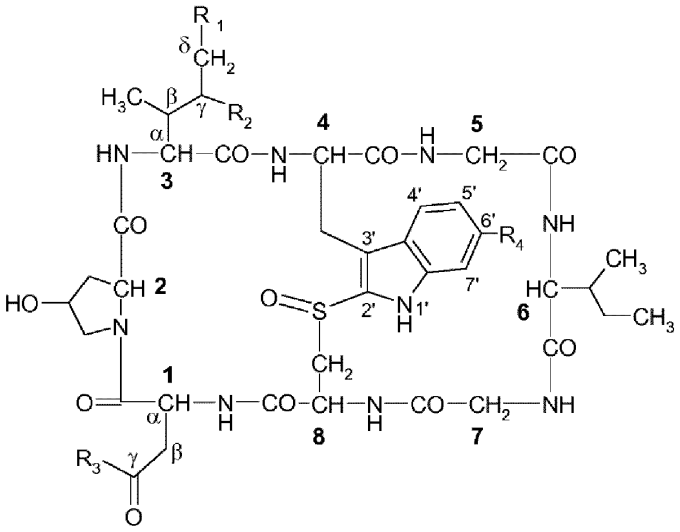


	R_1	R_2	R_3	R_4
α-amanitin	OH	OH	NH_2	OH
β-amanitin	OH	OH	OH	OH
γ-amanitin	H	OH	NH_2	OH
ε-amanitin	H	OH	OH	OH
amanin	OH	OH	OH	H
amaninamide	OH	OH	NH_2	H
amanullin	H	H	NH_2	OH
amanullinic acid	H	H	OH	OH
γ-amanin	H	OH	OH	H
γ-amaninamide	H	OH	NH2	H

FIG. 1

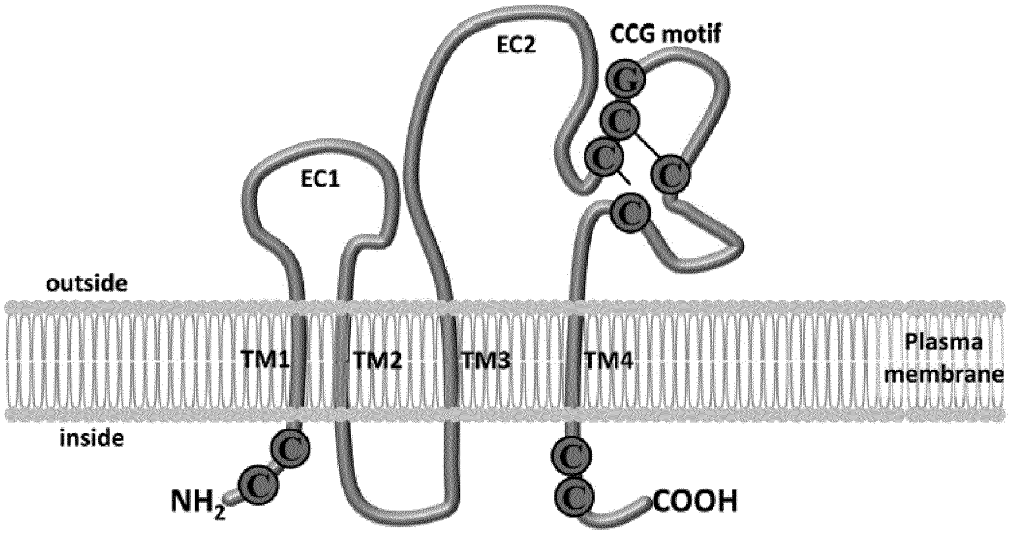

EC2
CCG motif
EC1
outside
TM1
TM2
TM3
TM4
Plasma membrane
inside
NH2
COOH

FIG. 2

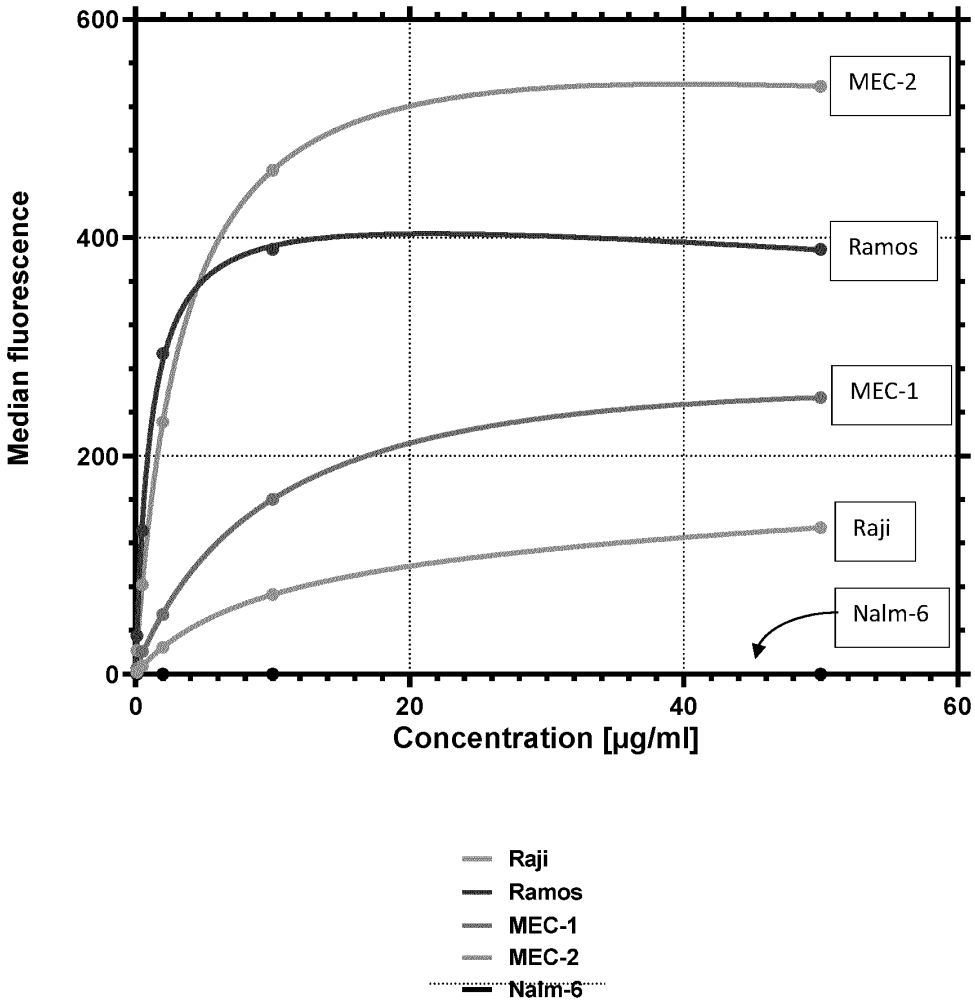
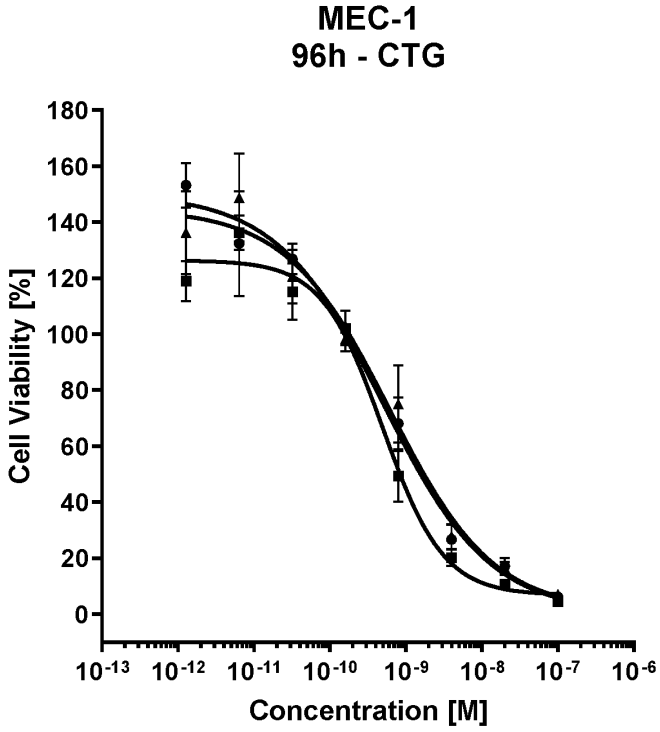
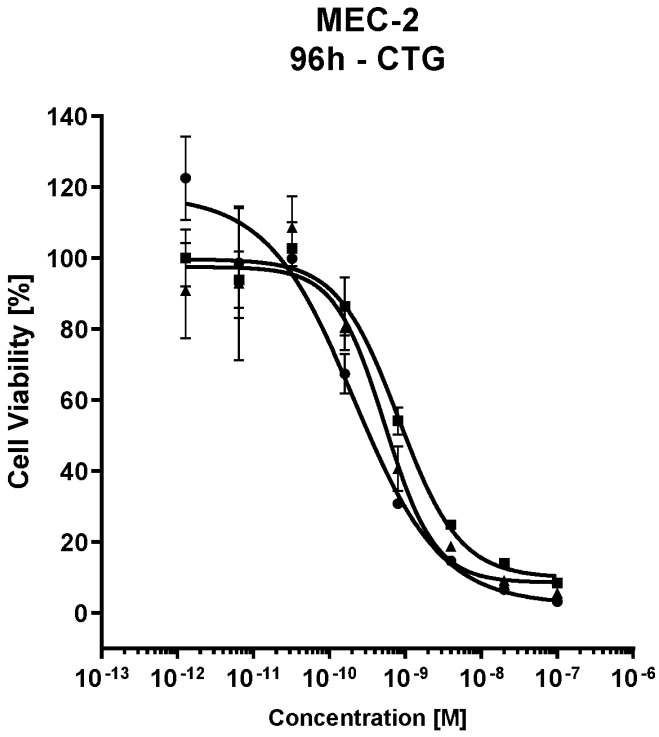

600
400
200
0
Median fluorescence
0
20
40
60
Concentration [µg/ml]
MEC-2
Ramos
MEC-1
Raji
Nalm-6
Raji
Ramos
MEC-1
MEC-2
Nalm-6

FIG. 3



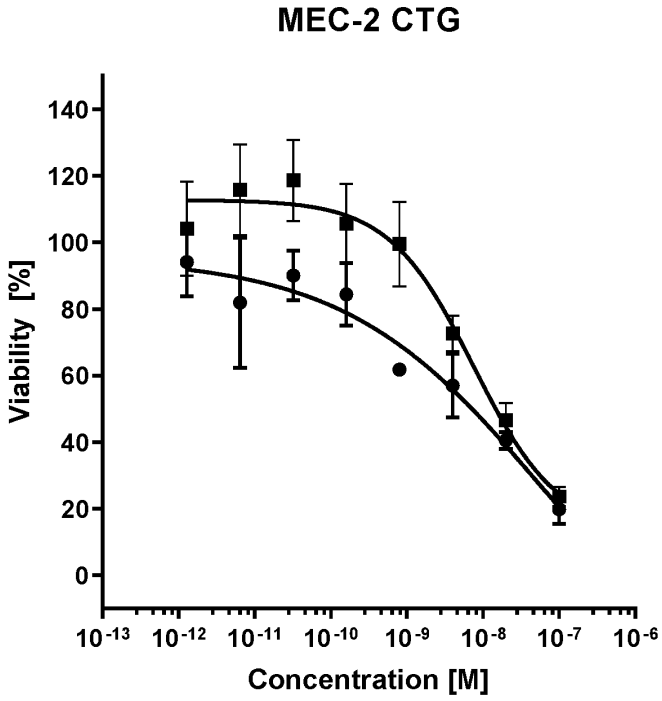
ATAC	DAR	EC 50 [M]
Conjugate XXVI	2.05	5.03×10^{-10}
Conjugate XXIV	2.00	4.96×10^{-10}
Conjugate XXIII	2.00	6.171×10^{-10}

