Fig. 1a

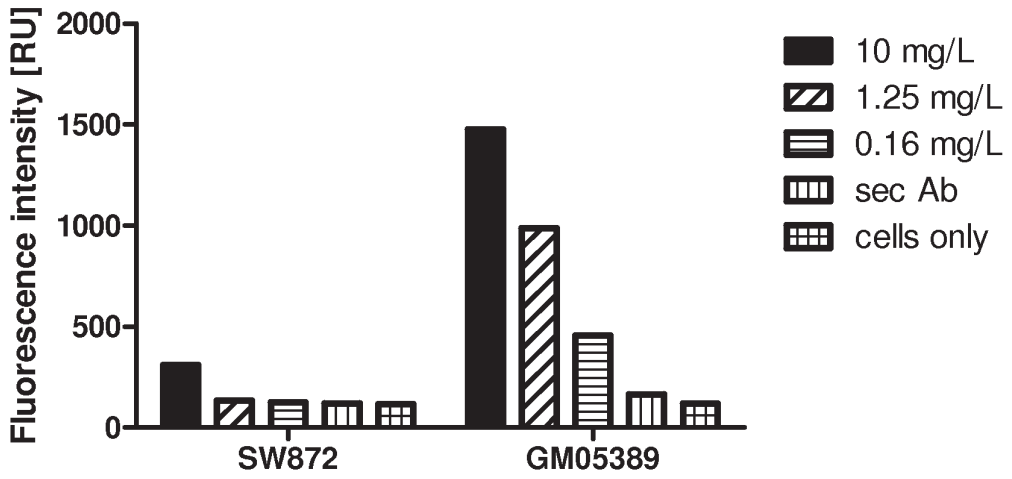

Fluorescence intensity [RU]
2000
1500
1000
500
0
SW872
GM05389
10 mg/L
1.25 mg/L
0.16 mg/L
sec Ab
cells only

Fig. 1b

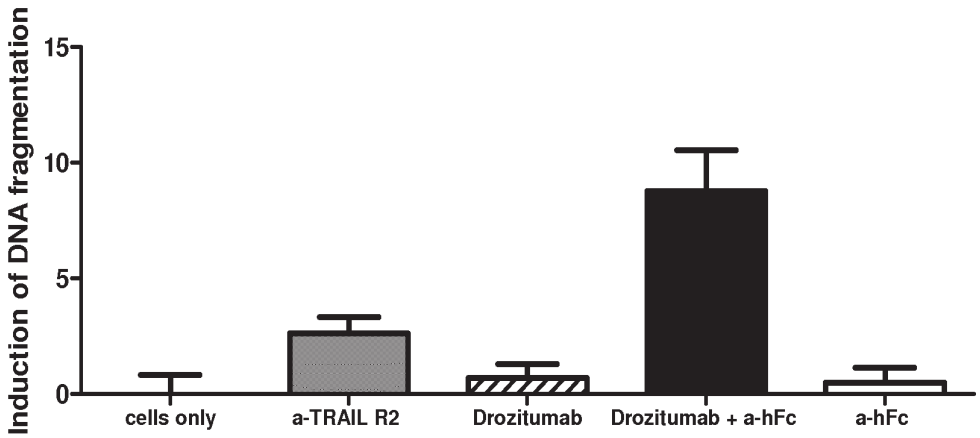

Induction of DNA fragmentation
15
10
5
0
cells only
a-TRAIL R2
Drozitumab
Drozitumab + a-hFc
a-hFc

Fig. 2

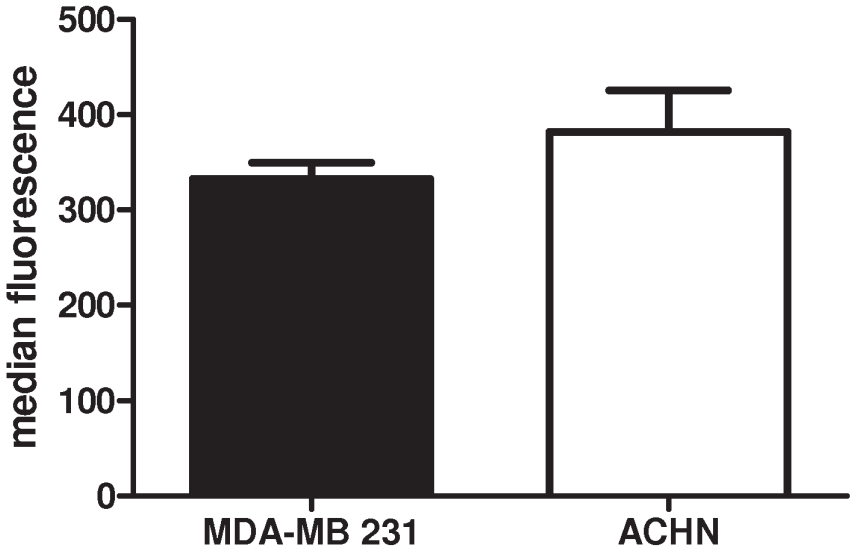


Fig. 3a

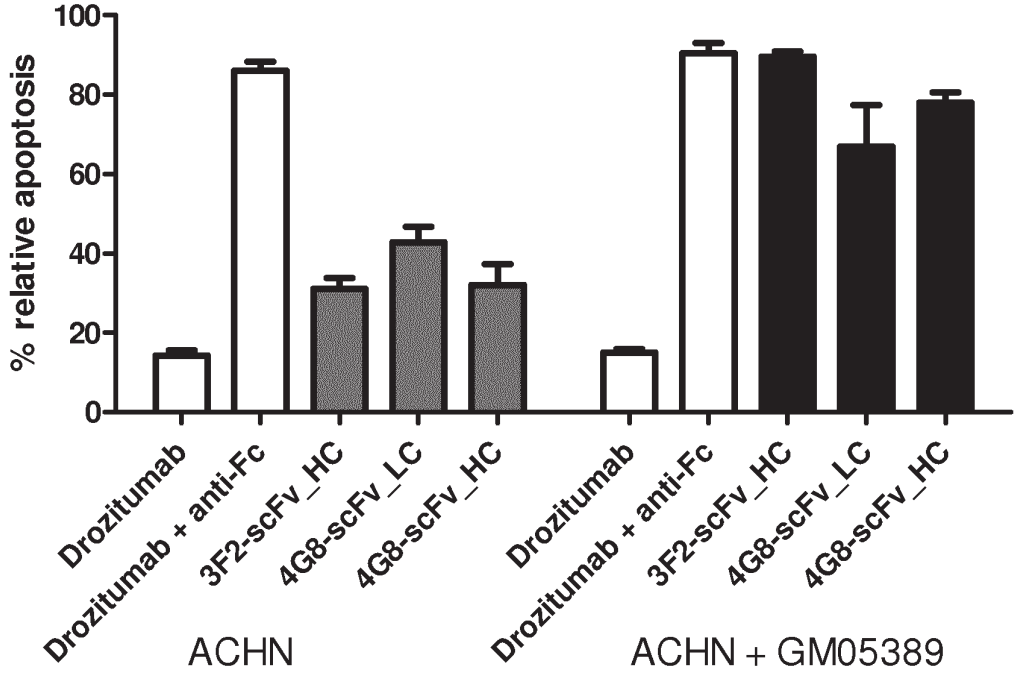

% relative apoptosis
100
80
60
40
20
0
Drozitumab
Drozitumab + anti-Fc
3F2-scFv_HC
4G8-scFv_LC
4G8-scFv_HC
Drozitumab
Drozitumab + anti-Fc
3F2-scFv_HC
4G8-scFv_LC
4G8-scFv_HC
ACHN
ACHN + GM05389

Fig. 3b

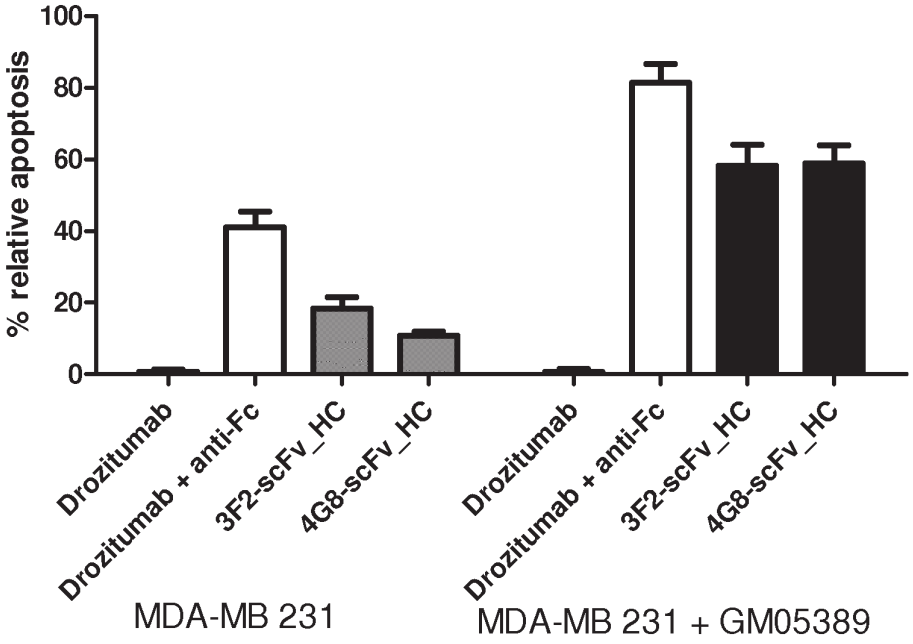

% relative apoptosis
100
80
60
40
20
0
Drozitumab
Drozitumab + anti-Fc
3F2-scFv_HC
4G8-scFv_HC
Drozitumab
Drozitumab + anti-Fc
3F2-scFv_HC
4G8-scFv_HC
MDA-MB 231
MDA-MB 231 + GM05389

