chain, wherein one or more of the carbons of the alkylenyl or heteroalkylenyl are optionally substituted (e.g., with an oxo moiety). In one embodiment, L is $-C(O)CH_2CH_2NH-$.

In some embodiments, the linker can be a linker which in the B16.F10 cell assay described herein, releases free taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel, of the taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel, in the CDP-conjugated taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel, such that the IC_{50} of the taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel, is less than 25 nM, 20 nM, 15 nM, 10 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.5 nM or 0.1 nM. In some embodiments, in the B16.F10 assay described herein, the linker releases taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel, from the CDP-conjugated taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel such that the IC_{50} of the taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel is less than 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.5 nM. Such linkers include linkers which are released by hydrolysis of an ester bond, which hydrolysis releases docetaxel conjugated to CDP from CDP and linkers which are released by chemical or enzymatic cleavage of a disulfide bond, whereby enzymatic cleavage releases taxane, e.g., docetaxel, paclitaxel and/or cabazitaxel conjugated to CDP from CDP. In one embodiment, the linker is selected from glycine, alanine glycolate and dithiolethyloxy-carbonate.

In certain embodiments, the present invention contemplates a CDP, wherein a plurality of taxanes are covalently attached to the polymer through attachments that are cleaved under biological conditions to release the therapeutic agents as discussed above, wherein administration of the polymer to a subject results in release of the therapeutic agent over a period of at least 2 hours, 3 hours, 5 hours, 6 hours, 8 hours, 10 hours, 15 hours, 20 hours, 1 day, 2 days, 3 days, 4 days, 7 days, 10 days, 14 days, 17 days, 20 days, 24 days, 27 days up to a month.

In some embodiments, the conjugation of the taxane to the CDP improves the aqueous solubility of the taxane and hence the bioavailability. Accordingly, in one embodiment of the invention, the taxane has a log P >0.4, >0.6, >0.8, >1, >2, >3, >4, or even >5.

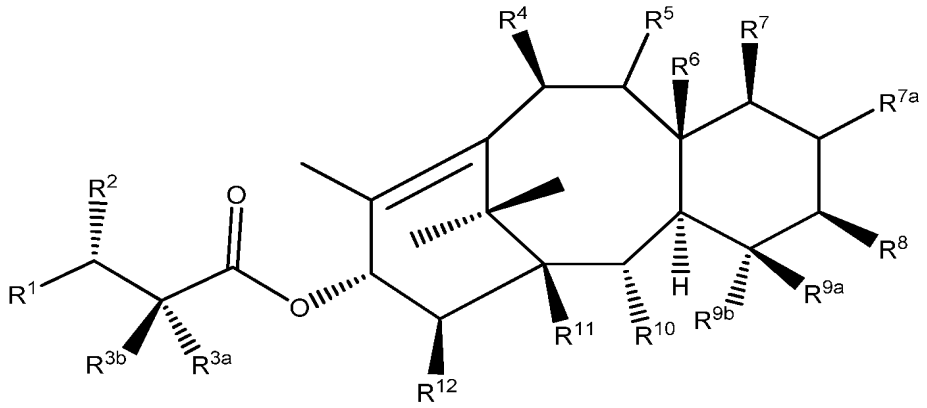
The CDP-taxane of the present invention preferably has a molecular weight in the range of 10,000 to 500,000; 30,000 to 200,000; or even 70,000 to 150,000 amu.

In certain embodiments, the present invention contemplates attenuating the rate of release of the taxane by introducing various tether and/or linking groups between the therapeutic agent and the polymer. Thus, in certain embodiments, the CDP-taxane conjugates of the present invention are compositions for controlled delivery of the taxane.

Taxanes

The term "taxane," as used herein, refers to any naturally occurring, synthetic, or semi-synthetic taxane structure, for example, known in the art. Exemplary taxanes include those compounds shown below, including, for example, formula (X), (XIIa), and (XIIb).

In one embodiment, the taxane is a compound of the following formula (X):



formula (X)

wherein;

R^1 is aryl (e.g., phenyl), heteroaryl (e.g., furanyl, thiophenyl, or pyridyl), alkyl (e.g., butyl such as isobutyl or tert-butyl), cycloalyl (e.g., cyclopropyl), heterocycloalkyl (epoxyl), or R^1, when taken together with one of R^{3b}, R^{9b}, or R^{10} and the carbons to which they are attached, forms a mono- or bi-cyclic ring system; wherein R^1 is optionally substituted with 1-3 R^{1a};

R^2 is $NR^{2a}R^{2b}$ or OR^{2c};

R^{3a} is H, OH, Opolymer, OC(O)alkyl, or OC(O)alkenyl;

R^{3b} is H or OH; or together with R^1 and the carbon to which it is attached, forms a mono- or bi-cyclic ring system;

R^4 is OH, alkoxy (e.g., methoxy), OC(O)alkyl (e.g., Oacyl), OC(O)cycloalkyl, heterocycloalkylalkyl; or R^4 together with R^5 and the carbons to which they are attached, form an optionally substituted ring; or R^4, together with the carbon to which it is attached, forms a ring (forming a spirocyclic ring) or an oxo;

R^5 is OH, OC(O)alkyl (e.g., Oacyl); or R^5 together with R^4 or R^7 and the carbons to which they are attached, form an optionally substituted ring; or R^5, together with the carbon to which it is attached, forms a ring (forming a spirocyclic ring) or an oxo;

R^6 is alkyl (e.g., methyl); or R^6 together with R^7 and the carbons to which they are attached, form an optionally substituted ring (e.g., a cyclopropyl ring);

R^7 is H, OH, alkoxy (e.g., methoxy), OC(O)Oalkyl, OalkylSalkyl (e.g., OCH_2SMe), or OalkylOalkyl (e.g., OCH_2OMe), thioalkyl, SalkylOalkyl (e.g.,