FIG. 4 A



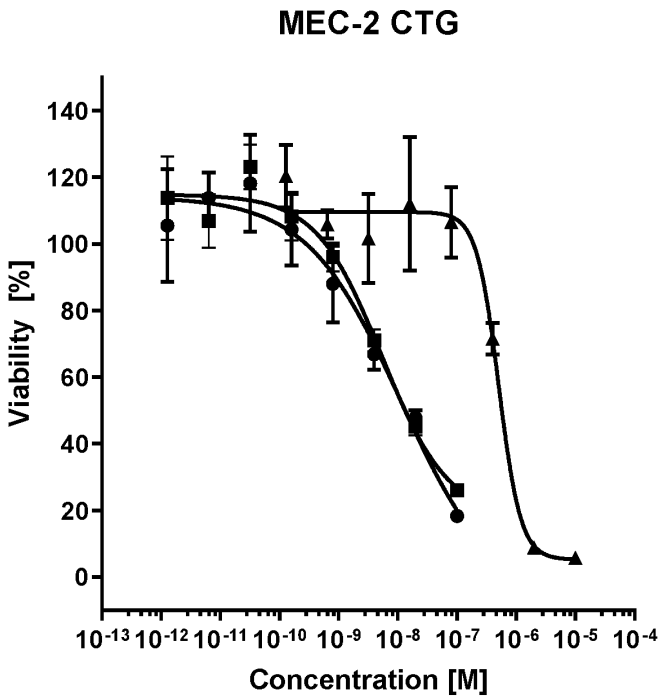
ATAC	DAR	EC 50 [M]
Conjugate XXVI	2.05	2.13×10^{-10}
Conjugate XXIV	2.00	8.19×10^{-10}
Conjugate XXIII	2.00	5.39×10^{-10}

FIG. 4 B



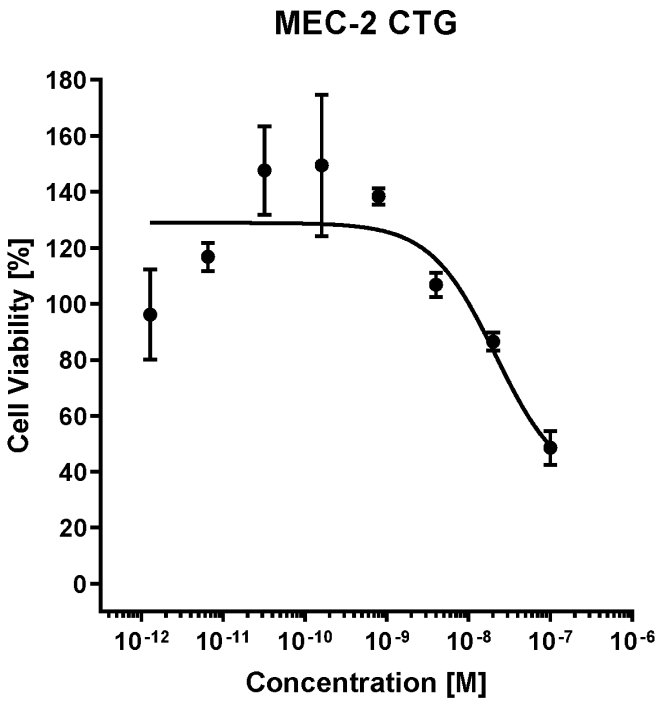
Conjugate	DAR	EC50 [M]
chHH1-HDP-(XV)	3.36	$60.6x10^{-09}$
conjugate XXVI	2.03	$7.54x10^{-09}$

FIG. 4 C



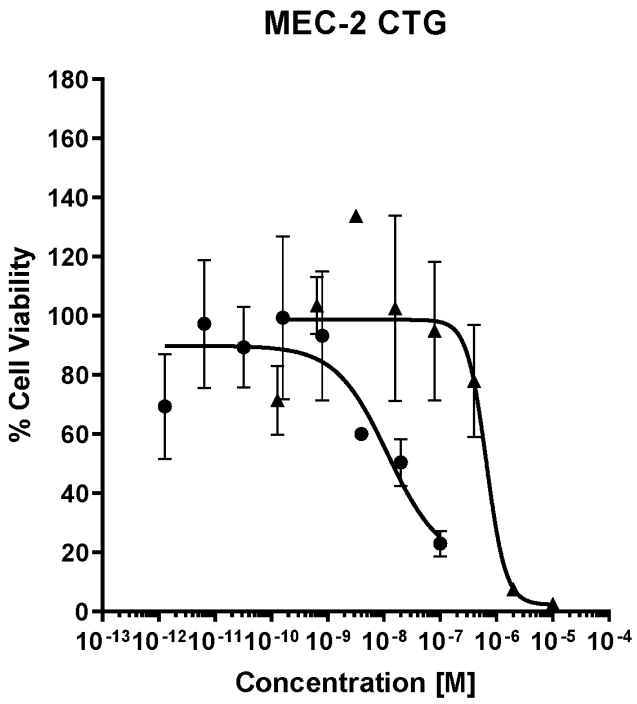
ATAC	DAR	EC 50 [M]
Conjugate XXVI	2.03	11.1×10^{-09}
Conjugate XXIV	2.00	5.41×10^{-09}
α-Amanitin		5.06×10^{-07}

FIG. 4 D



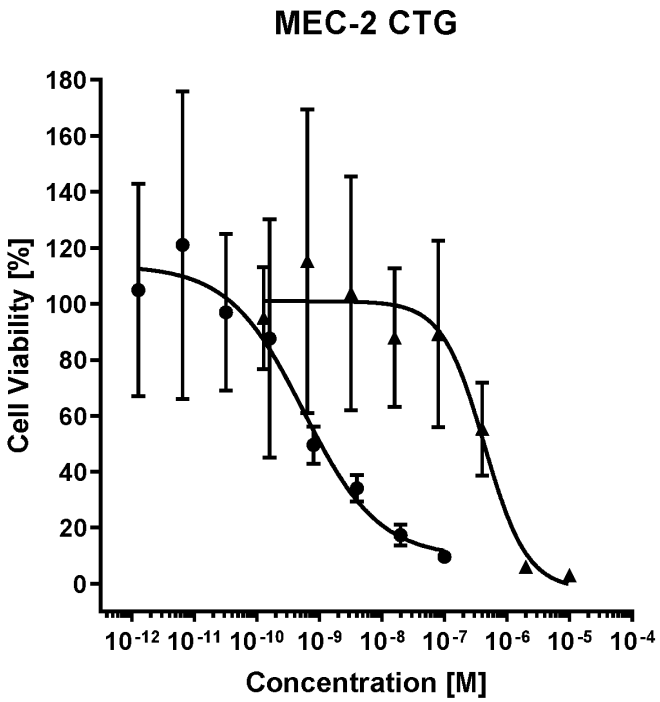
	Conjugate	DAR	EC 50 [M]
●—	Conjugate XXIII	2.03	2.14×10^{-08}

FIG. 4 E



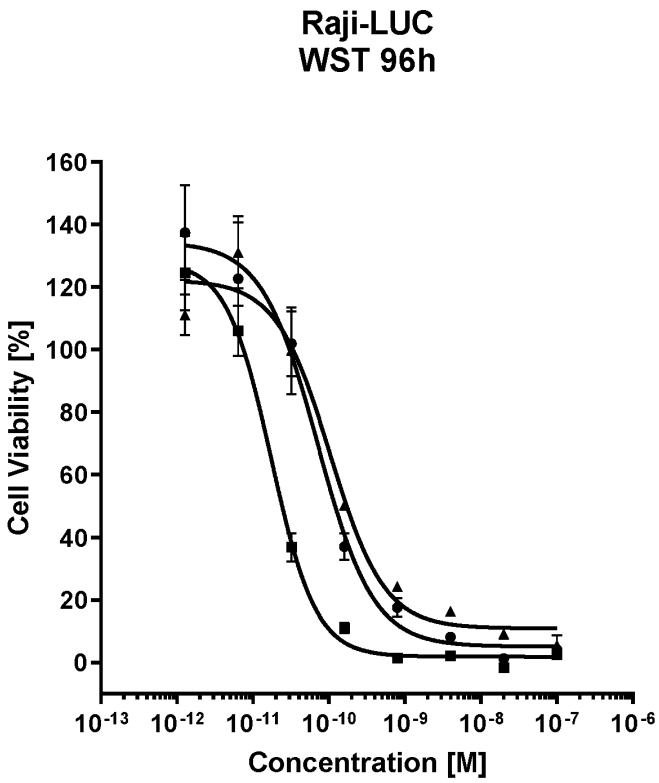
ATAC	DAR	EC 50 [M]
Conjugate XXIV	tbd	1.19×10^{-08}
α-Amanitin	-	6.63×10^{-07}

FIG. 4 F



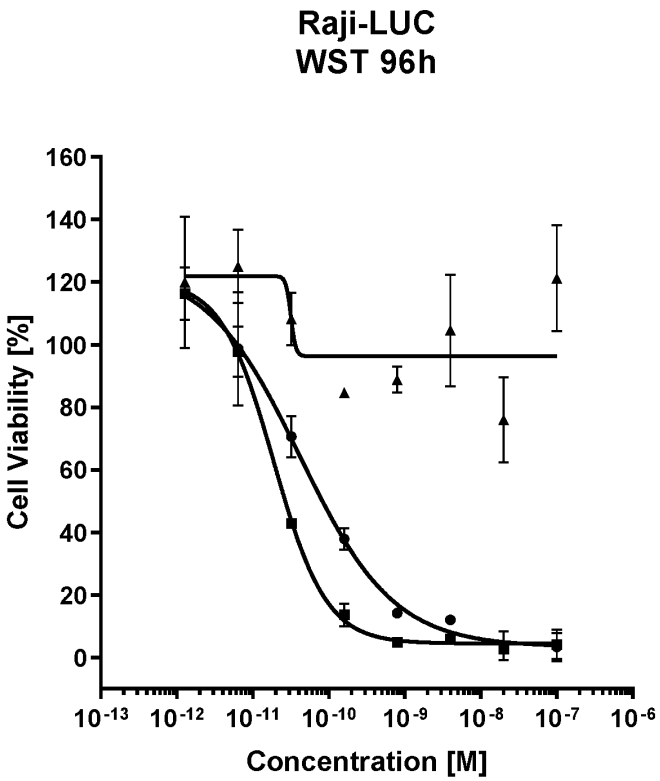
ATAC	DAR	EC 50 [M]
chHH1-HDP-(XIII)	tbd	5.59×10^{-10}
α-Amanitin	-	4.37×10^{-07}

FIG. 4 G



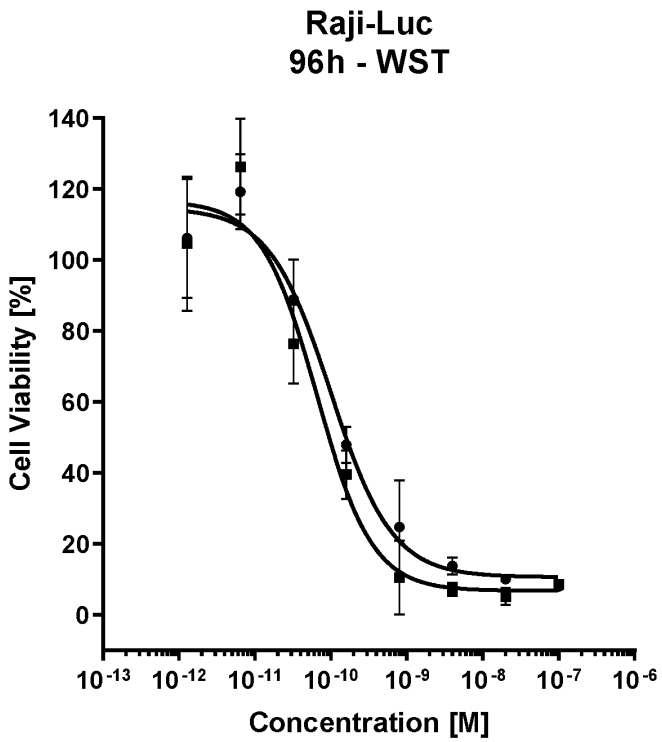
ATAC	DAR	EC 50 $X10^{-10}$ [M]
Conjugate XXIII	2.05	0.71
Conjugate XXIV	2.00	0.17
Conjuagte XXXI	1.90	1.04