Fig. 4a

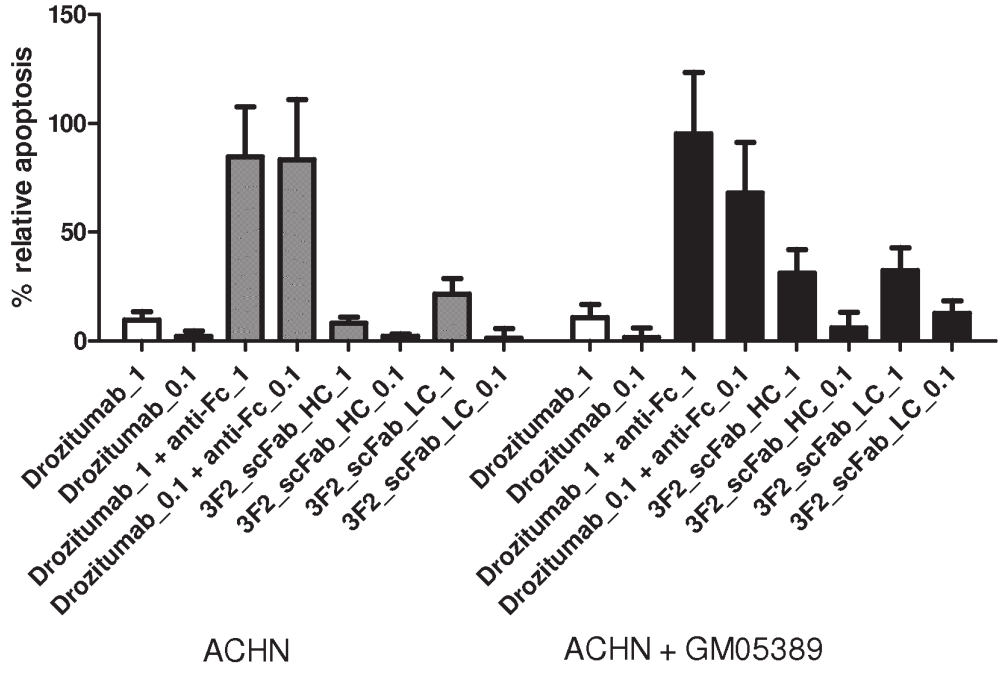

% relative apoptosis
150
100
50
0
Drozitumab_1
Drozitumab_0.1
Drozitumab_1 + anti-Fc_1
Drozitumab_0.1 + anti-Fc_1
3F2_scFab_HC_1
3F2_scFab_HC_0.1
3F2_scFab_LC_1
3F2_scFab_LC_0.1
Drozitumab_1
Drozitumab_0.1
Drozitumab_1 + anti-Fc_1
Drozitumab_0.1 + anti-Fc_1
3F2_scFab_HC_1
3F2_scFab_HC_0.1
3F2_scFab_LC_1
3F2_scFab_LC_0.1
ACHN
ACHN + GM05389

Fig. 4b

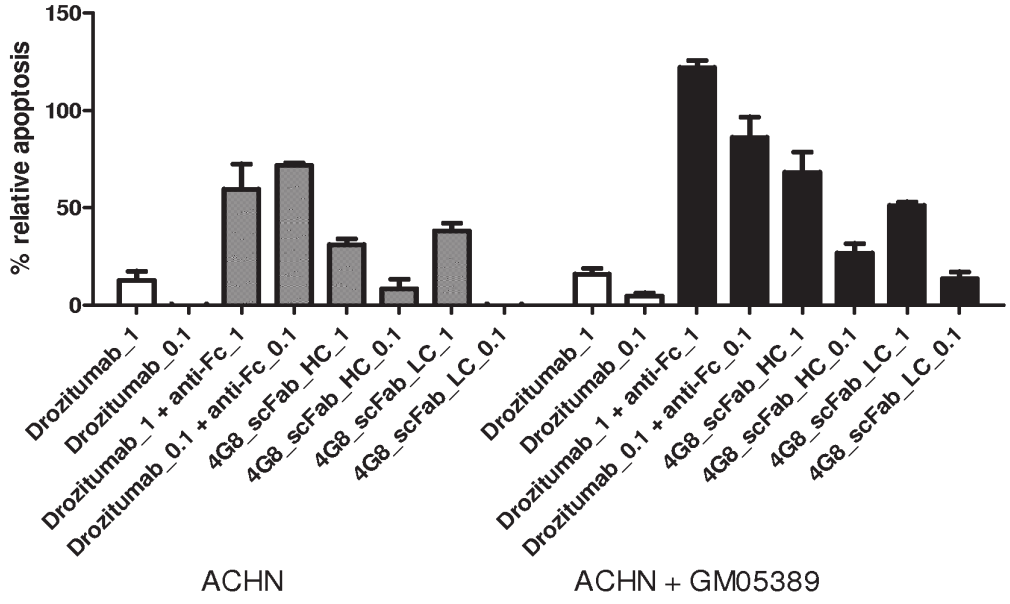

% relative apoptosis
150
100
50
0
Drozitumab_1
Drozitumab_0.1
Drozitumab_1 + anti-Fc_1
Drozitumab_0.1 + anti-Fc_1
4G8_scFab_HC_1
4G8_scFab_HC_0.1
4G8_scFab_LC_1
4G8_scFab_LC_0.1
Drozitumab_1
Drozitumab_0.1
Drozitumab_1 + anti-Fc_1
Drozitumab_0.1 + anti-Fc_1
4G8_scFab_HC_1
4G8_scFab_HC_0.1
4G8_scFab_LC_1
4G8_scFab_LC_0.1
ACHN
ACHN + GM05389