FIG. 5 A



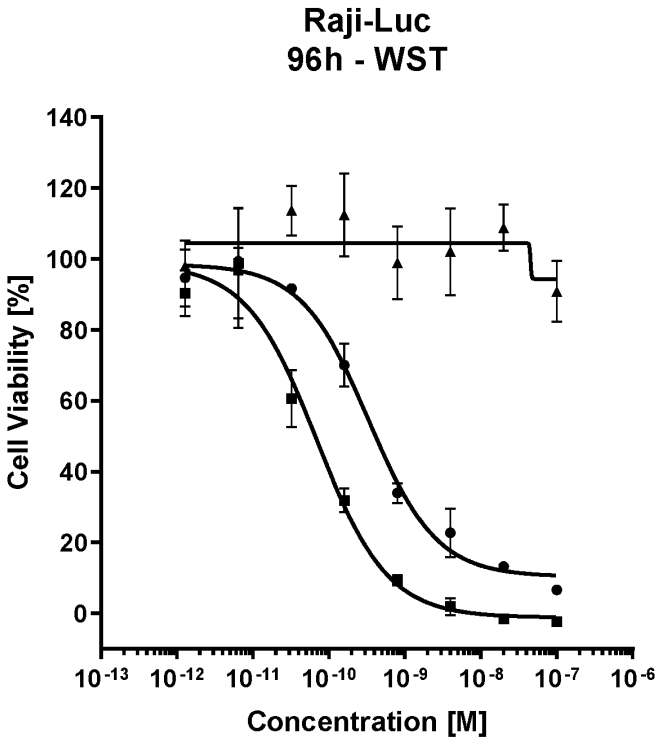
ATAC	DAR	EC 50 X10^{-10} [M]
Conjugate XXIII (CHO)	2.05	0.42
Conjugate XXIV (CHO)	2.00	0.19
chHH1-HDP-LALA-D265C (CHO)		-

FIG. 5 B



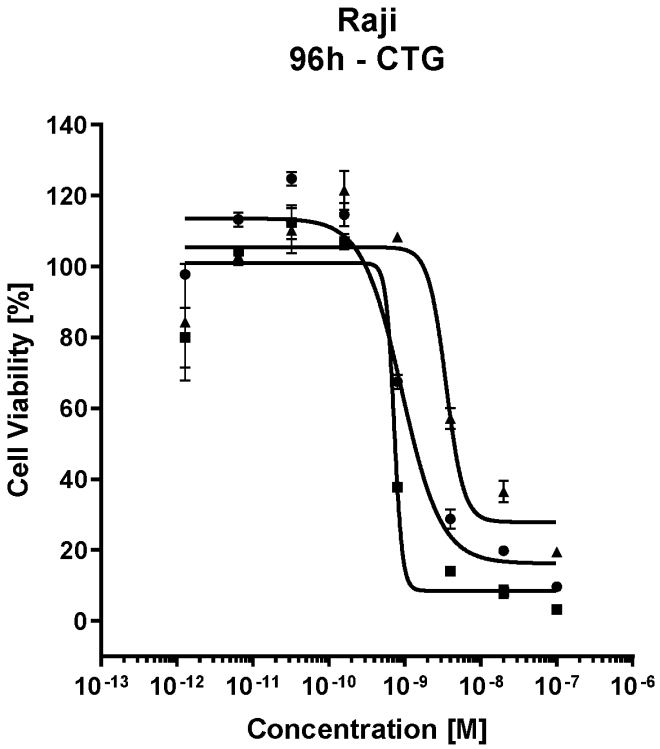
ATAC	DAR	EC 50 X10^{-10} [M]
Conjugate XXVI	2.05	0.87
Conjugate XXIV	2.00	0.56

FIG. 5 C



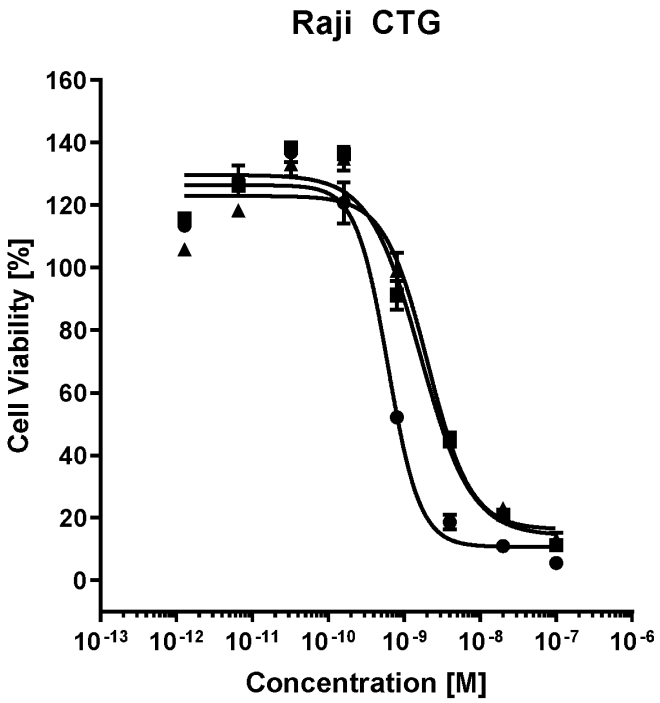
ATAC	DAR	EC 50 X10^{-10} [M]
Conjugate XXXI	2.00	3.37
Conjugate XXV	1.89	0.68
chHH1-HDP-LALA-D265C		-

FIG. 5 D



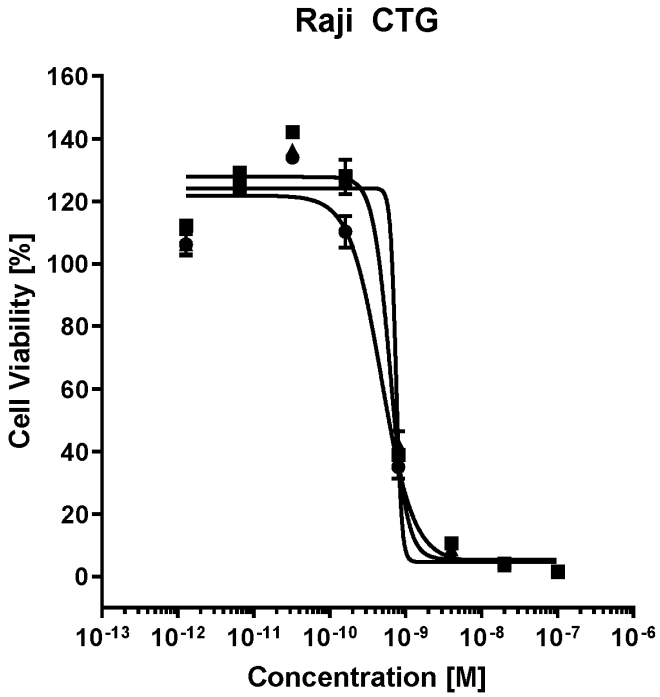
ATAC	DAR	EC 50 $X10^{-10}$ [M]
Conjugate XXVI	2.00	9.16
Conjugate XXIV	2	7.28
Conjugate XXIII	2	35

FIG 6 A



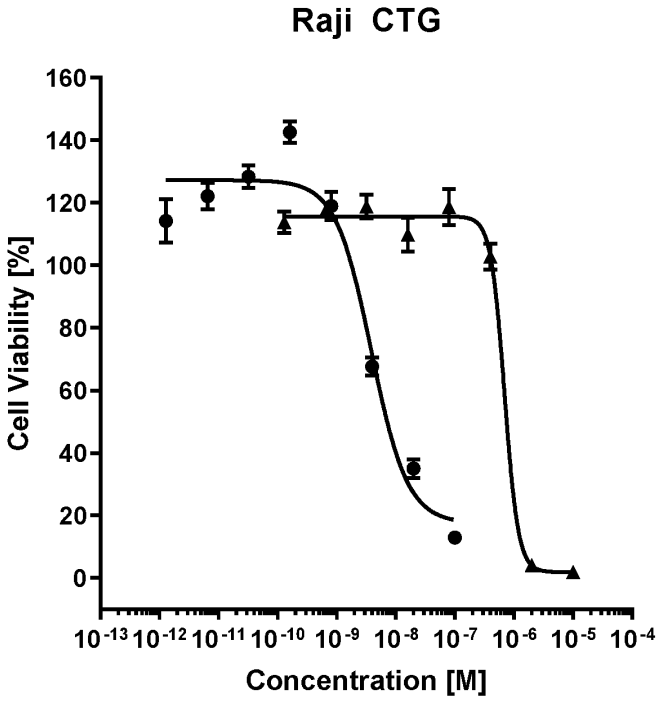
ATAC	DAR	EC 50 [nM]
chHH1-HDP-(XV)	3.36	0.61
Conjugate XXVII	2.03	1.63
Conjugate XXVI	2.03	2.04

FIG. 6 B



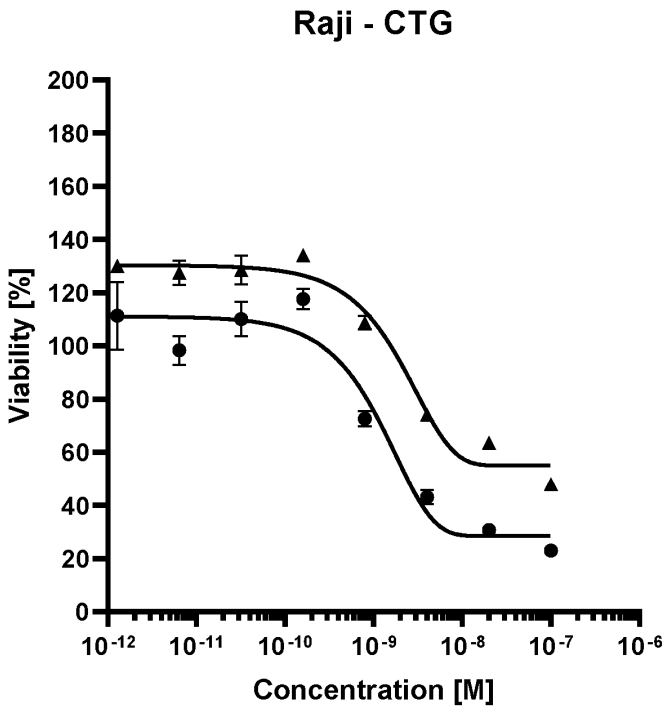
ATAC	DAR	EC 50 [nM]
chHH1-HDP-(XIII)	tbd	0.48
chHH1-HDP-D265C-(XIII)	1.96	0.62
Conjugate XXIV	tbd	0.75

FIG. 6 C



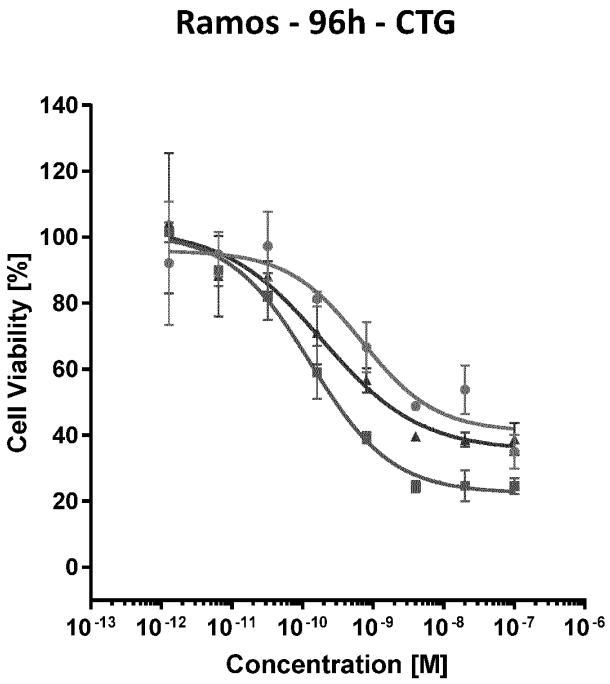
	ATAC	DAR	EC 50 [nM]
▲	chHH1-HDP-D265C-(XII)	2.03	3.9
●	α–Amanitin		*694*

FIG. 6 D



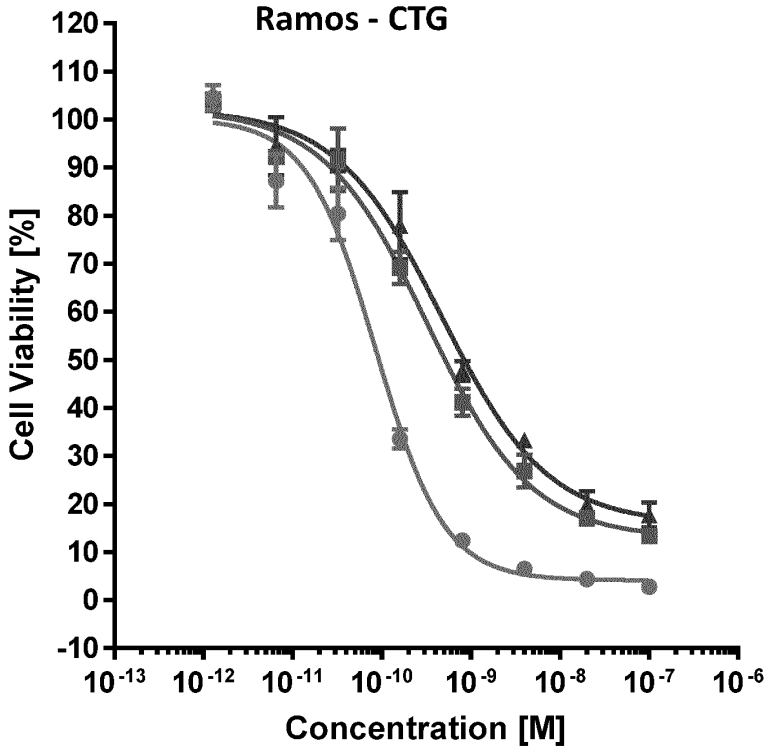
ATAC	DAR	EC 50 [nM]
chHH1-(XIII) (old Raji cells)	tbd	0.995
chHH1-(XIII) (new Raji cells)	tbd	1.93

FIG. 6 E



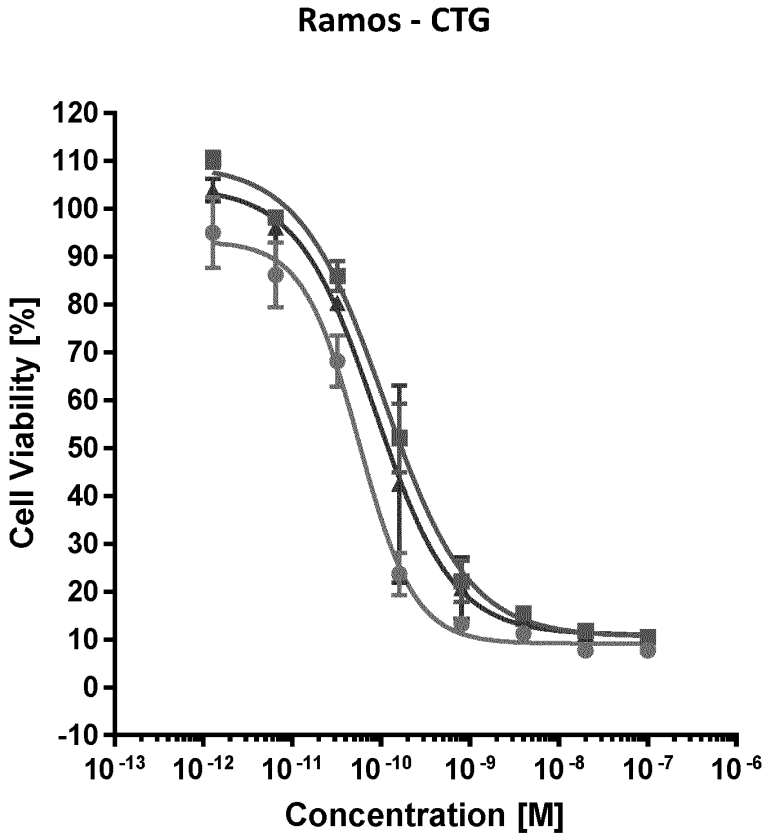
ATAC	DAR	EC 50 X10^{-10} [M]
Conjugate XXVI	2.05	6.85
Conjugate XXIV	2	1.3
Conjugate XXIII	2	1.88

FIG. 7 A



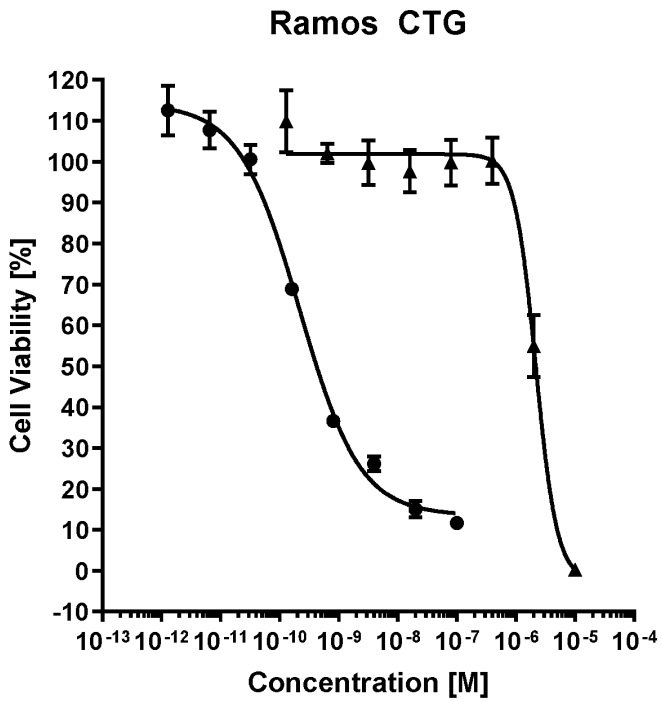
	ATAC	DAR	EC 50 [nM]
●	chHH1-HDP-(XV)	3.36	0.085
■	chHH1-HDP-D265C-(XV)	2.03	0.32
▲	Conjugate XXVI	2.03	0.47

FIG. 7 B



ATAC	DAR	EC 50 [nM]
chHH1-HDP-(XV)	tbd	0.056
chHH1-HDP-D265C-(XIII)	1.96	0.11
Conjugate XXIV	tbd	0.086

FIG 7 C



	ATAC	DAR	EC 50 [nM]
●	chHH1-HDP-D265C-(XII)	2.03	0.22
▲	α–Amanitin		217

FIG. 7 D

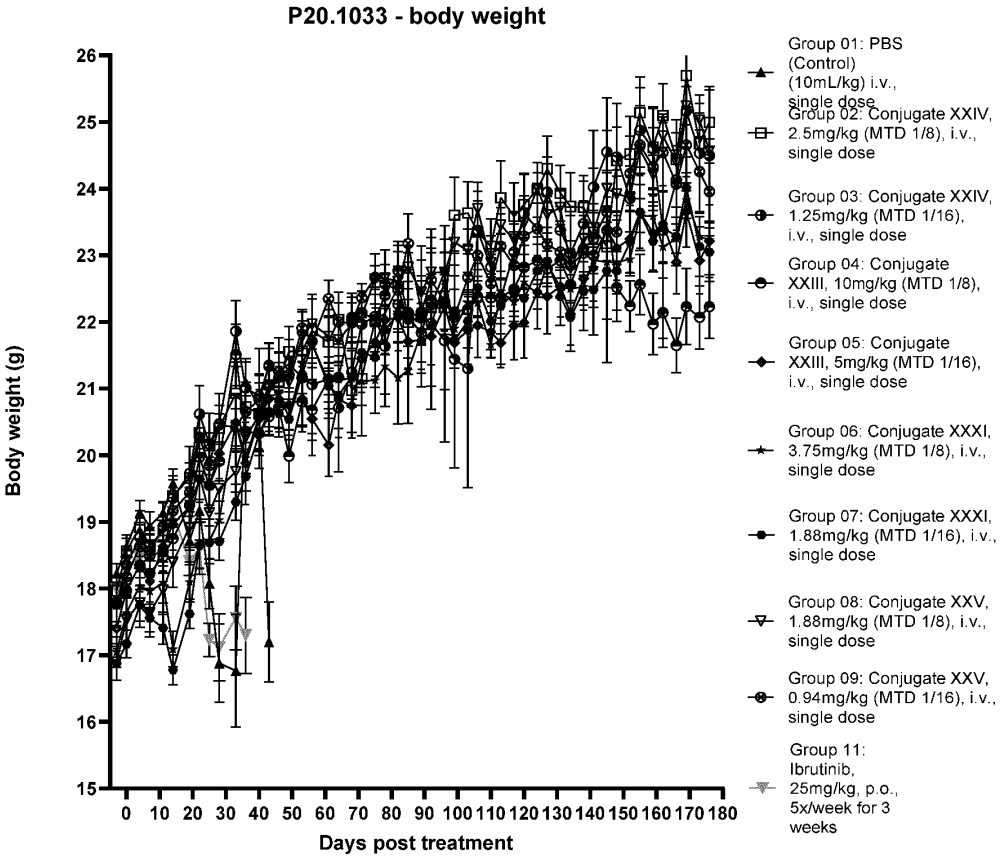

P20.1033 - body weight
Body weight (g)
26
25
24
23
22
21
20
19
18
17
16
15
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180
Days post treatment
Group 01: PBS (Control) (10mL/kg) i.v., single dose
Group 02: Conjugate XXIV, 2.5mg/kg (MTD 1/8), i.v., single dose
Group 03: Conjugate XXIV, 1.25mg/kg (MTD 1/16), i.v., single dose
Group 04: Conjugate XXIII, 10mg/kg (MTD 1/8), i.v., single dose
Group 05: Conjugate XXIII, 5mg/kg (MTD 1/16), i.v., single dose
Group 06: Conjugate XXXI, 3.75mg/kg (MTD 1/8), i.v., single dose
Group 07: Conjugate XXXI, 1.88mg/kg (MTD 1/16), i.v., single dose
Group 08: Conjugate XXV, 1.88mg/kg (MTD 1/8), i.v., single dose
Group 09: Conjugate XXV, 0.94mg/kg (MTD 1/16), i.v., single dose
Group 11: Ibrutinib, 25mg/kg, p.o., 5x/week for 3 weeks

FIG. 8

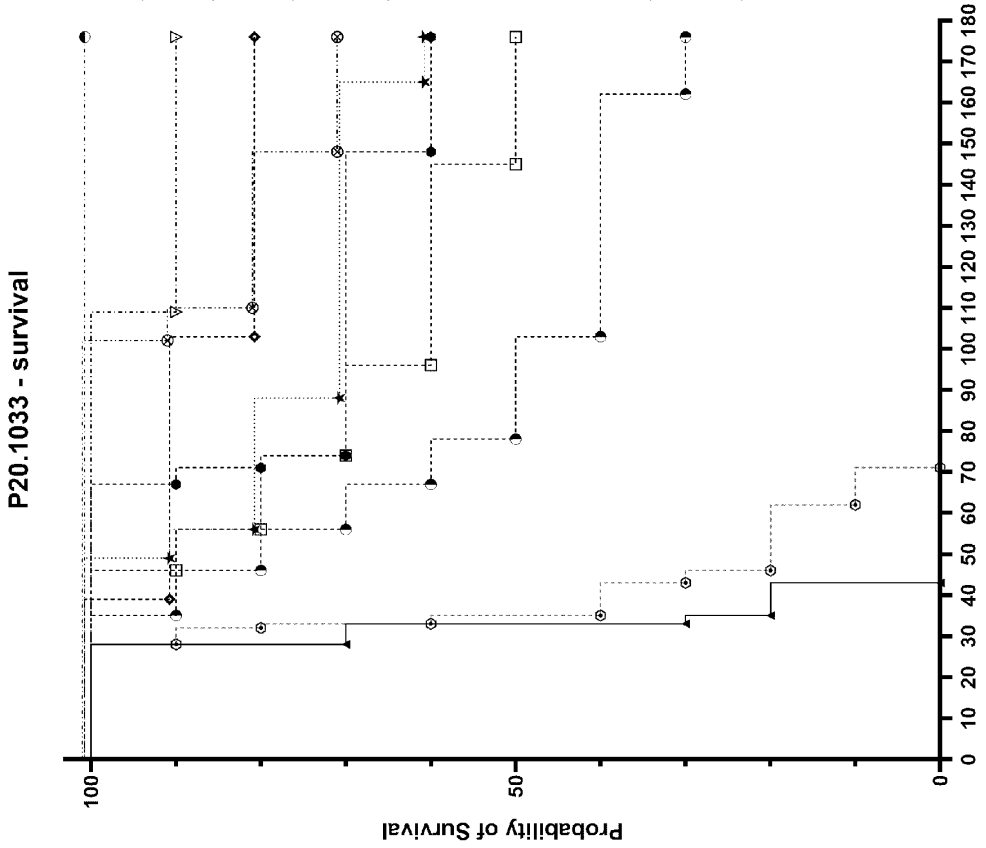

P20.1033 - survival
Probability of Survival
100
50
0
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180
Days Post Group Allocation
Group 01: PBS (Control) (10mL/kg) i.v., single dose
Group 02: Conjugate XXIV, 2,5mg/kg (MTD 1/8), i.v., single dose
Group 03: Conjugate XXIV, 1,25mg/kg (MTD 1/16), i.v., single dose
Group 04: Conjugate XXIII, 10mg/kg (MTD 1/8), i.v., single dose
Group 05: Conjugate XXIII, 5mg/kg (MTD 1/16), i.v., single dose
Group 06: Conjugate XXXI, 3,75mg/kg (MTD 1/8), i.v., single dose
Group 07: Conjugate XXXI, 1,88mg/kg (MTD 1/16), i.v., single dose
Group 08: Conjugate XXV, 1,88mg/kg (MTD 1/8), i.v., single dose
Group 09: Conjugate XXV, 0,94mg/kg (MTD 1/16), i.v., single dose
Group 11: Ibrutinib, 25mg/kg, p.o., 5x/week for 3 weeks