Fig.5

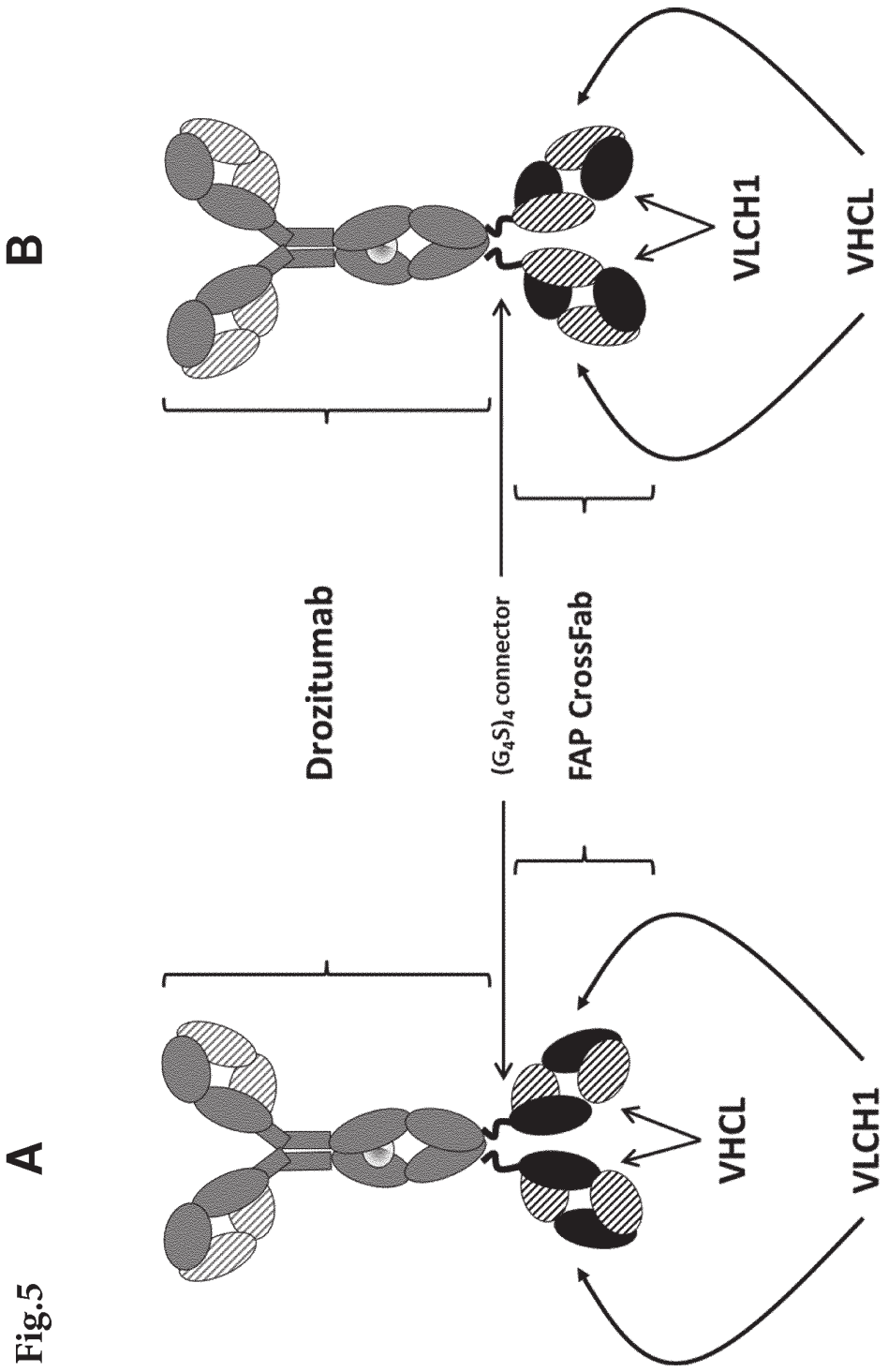

A
B
Drozitumab
(G4S)4 connector
FAP CrossFab
VHCL
VLCH1
VLCH1
VHCL

Fig. 6

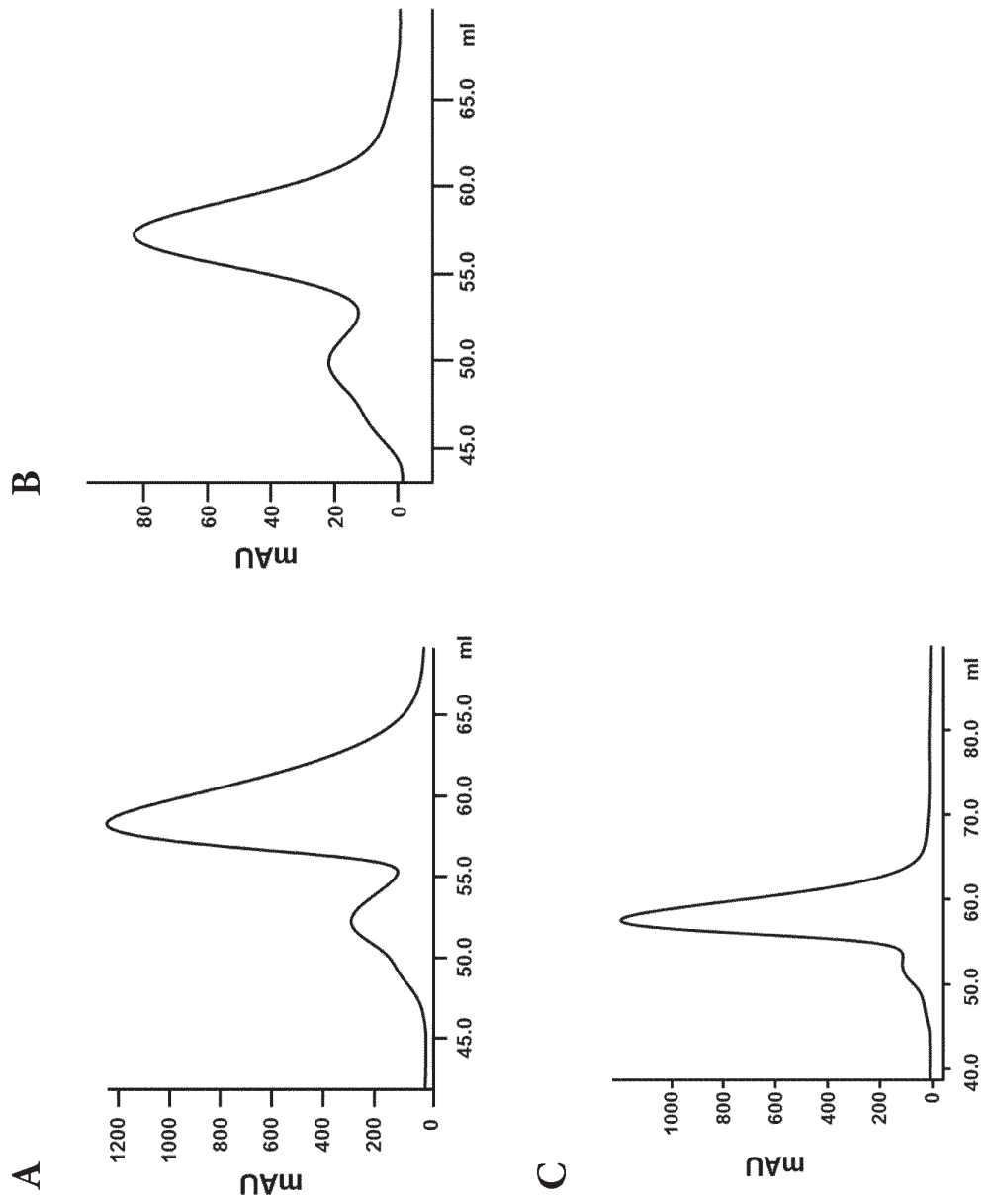

A
mAU
1200
1000
800
600
400
200
0
45.0
50.0
55.0
60.0
65.0
ml
B
mAU
80
60
40
20
0
45.0
50.0
55.0
60.0
65.0
ml
C
mAU
1000
800
600
400
200
0
40.0
50.0
60.0
70.0
80.0
ml

Fig. 7

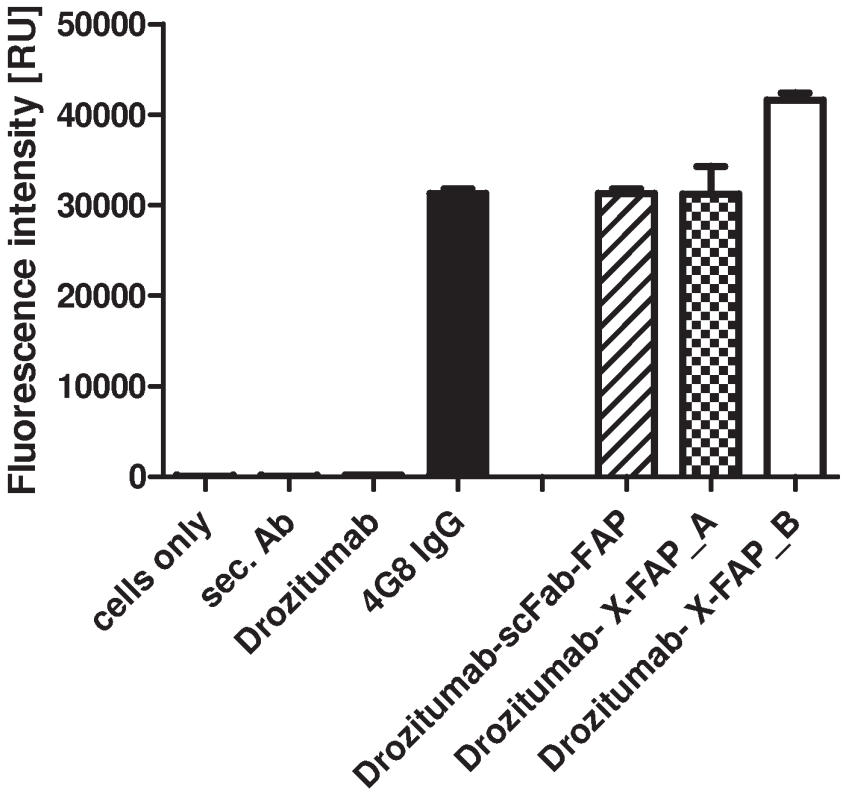

Fluorescence intensity [RU]
50000
40000
30000
20000
10000
0
cells only
sec. Ab
Drozitumab
4G8 IgG
Drozitumab-scFab-FAP
Drozitumab- X-FAP _A
Drozitumab- X-FAP _B

Fig. 8

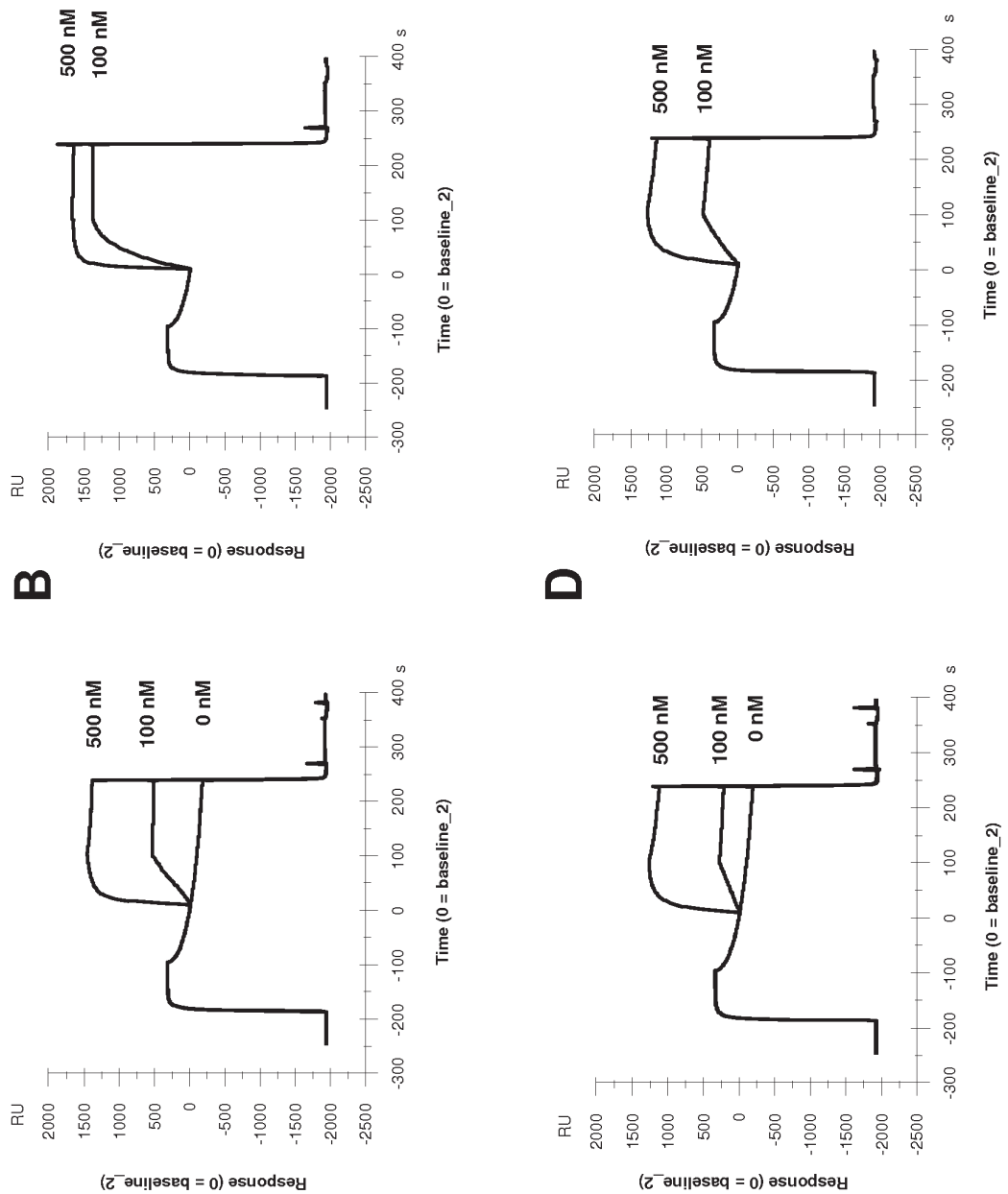

A
B
C
D
500 nM
100 nM
0 nM
RU
2000
1500
1000
500
0
-500
-1000
-1500
-2000
-2500
-300
-200
-100
0
100
200
300
400 s
Response (0 = baseline_2)
Time (0 = baseline_2)