FIG. 9

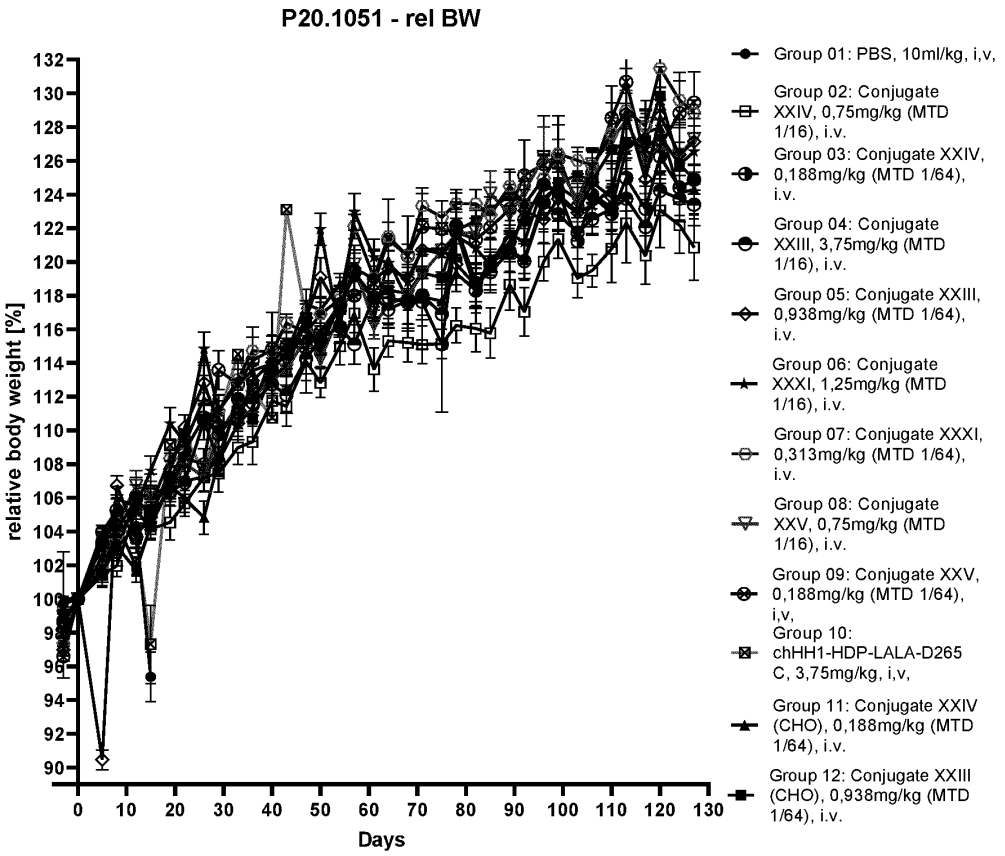

P20.1051 - rel BW
relative body weight [%]
Days
Group 01: PBS, 10ml/kg, i,v,
Group 02: Conjugate XXIV, 0,75mg/kg (MTD 1/16), i.v.
Group 03: Conjugate XXIV, 0,188mg/kg (MTD 1/64), i.v.
Group 04: Conjugate XXIII, 3,75mg/kg (MTD 1/16), i.v.
Group 05: Conjugate XXIII, 0,938mg/kg (MTD 1/64), i.v.
Group 06: Conjugate XXXI, 1,25mg/kg (MTD 1/16), i.v.
Group 07: Conjugate XXXI, 0,313mg/kg (MTD 1/64), i.v.
Group 08: Conjugate XXV, 0,75mg/kg (MTD 1/16), i.v.
Group 09: Conjugate XXV, 0,188mg/kg (MTD 1/64), i,v,
Group 10: chHH1-HDP-LALA-D265 C, 3,75mg/kg, i,v,
Group 11: Conjugate XXIV (CHO), 0,188mg/kg (MTD 1/64), i.v.
Group 12: Conjugate XXIII (CHO), 0,938mg/kg (MTD 1/64), i.v.

FIG. 10

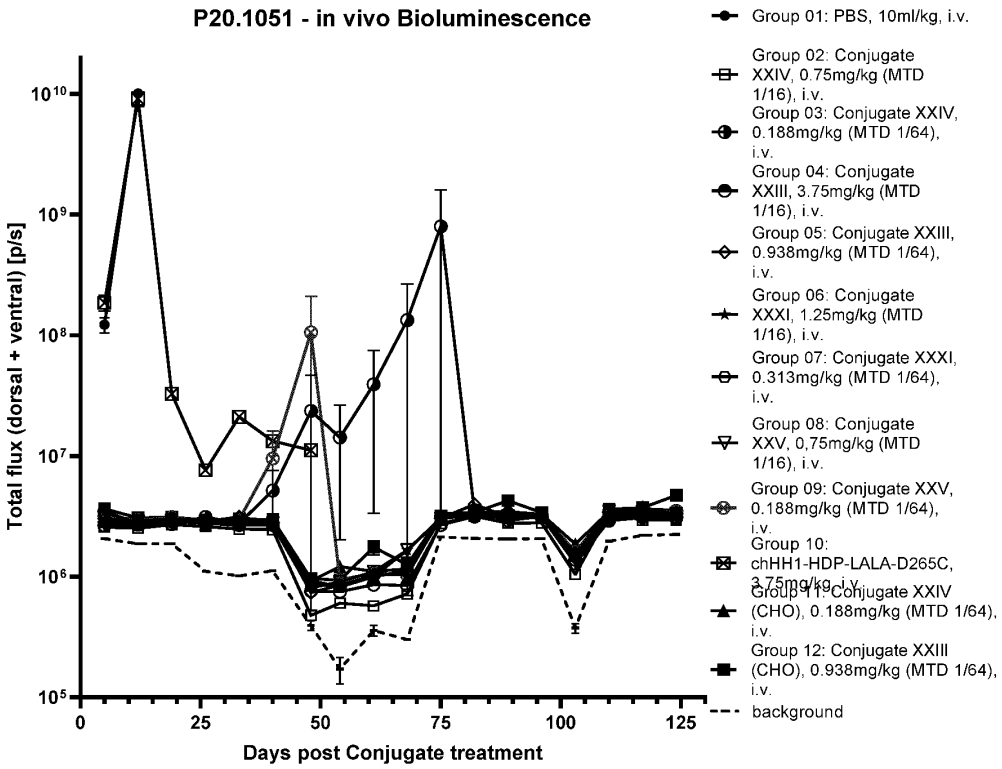

P20.1051 - in vivo Bioluminescence
Total flux (dorsal + ventral) [p/s]
10^{10}
10^{9}
10^{8}
10^{7}
10^{6}
10^{5}
0
25
50
75
100
125
Days post Conjugate treatment
Group 01: PBS, 10ml/kg, i.v.
Group 02: Conjugate XXIV, 0.75mg/kg (MTD 1/16), i.v.
Group 03: Conjugate XXIV, 0.188mg/kg (MTD 1/64), i.v.
Group 04: Conjugate XXIII, 3.75mg/kg (MTD 1/16), i.v.
Group 05: Conjugate XXIII, 0.938mg/kg (MTD 1/64), i.v.
Group 06: Conjugate XXXI, 1.25mg/kg (MTD 1/16), i.v.
Group 07: Conjugate XXXI, 0.313mg/kg (MTD 1/64), i.v.
Group 08: Conjugate XXV, 0,75mg/kg (MTD 1/16), i.v.
Group 09: Conjugate XXV, 0.188mg/kg (MTD 1/64), i.v.
Group 10: chHH1-HDP-LALA-D265C, 3.75mg/kg, i.v.
Group 11: Conjugate XXIV (CHO), 0.188mg/kg (MTD 1/64), i.v.
Group 12: Conjugate XXIII (CHO), 0.938mg/kg (MTD 1/64), i.v.
background

FIG. 11

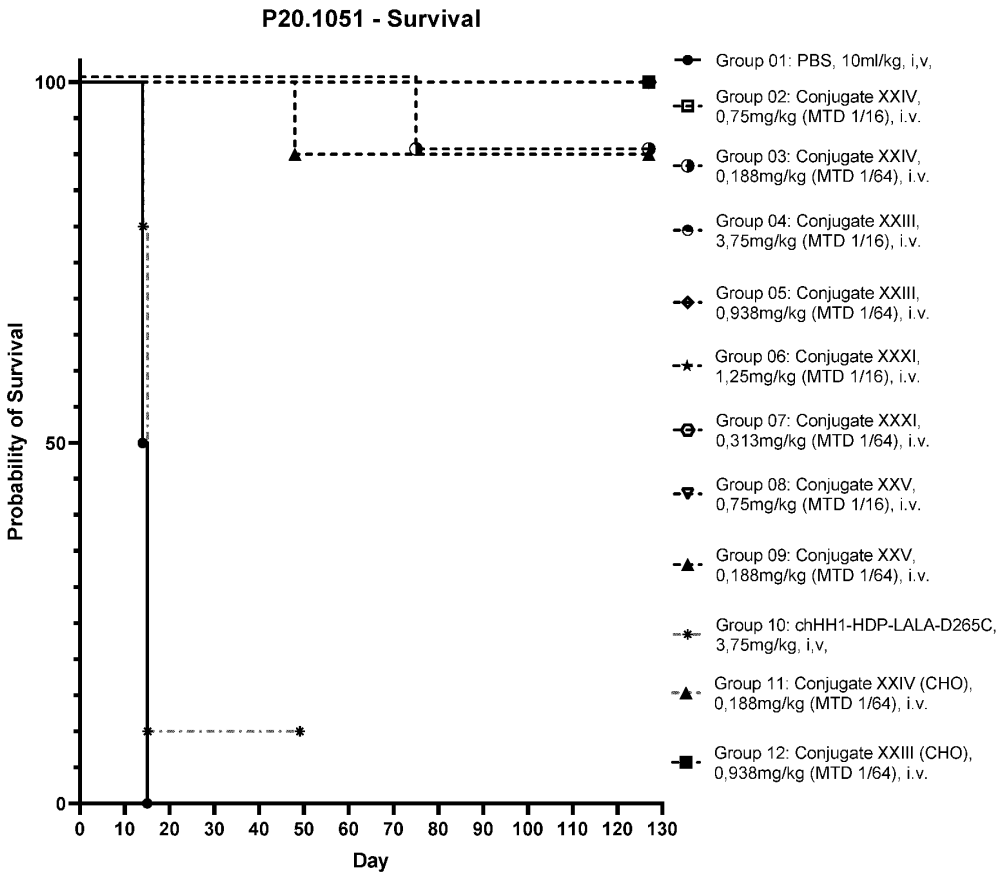
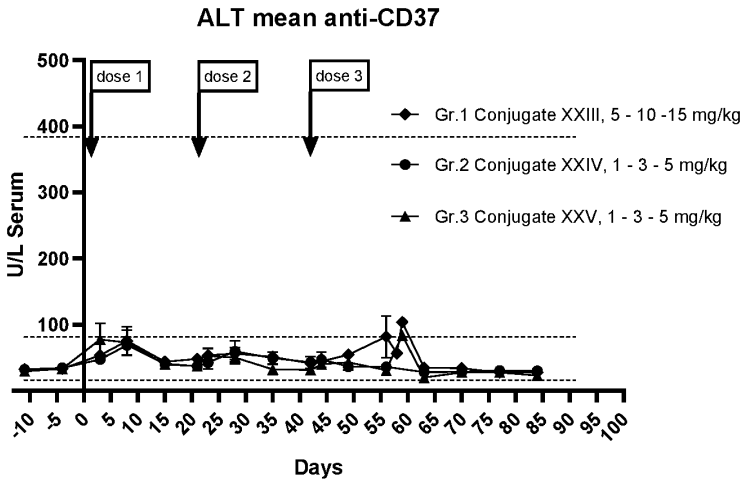
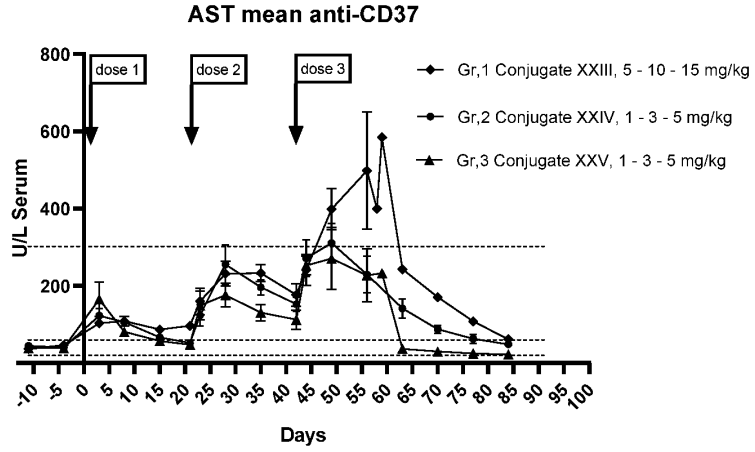

P20.1051 - Survival
Probability of Survival
100
50
0
0 10 20 30 40 50 60 70 80 90 100 110 120 130
Day
Group 01: PBS, 10ml/kg, i,v,
Group 02: Conjugate XXIV, 0,75mg/kg (MTD 1/16), i.v.
Group 03: Conjugate XXIV, 0,188mg/kg (MTD 1/64), i.v.
Group 04: Conjugate XXIII, 3,75mg/kg (MTD 1/16), i.v.
Group 05: Conjugate XXIII, 0,938mg/kg (MTD 1/64), i.v.
Group 06: Conjugate XXXI, 1,25mg/kg (MTD 1/16), i.v.
Group 07: Conjugate XXXI, 0,313mg/kg (MTD 1/64), i.v.
Group 08: Conjugate XXV, 0,75mg/kg (MTD 1/16), i.v.
Group 09: Conjugate XXV, 0,188mg/kg (MTD 1/64), i.v.
Group 10: chHH1-HDP-LALA-D265C, 3,75mg/kg, i,v,
Group 11: Conjugate XXIV (CHO), 0,188mg/kg (MTD 1/64), i.v.
Group 12: Conjugate XXIII (CHO), 0,938mg/kg (MTD 1/64), i.v.

FIG. 12

A


ALT mean anti-CD37
dose 1
dose 2
dose 3
Gr.1 Conjugate XXIII, 5 - 10 -15 mg/kg
Gr.2 Conjugate XXIV, 1 - 3 - 5 mg/kg
Gr.3 Conjugate XXV, 1 - 3 - 5 mg/kg
U/L Serum
Days

B


AST mean anti-CD37
dose 1
dose 2
dose 3
Gr,1 Conjugate XXIII, 5 - 10 - 15 mg/kg
Gr,2 Conjugate XXIV, 1 - 3 - 5 mg/kg
Gr,3 Conjugate XXV, 1 - 3 - 5 mg/kg
U/L Serum
Days

C

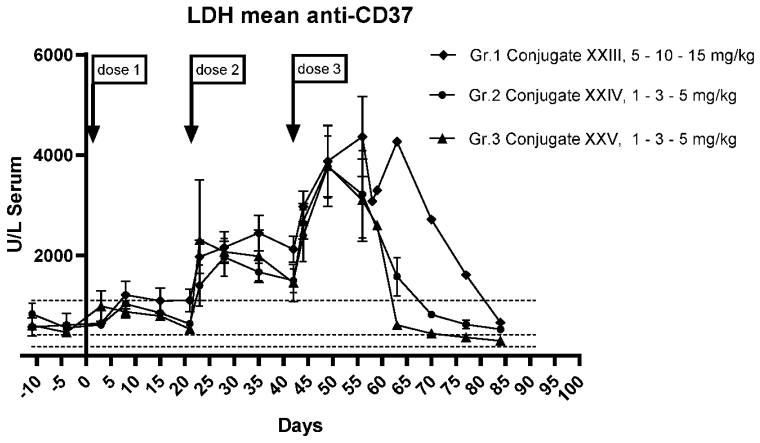
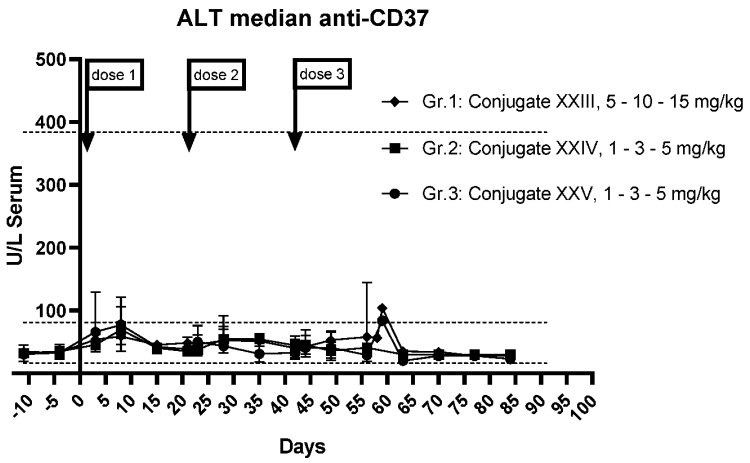
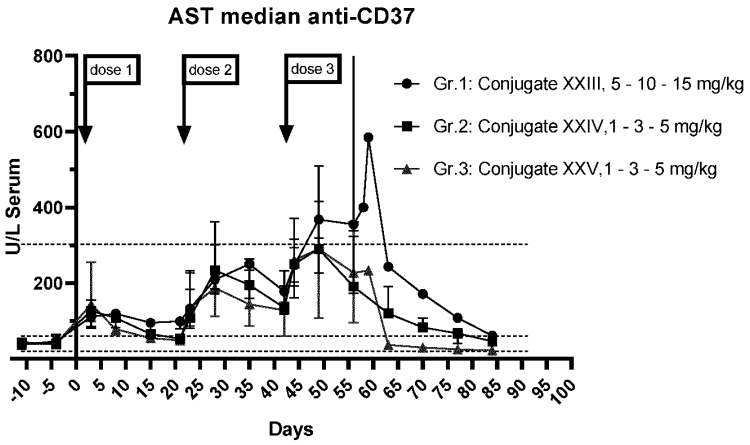

LDH mean anti-CD37
dose 1
dose 2
dose 3
Gr.1 Conjugate XXIII, 5 - 10 - 15 mg/kg
Gr.2 Conjugate XXIV, 1 - 3 - 5 mg/kg
Gr.3 Conjugate XXV, 1 - 3 - 5 mg/kg
U/L Serum
Days

FIG. 13

D



E



F

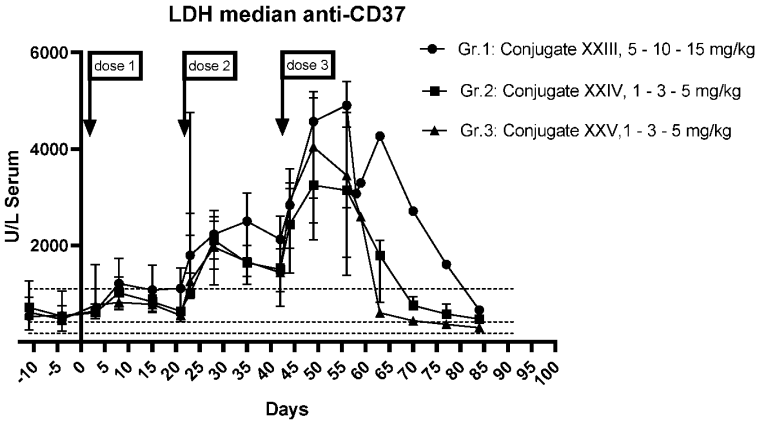
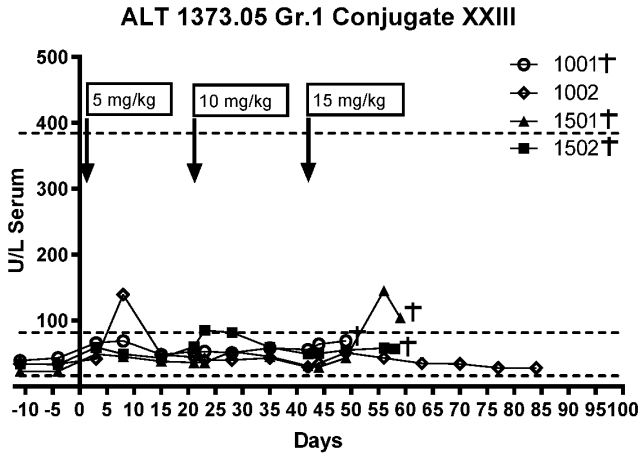
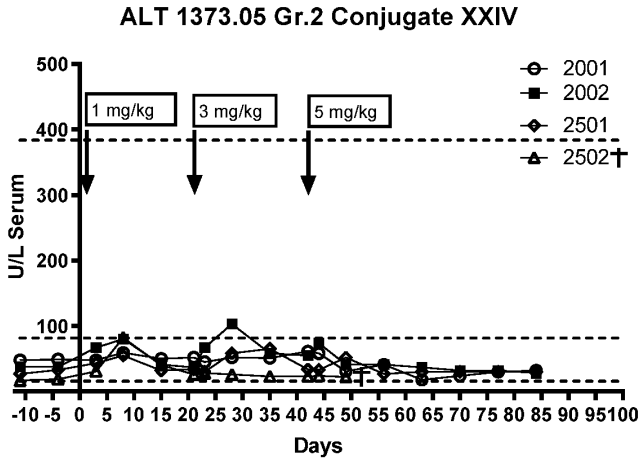


FIG. 13 (cont.)