Fig. 9a

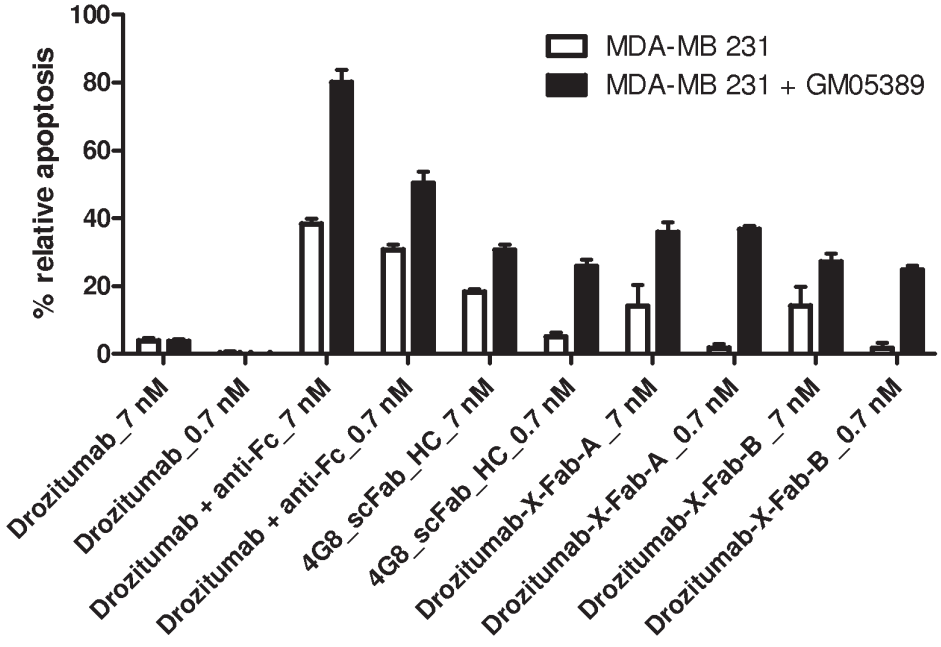

100
80
60
40
20
0
% relative apoptosis
MDA-MB 231
MDA-MB 231 + GM05389
Drozitumab_7 nM
Drozitumab_0.7 nM
Drozitumab + anti-Fc_7 nM
Drozitumab + anti-Fc_0.7 nM
4G8_scFab_HC_7 nM
4G8_scFab_HC_0.7 nM
Drozitumab-X-Fab-A _7 nM
Drozitumab-X-Fab-A _0.7 nM
Drozitumab-X-Fab-B _7 nM
Drozitumab-X-Fab-B _0.7 nM

Fig. 9b

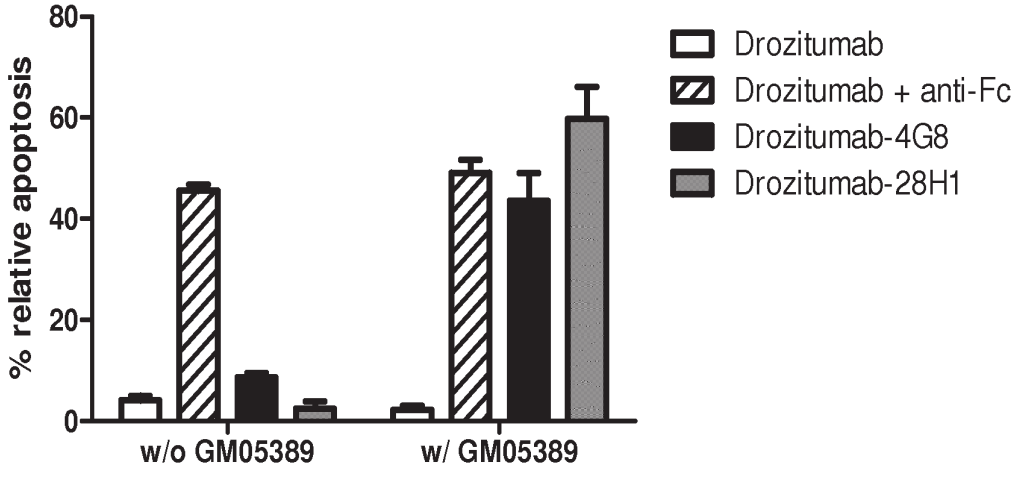

80
60
40
20
0
% relative apoptosis
Drozitumab
Drozitumab + anti-Fc
Drozitumab-4G8
Drozitumab-28H1
w/o GM05389
w/ GM05389

Fig. 10

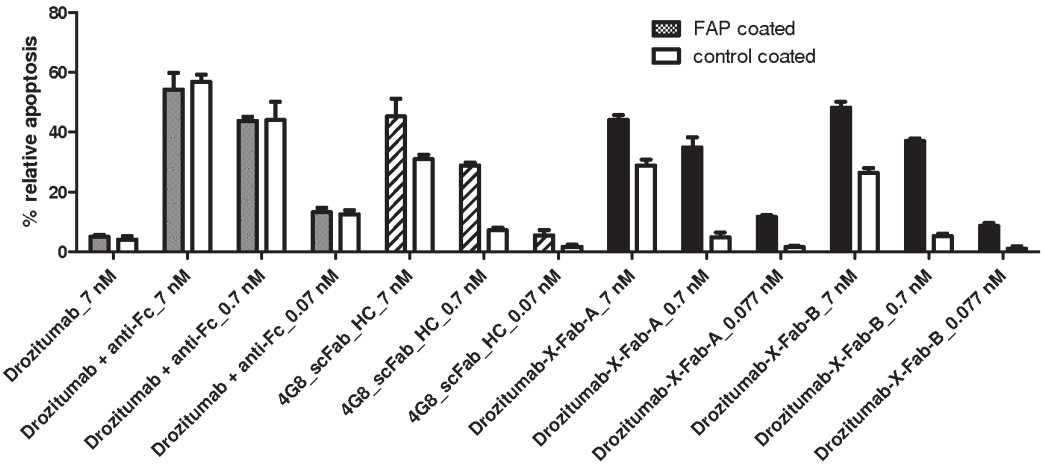
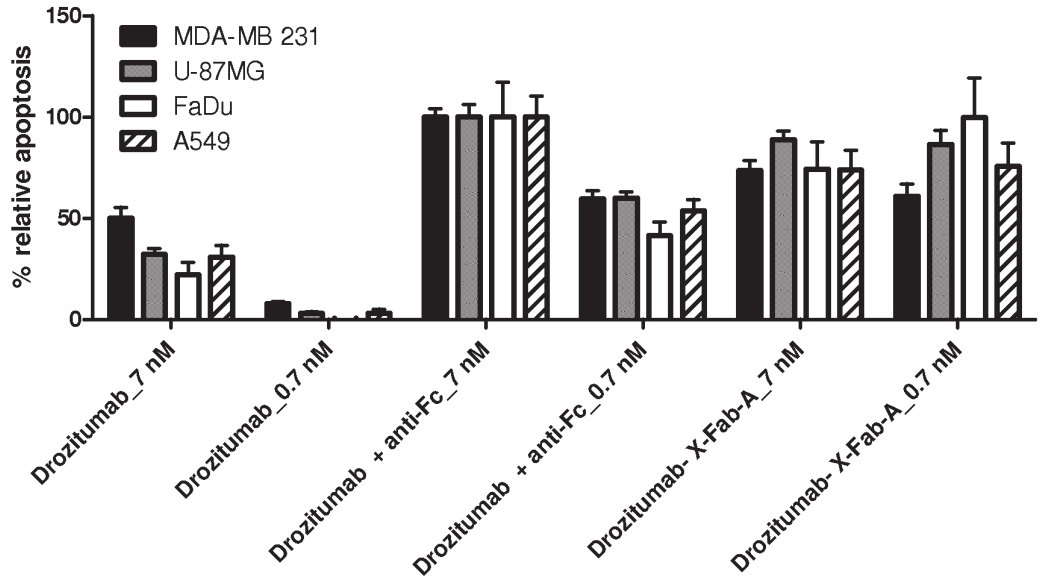
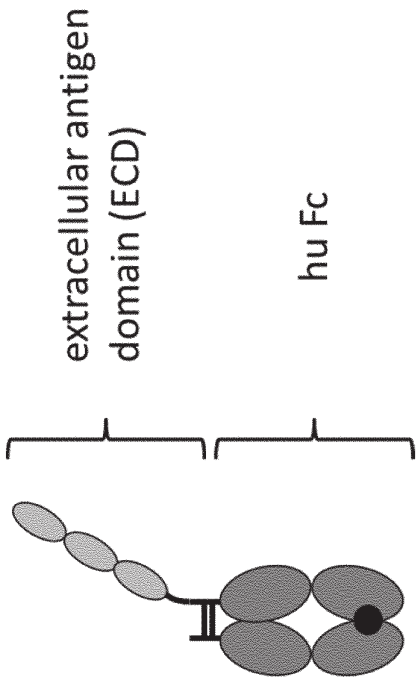

% relative apoptosis
80
60
40
20
0
FAP coated
control coated
Drozitumab_7 nM
Drozitumab + anti-Fc_7 nM
Drozitumab + anti-Fc_0.7 nM
Drozitumab + anti-Fc_0.07 nM
4G8_scFab_HC_7 nM
4G8_scFab_HC_0.7 nM
4G8_scFab_HC_0.07 nM
Drozitumab-X-Fab-A_7 nM
Drozitumab-X-Fab-A_0.7 nM
Drozitumab-X-Fab-A_0.077 nM
Drozitumab-X-Fab-B_7 nM
Drozitumab-X-Fab-B_0.7 nM
Drozitumab-X-Fab-B_0.077 nM

Fig. 11


% relative apoptosis
150
100
50
0
MDA-MB 231
U-87MG
FaDu
A549
Drozitumab_7 nM
Drozitumab_0.7 nM
Drozitumab + anti-Fc_7 nM
Drozitumab + anti-Fc_0.7 nM
Drozitumab- X-Fab-A_7 nM
Drozitumab- X-Fab-A_0.7 nM




A B C

Fig. 12

Fig. 13a

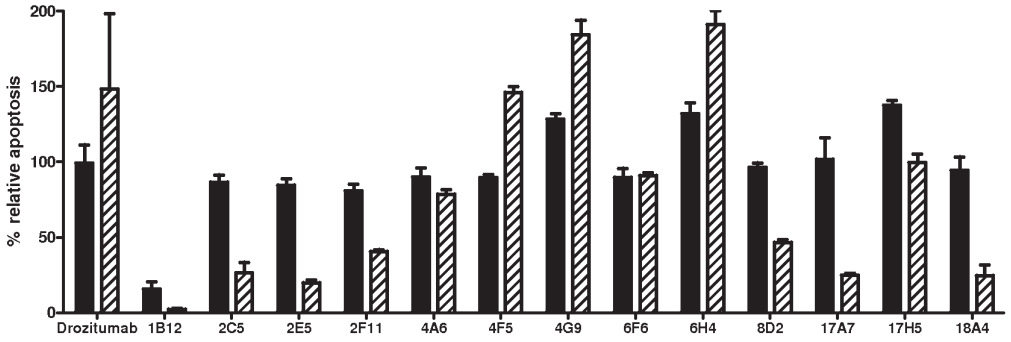



Fig. 13b

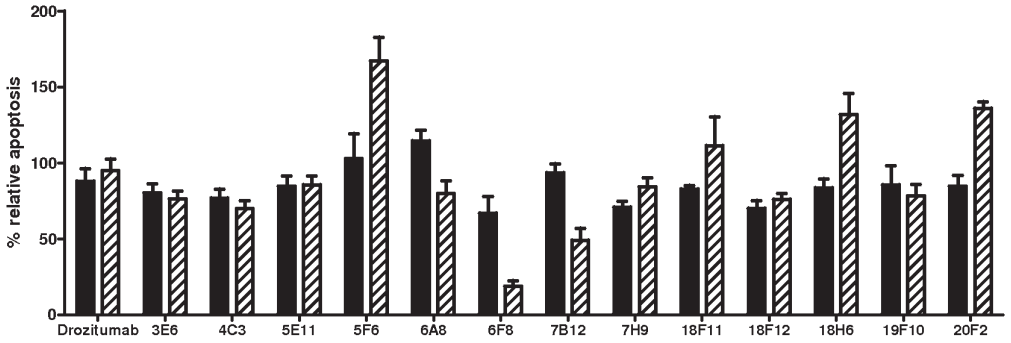



Fig. 13c

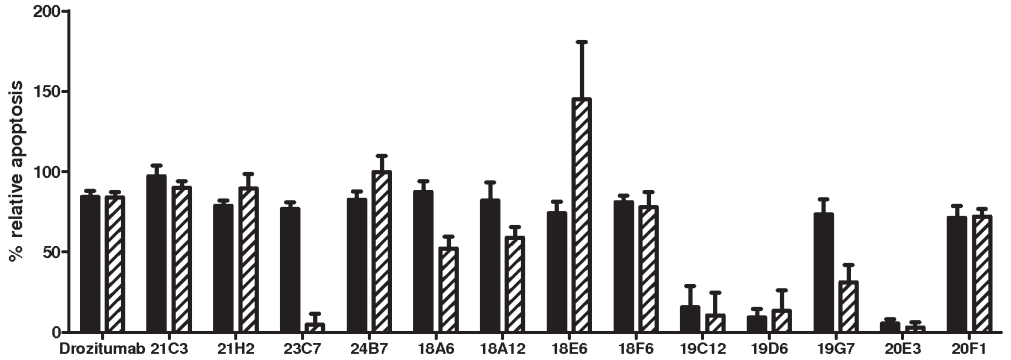


Fig. 13d

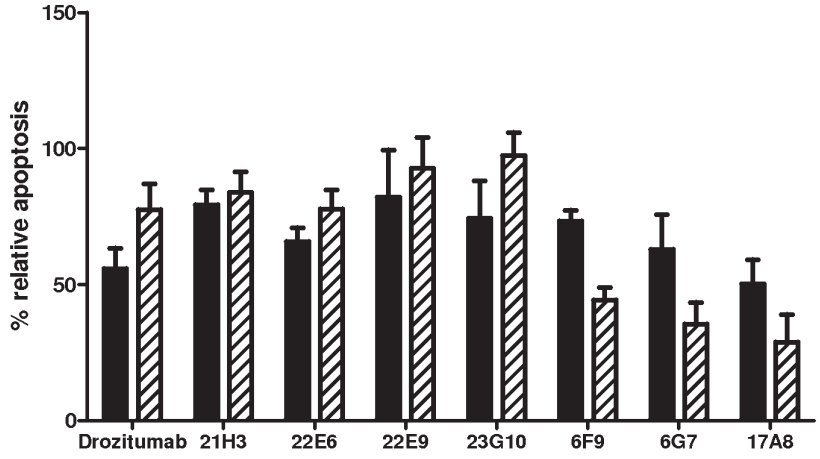



Fig. 14a

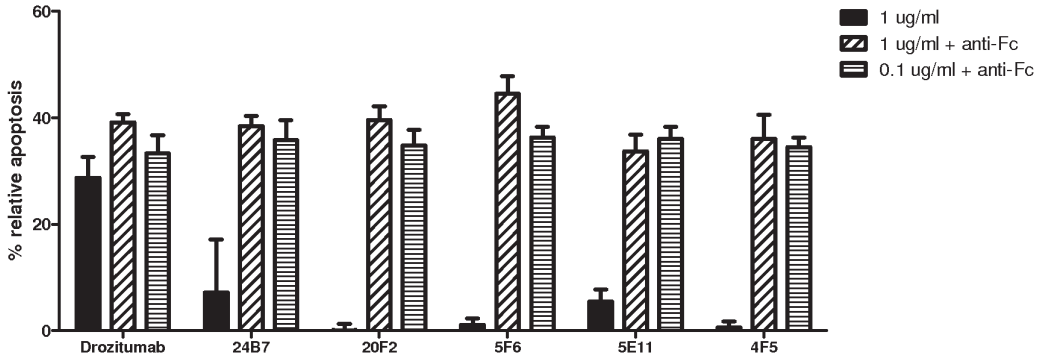


Fig. 14b

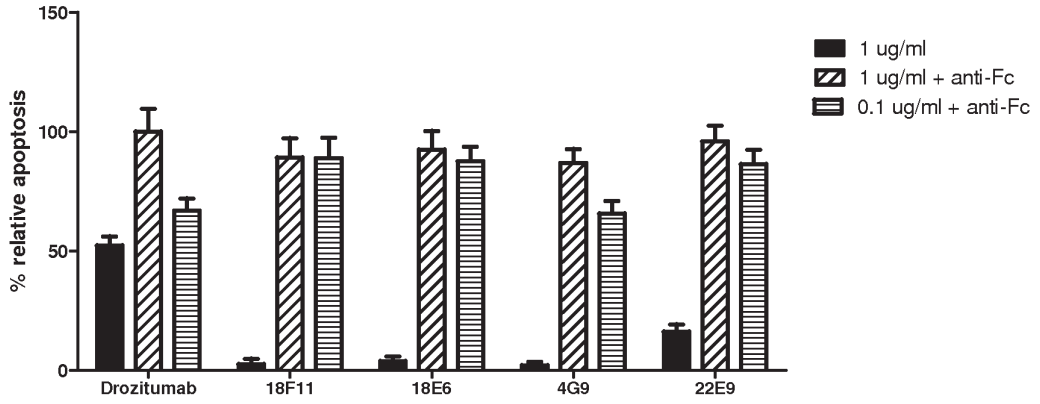
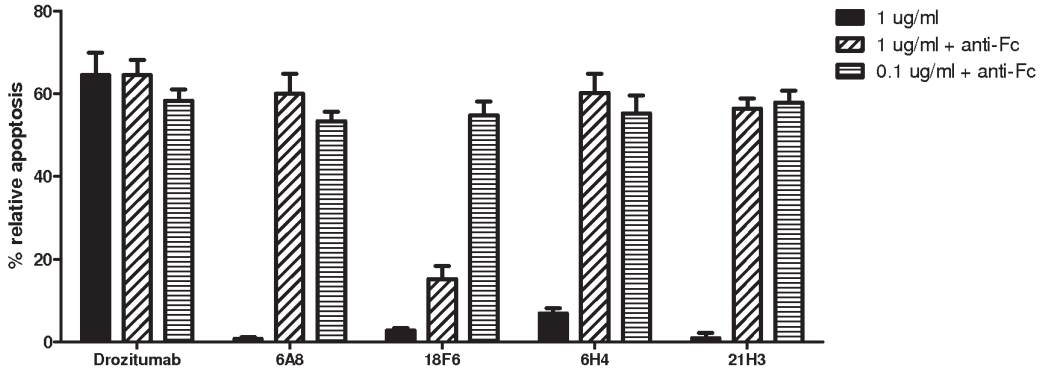



Fig. 14c



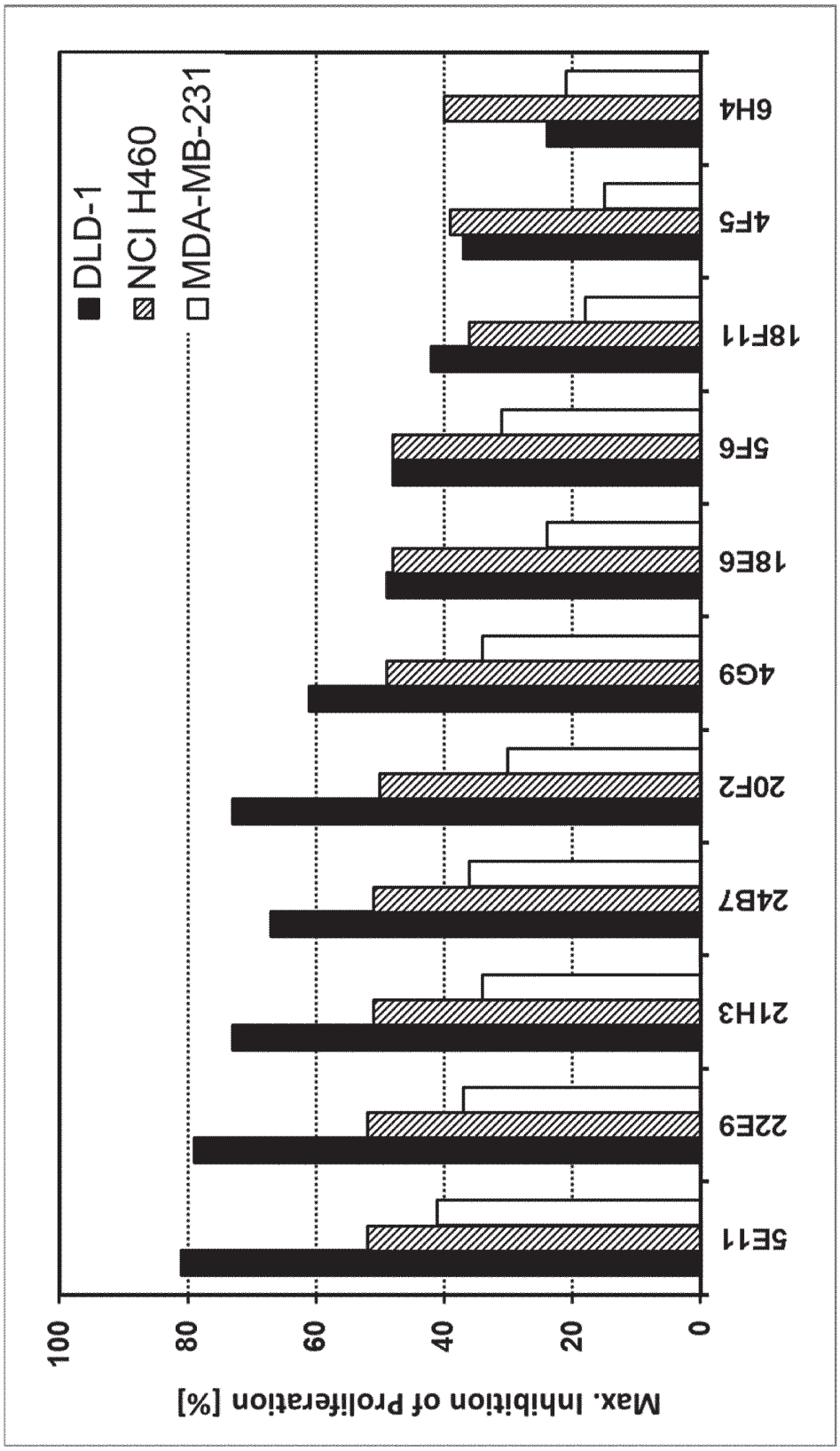

DLD-1
NCI H460
MDA-MB-231
Max. Inhibition of Proliferation [%]
0
20
40
60
80
100
5E11
22E9
21H3
24B7
20F2
4G9
18E6
5F6
18F11
4F5
6H4