A


ALT 1373.05 Gr.1 Conjugate XXIII
5 mg/kg
10 mg/kg
15 mg/kg
1001†
1002
1501†
1502†
U/L Serum
500
400
300
200
100
-10 -5 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95100
Days

B


ALT 1373.05 Gr.2 Conjugate XXIV
1 mg/kg
3 mg/kg
5 mg/kg
2001
2002
2501
2502†
U/L Serum
500
400
300
200
100
-10 -5 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95100
Days

C

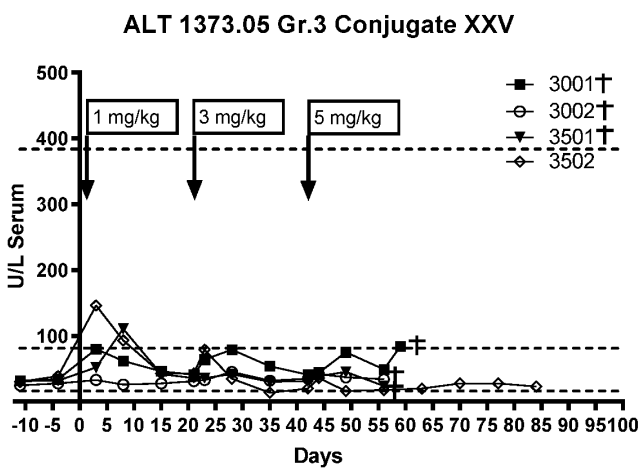
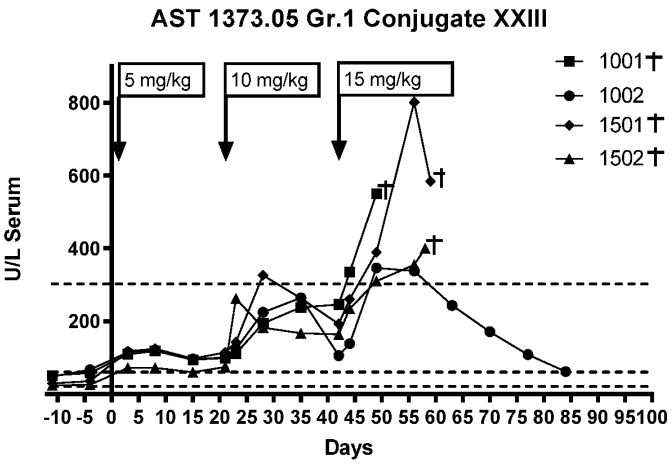
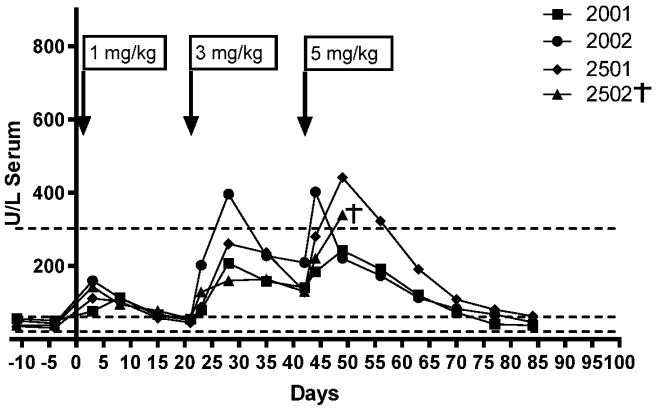

ALT 1373.05 Gr.3 Conjugate XXV
1 mg/kg
3 mg/kg
5 mg/kg
3001†
3002†
3501†
3502
U/L Serum
500
400
300
200
100
-10 -5 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95100
Days

FIG. 14

D



E



F

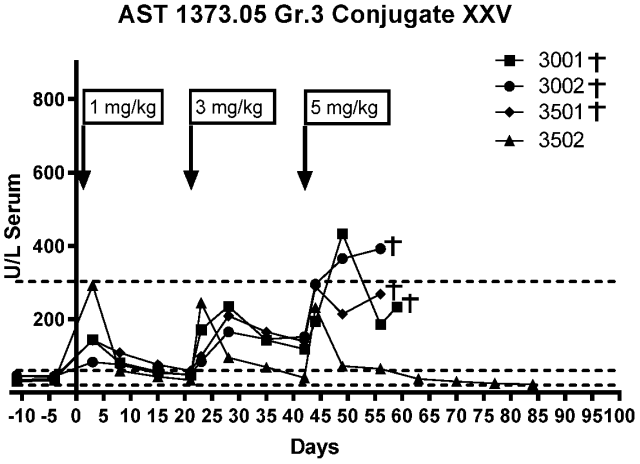
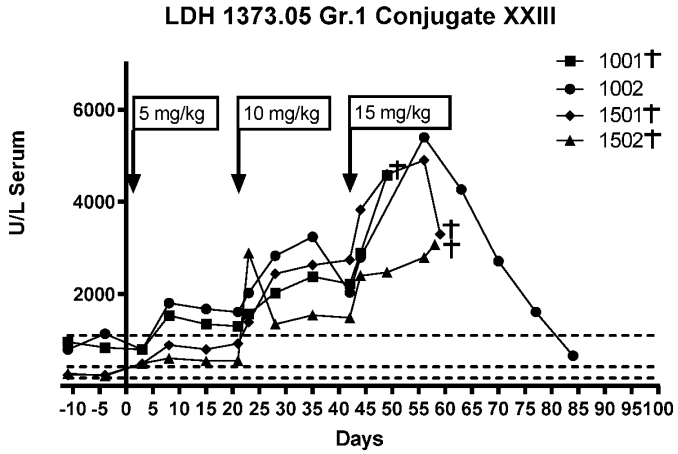
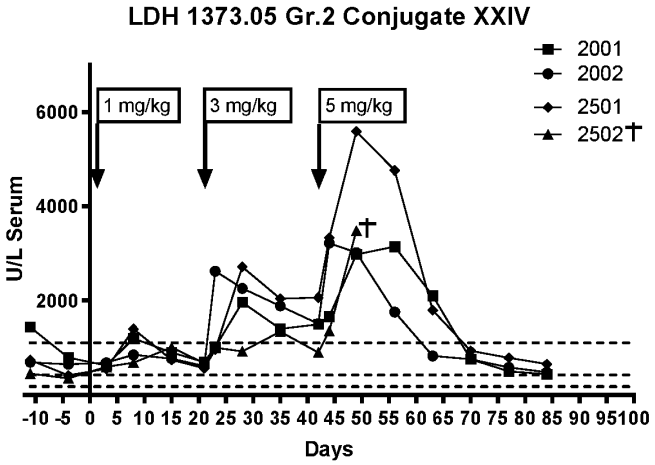


FIG. 14 (cont.)

G



H



I

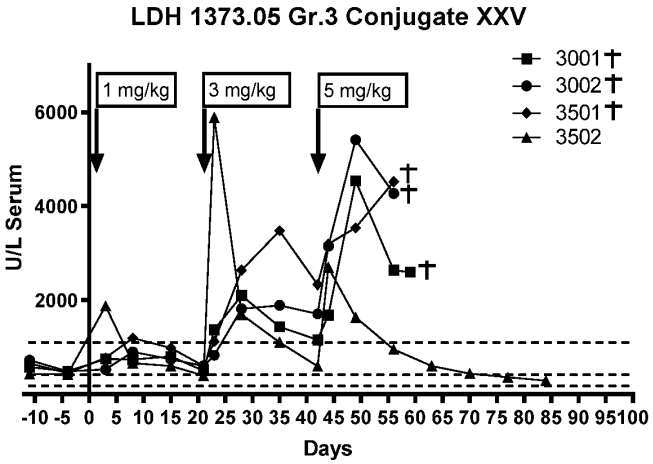
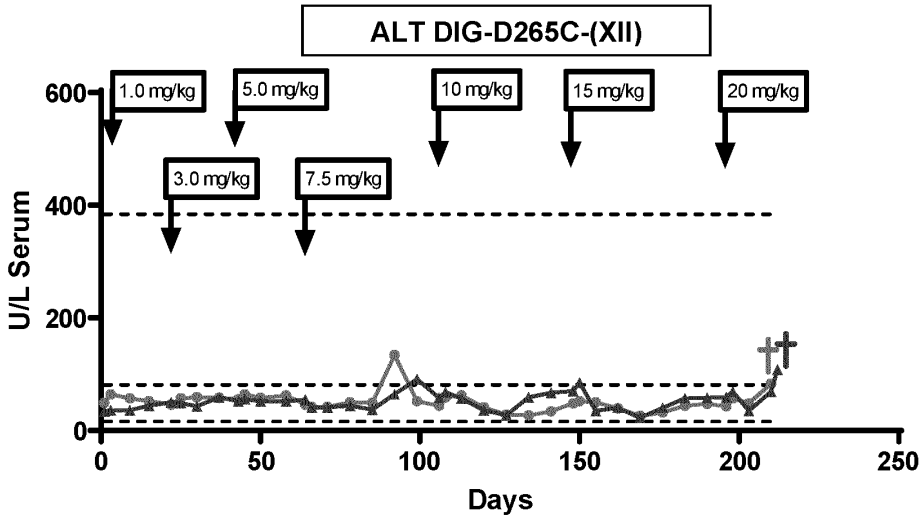


FIG. 14 (cont.)

A


ALT DIG-D265C-(XII)
1.0 mg/kg
5.0 mg/kg
10 mg/kg
15 mg/kg
20 mg/kg
3.0 mg/kg
7.5 mg/kg
U/L Serum
600
400
200
0
0
50
100
150
200
250
Days

B

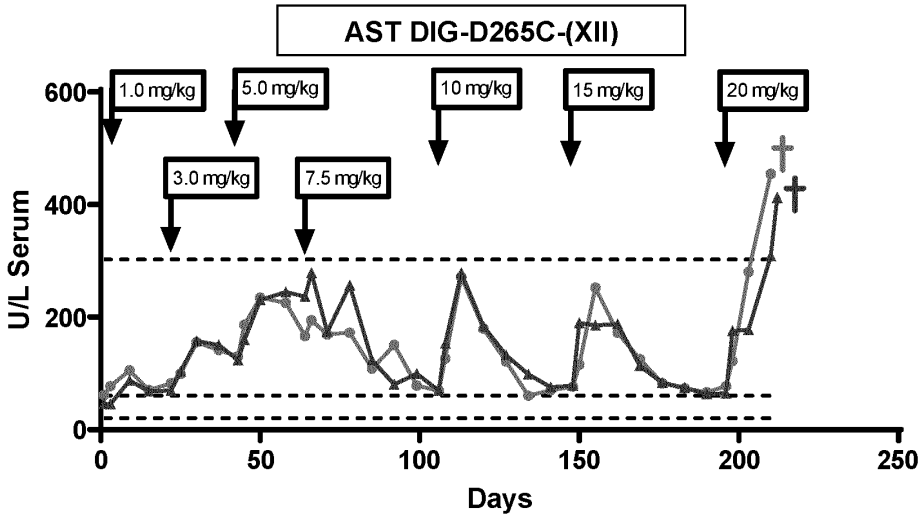

AST DIG-D265C-(XII)
1.0 mg/kg
5.0 mg/kg
10 mg/kg
15 mg/kg
20 mg/kg
3.0 mg/kg
7.5 mg/kg
U/L Serum
600
400
200
0
0
50
100
150
200
250
Days