Fig. 15

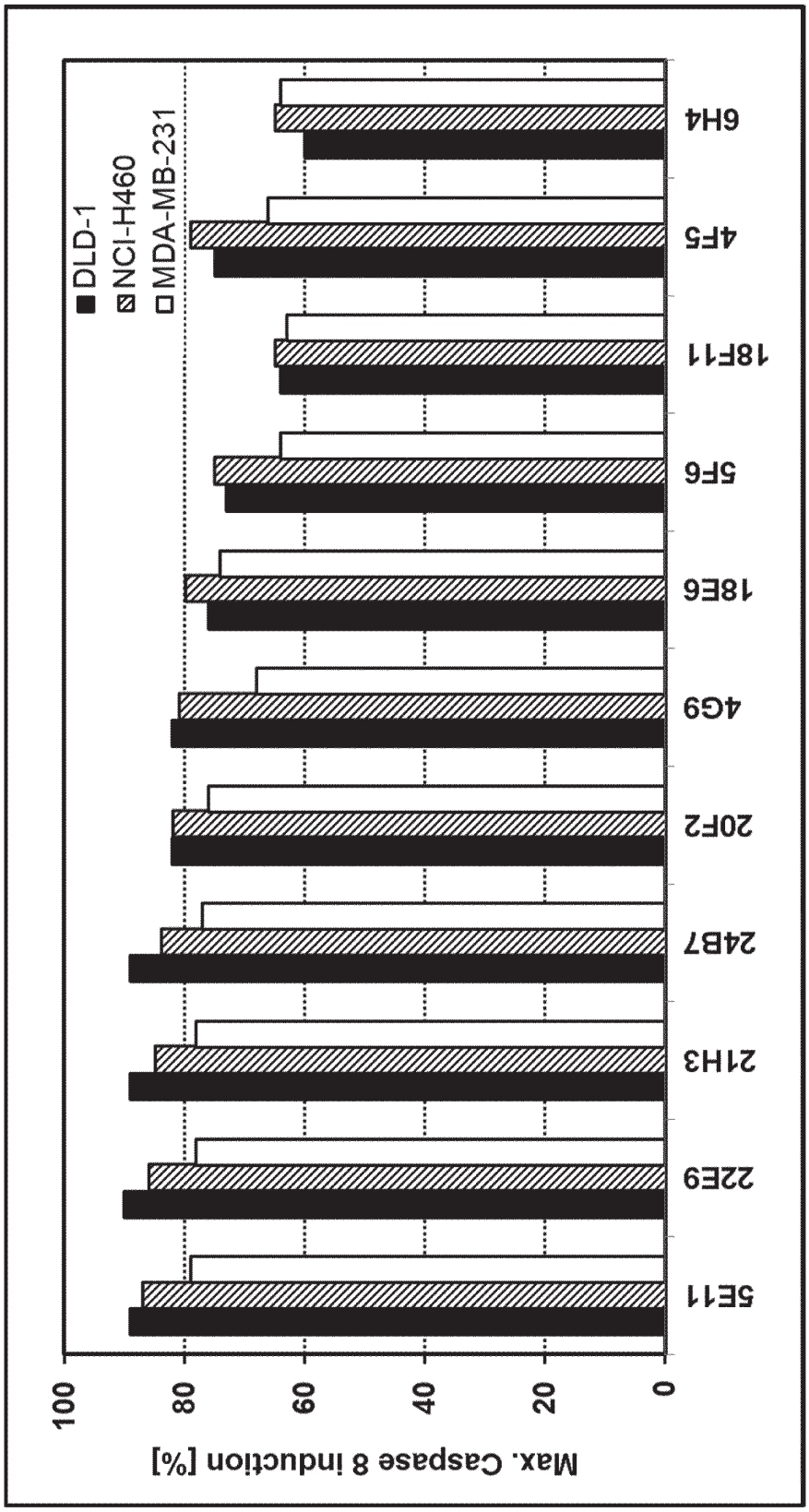

Max. Caspase 8 induction [%]
0
20
40
60
80
100
DLD-1
NCI-H460
MDA-MB-231
5E11
22E9
21H3
24B7
20F2
4G9
18E6
5F6
18F11
4F5
6H4

Fig. 16

Fig. 17

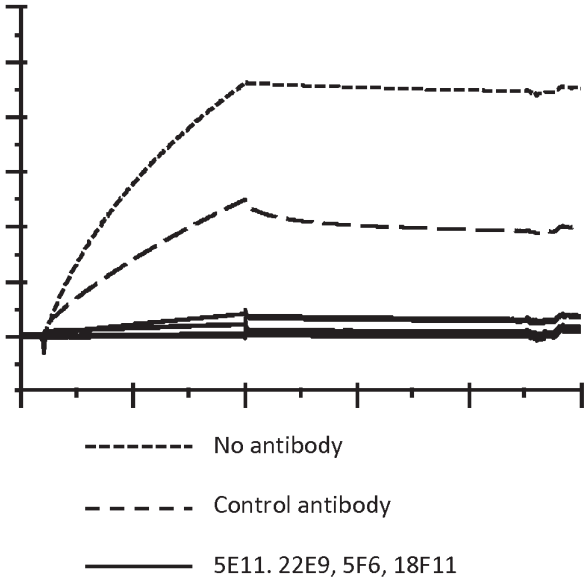
| | 5E11 | 22E9 | 174 | 422 | Drozitumab |
|---|---|---|---|---|---|
| 5E11 | 0 | 0 | 0 | 1 | 1 |
| 22E9 | 0 | 0 | 0 | 1 | 1 |
| 174 | 0 | 0 | 0 | 1 | 1 |
| 422 | 0 | 0 | 1 | 0 | 0 |
| Drozitumab | 1 | 1 | 1 | 1 | 0 |

1 = additional binding

0 = no additional binding

Fig. 18

A


No antibody
Control antibody
5E11. 22E9, 5F6, 18F11

B

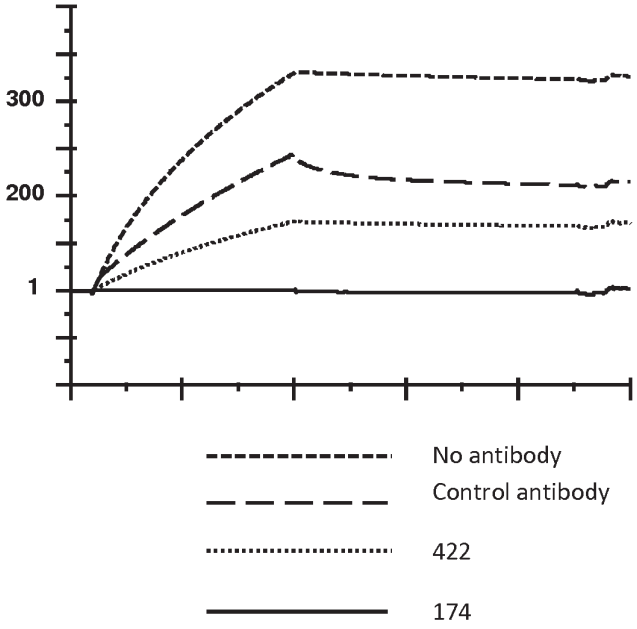

300
200
1
No antibody
Control antibody
422
174

Fig. 19

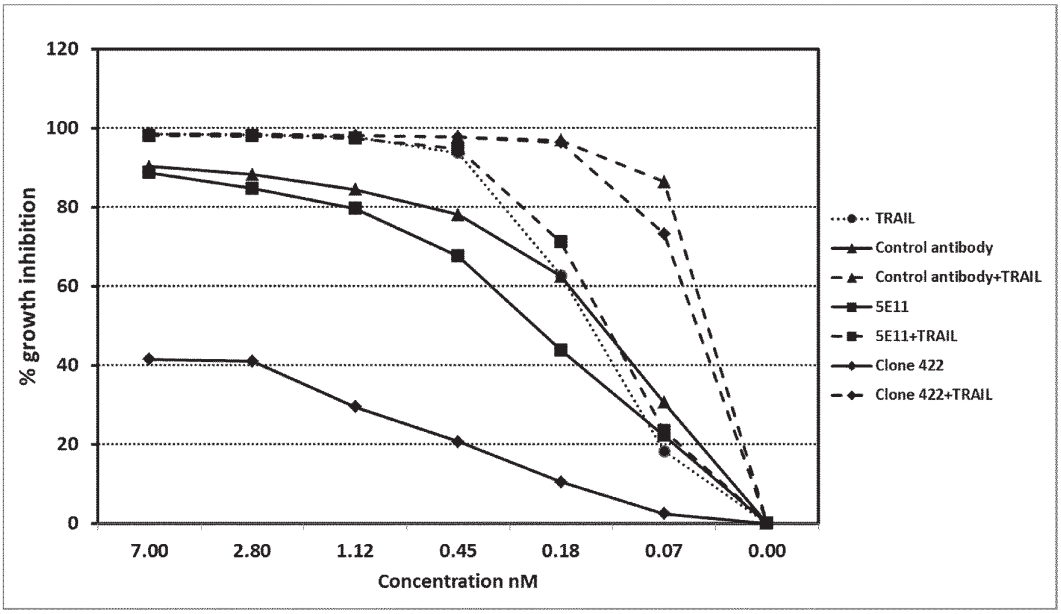



Fig. 20a

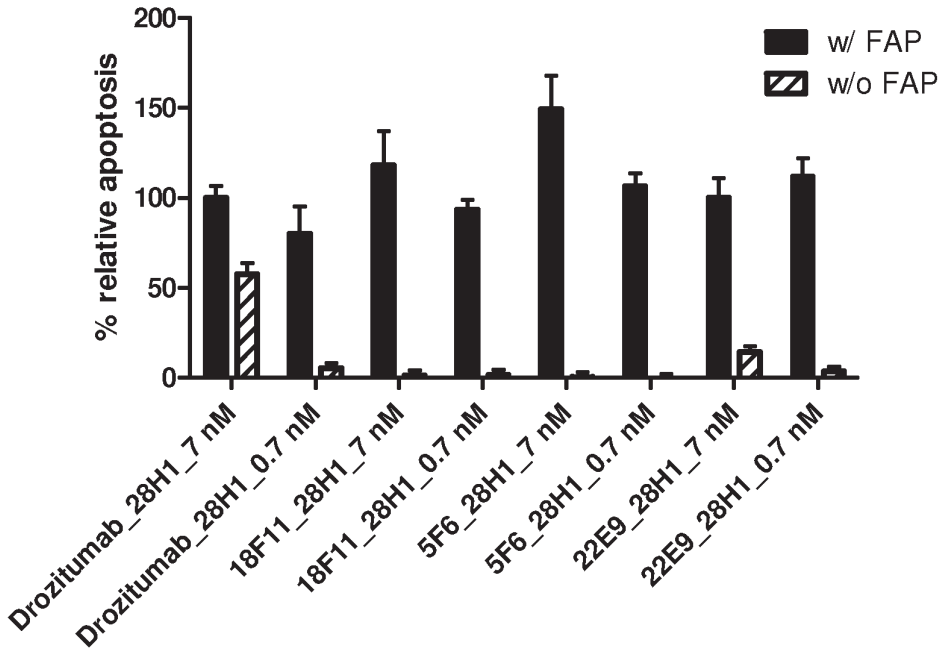


Fig. 20b

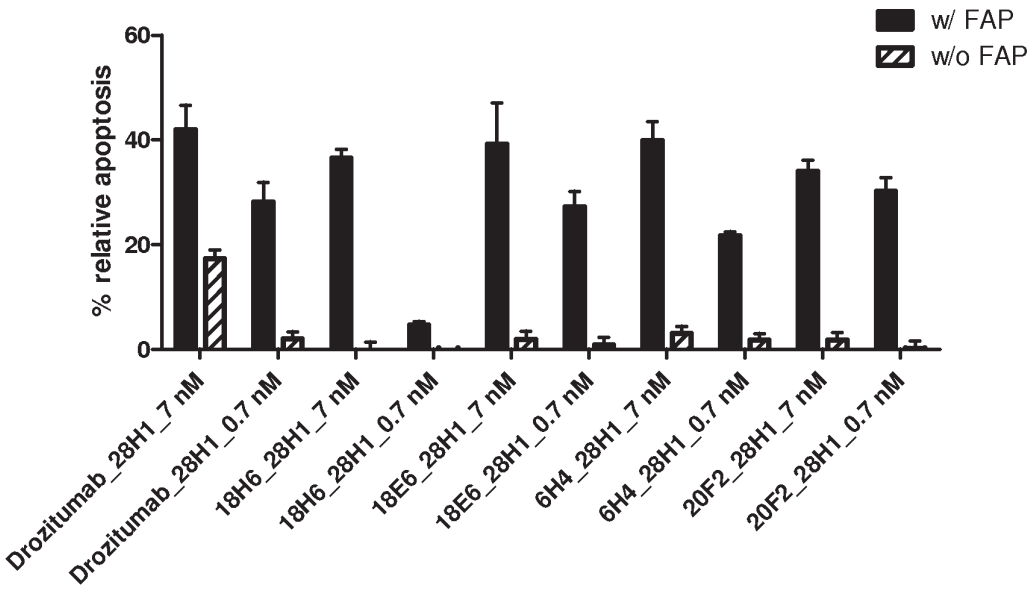



Fig. 21

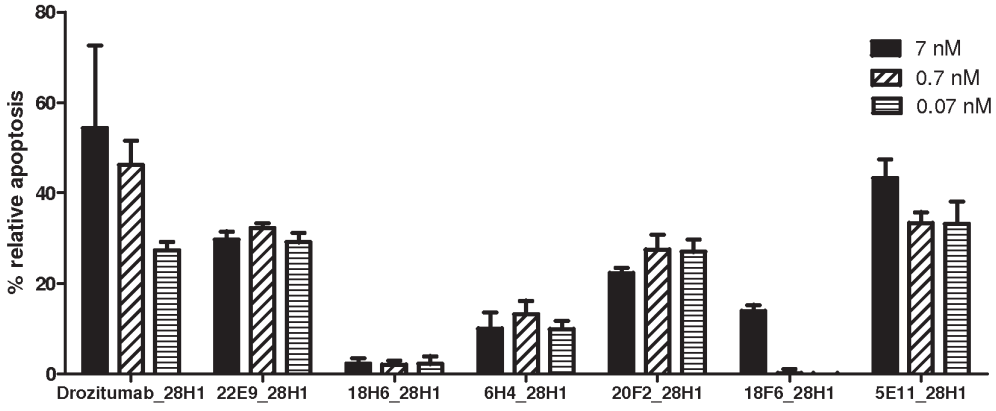


Fig. 22 a

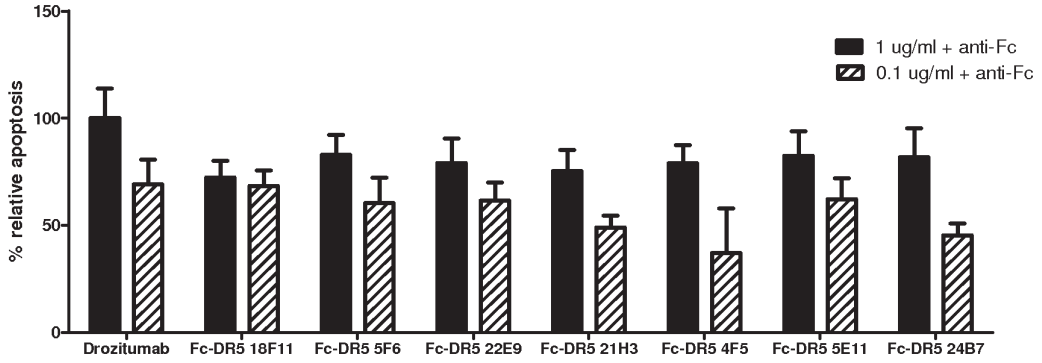
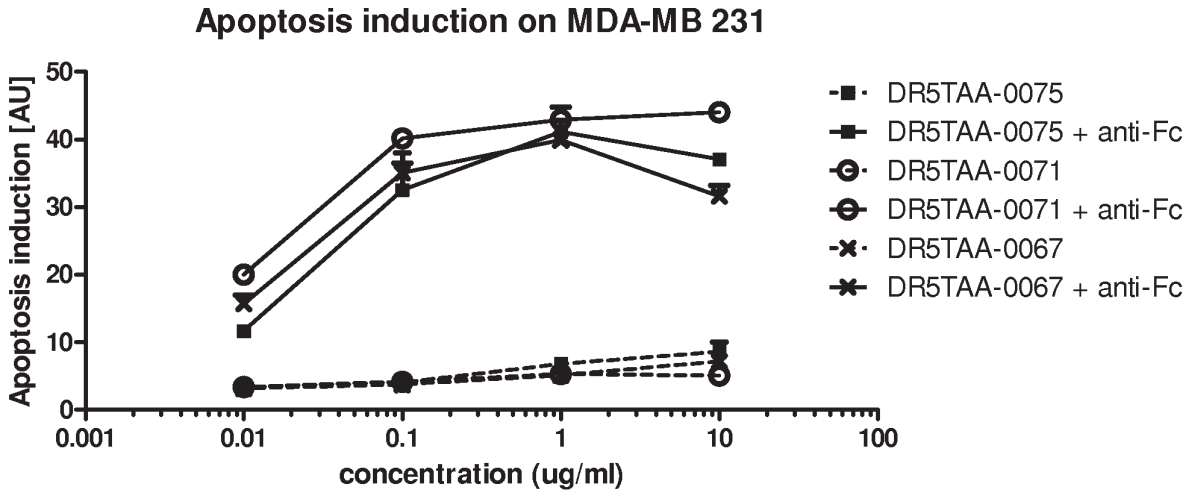
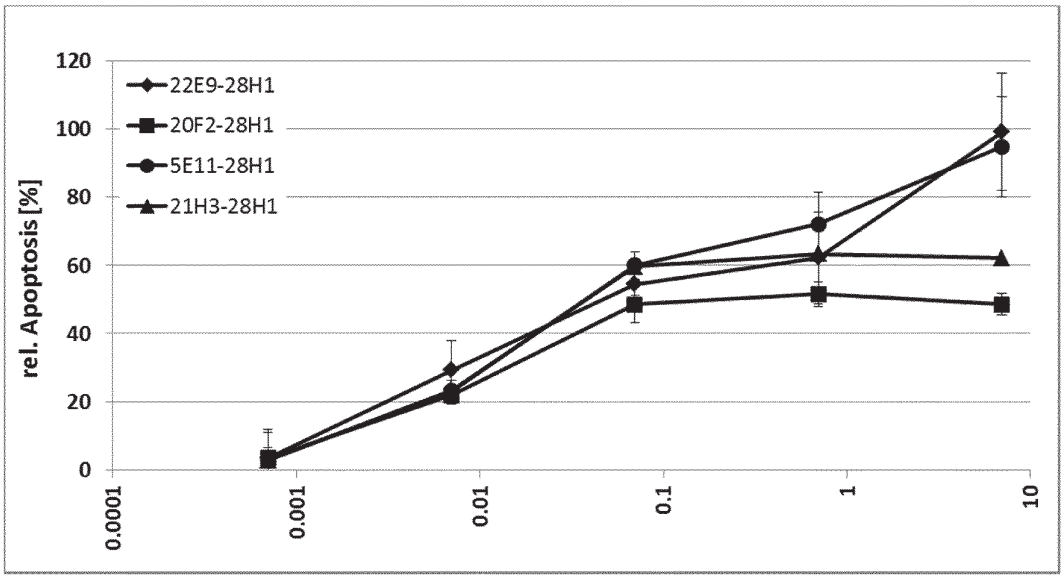