FIG. 15

C

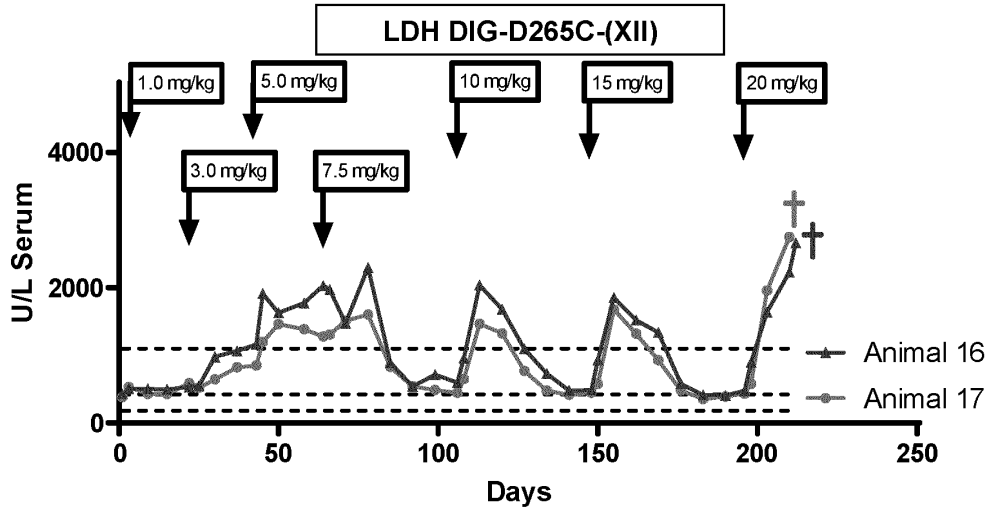
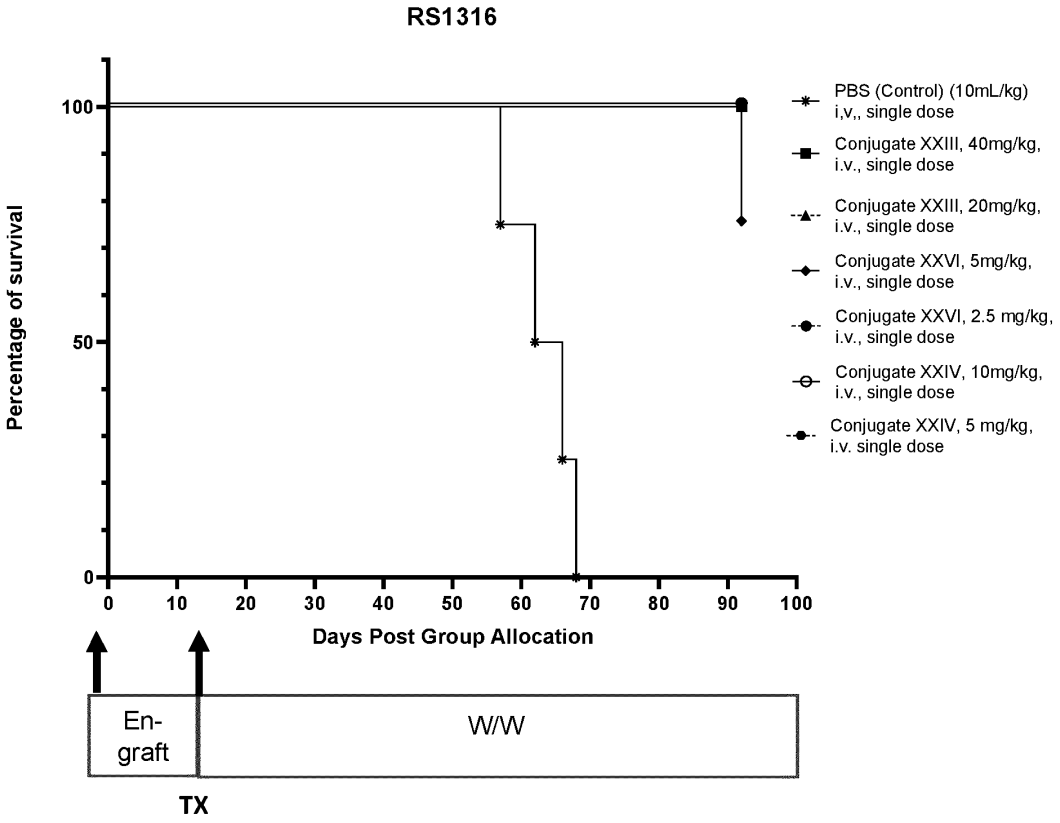

LDH DIG-D265C-(XII)
1.0 mg/kg
5.0 mg/kg
10 mg/kg
15 mg/kg
20 mg/kg
3.0 mg/kg
7.5 mg/kg
U/L Serum
4000
2000
0
0
50
100
150
200
250
Days
Animal 16
Animal 17

FIG. 15 (cont.)


RS1316
Percentage of survival
100
50
0
0 10 20 30 40 50 60 70 80 90 100
Days Post Group Allocation
PBS (Control) (10mL/kg) i,v,, single dose
Conjugate XXIII, 40mg/kg, i.v., single dose
Conjugate XXIII, 20mg/kg, i.v., single dose
Conjugate XXVI, 5mg/kg, i.v., single dose
Conjugate XXVI, 2.5 mg/kg, i.v., single dose
Conjugate XXIV, 10mg/kg, i.v., single dose
Conjugate XXIV, 5 mg/kg, i.v. single dose
En-graft
W/W
TX

B

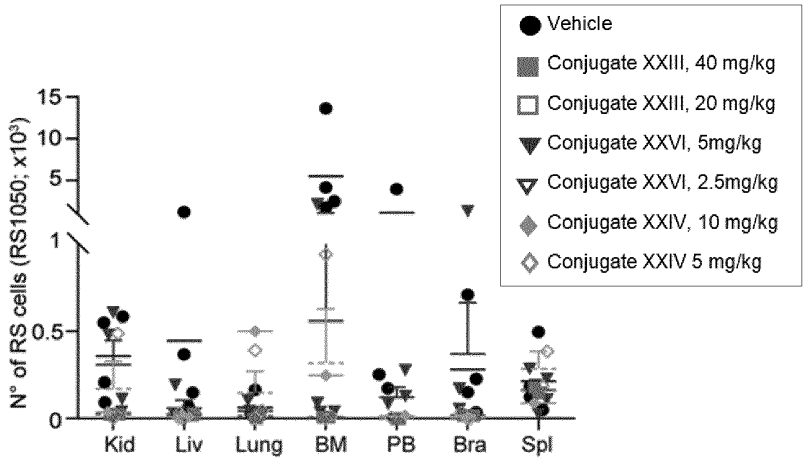

N° of RS cells (RS1050; x10³)
15
10
5
1
0.5
0
Kid
Liv
Lung
BM
PB
Bra
Spl
Vehicle
Conjugate XXIII, 40 mg/kg
Conjugate XXIII, 20 mg/kg
Conjugate XXVI, 5mg/kg
Conjugate XXVI, 2.5mg/kg
Conjugate XXIV, 10 mg/kg
Conjugate XXIV 5 mg/kg

Fig. 16

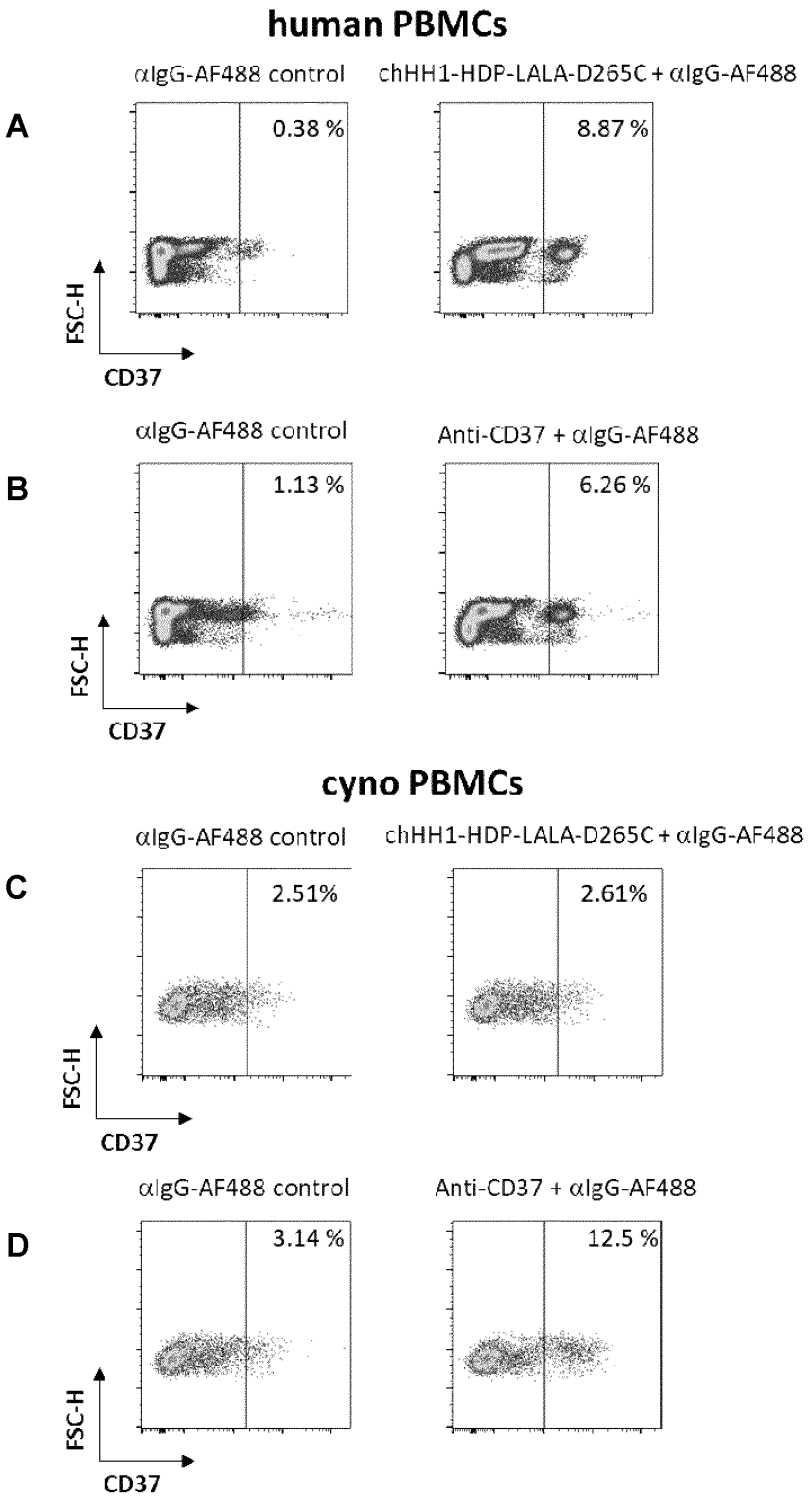
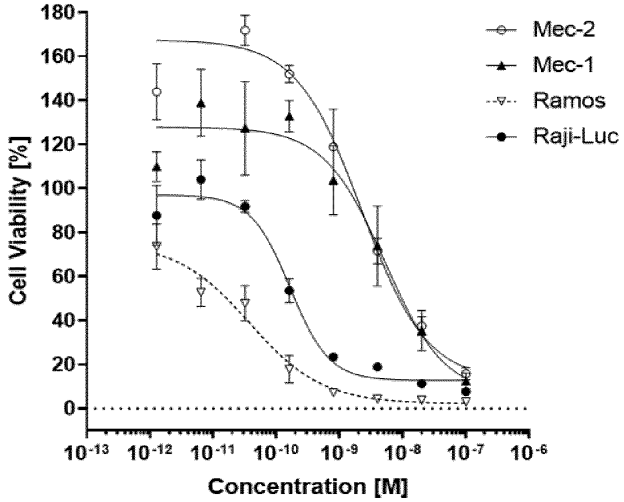

human PBMCs
αIgG-AF488 control
chHH1-HDP-LALA-D265C + αIgG-AF488
A
0.38 %
8.87 %
FSC-H
CD37
αIgG-AF488 control
Anti-CD37 + αIgG-AF488
B
1.13 %
6.26 %
FSC-H
CD37
cyno PBMCs
αIgG-AF488 control
chHH1-HDP-LALA-D265C + αIgG-AF488
C
2.51%
2.61%
FSC-H
CD37
αIgG-AF488 control
Anti-CD37 + αIgG-AF488
D
3.14 %
12.5 %
FSC-H
CD37

Fig. 17

Conjugate XXV

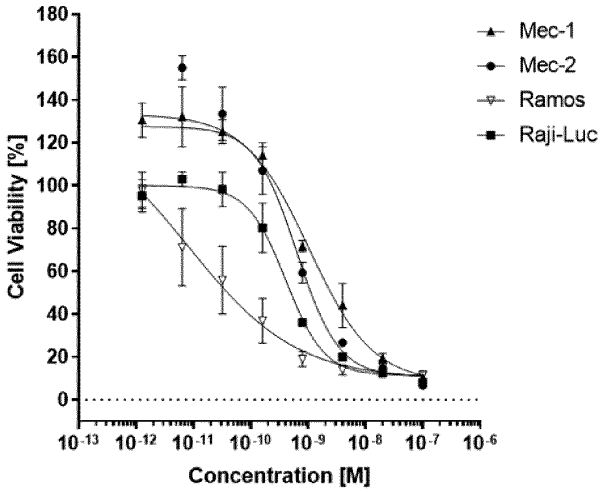
A



	EC_{50} [M] x 10^{-12}	Antibodies bound per cell (number of epitopes)
MEC-1	5173	33 000
MEC-2	2248	137 500
Ramos	37.7	31 500
Raji-Luc	165	32 500

Conjugate XIII

B



	EC_{50} [M] x 10^{-12}	Antibodies bound per cell (number of epitopes)
MEC-1	1033	33 000
MEC-2	631	137 500
Ramos	8.34	31 500
Raji-Luc	411	32 500

Fig. 18