Fig. 22 b

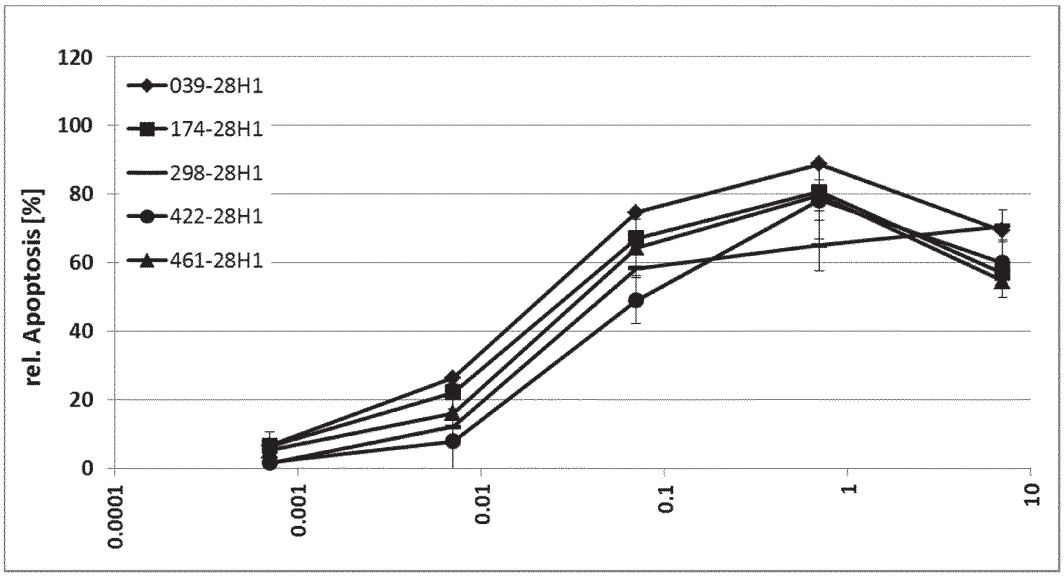


# Fig. 23

## A

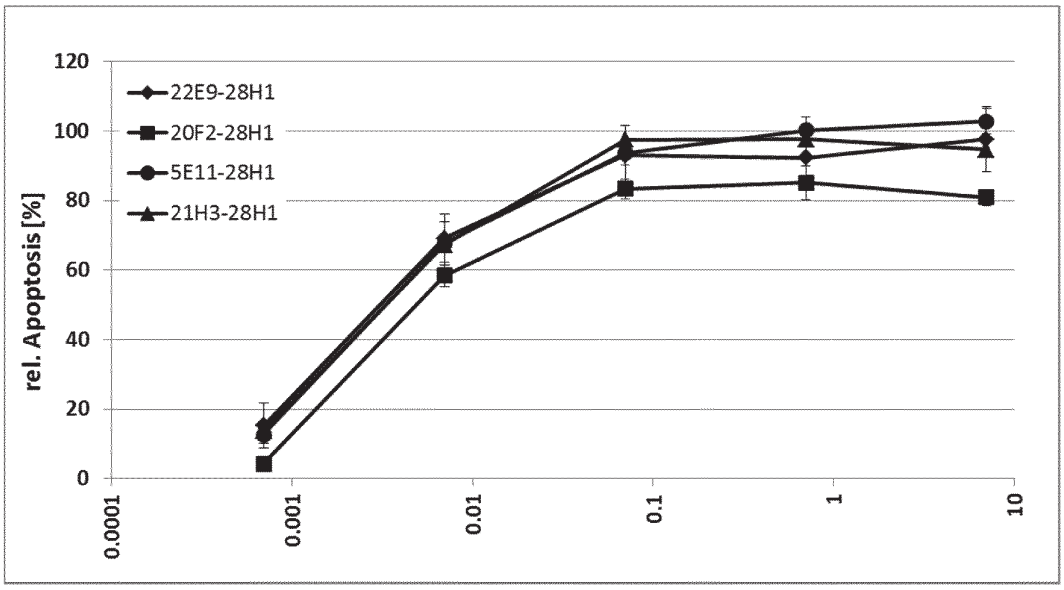

120
100
80
60
40
20
0
rel. Apoptosis [%]
22E9-28H1
20F2-28H1
5E11-28H1
21H3-28H1
0.0001
0.001
0.01
0.1
1
10

## B


120
100
80
60
40
20
0
rel. Apoptosis [%]
039-28H1
174-28H1
298-28H1
422-28H1
461-28H1
0.0001
0.001
0.01
0.1
1
10

# Fig. 24

A


120
100
80
60
40
20
0
rel. Apoptosis [%]
22E9-28H1
20F2-28H1
5E11-28H1
21H3-28H1
0.0001
0.001
0.01
0.1
1
10

B

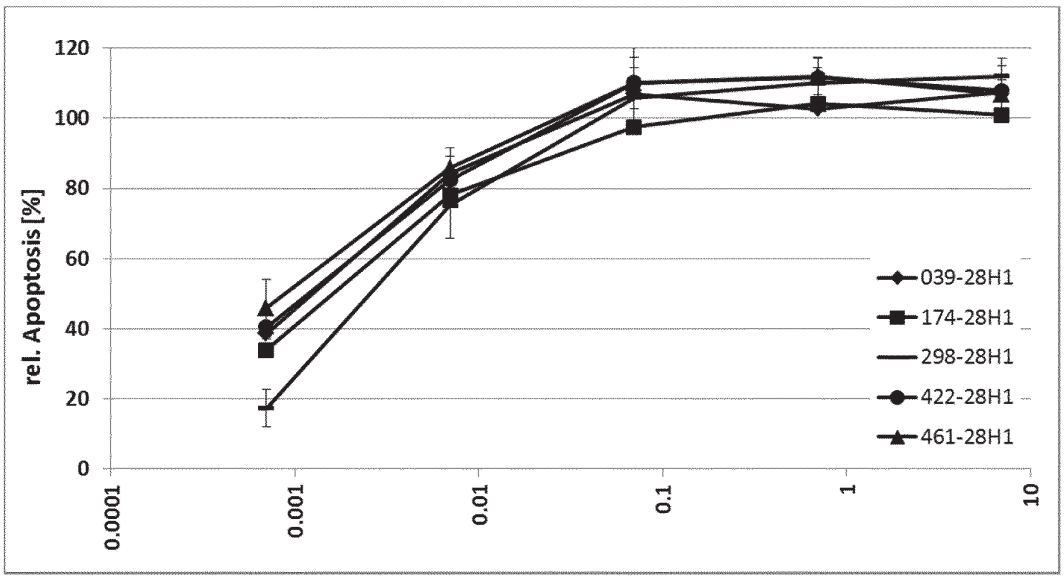

120
100
80
60
40
20
0
rel. Apoptosis [%]
039-28H1
174-28H1
298-28H1
422-28H1
461-28H1
0.0001
0.001
0.01
0.1
1
10

Fig. 25

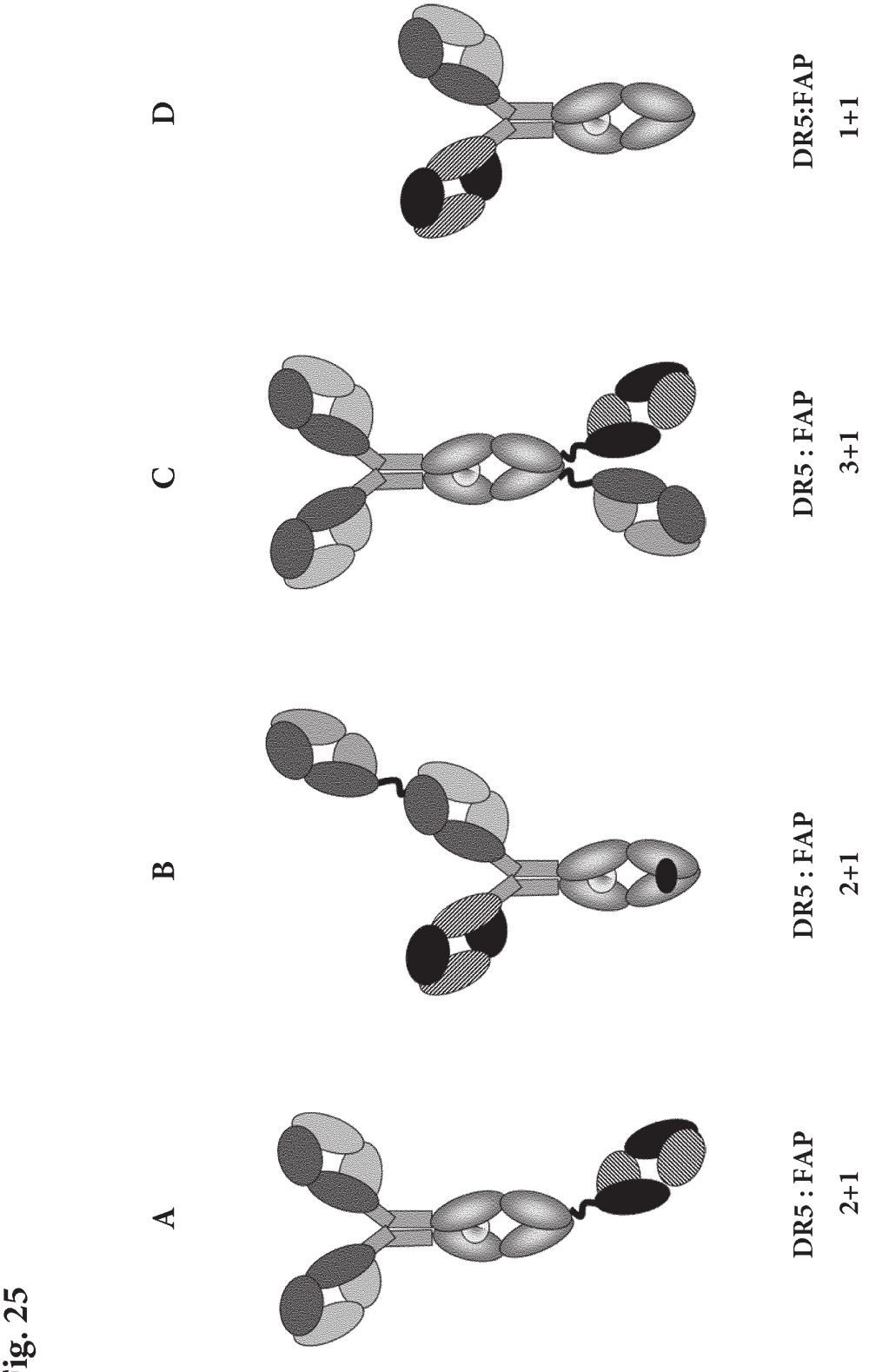


Fig. 26a

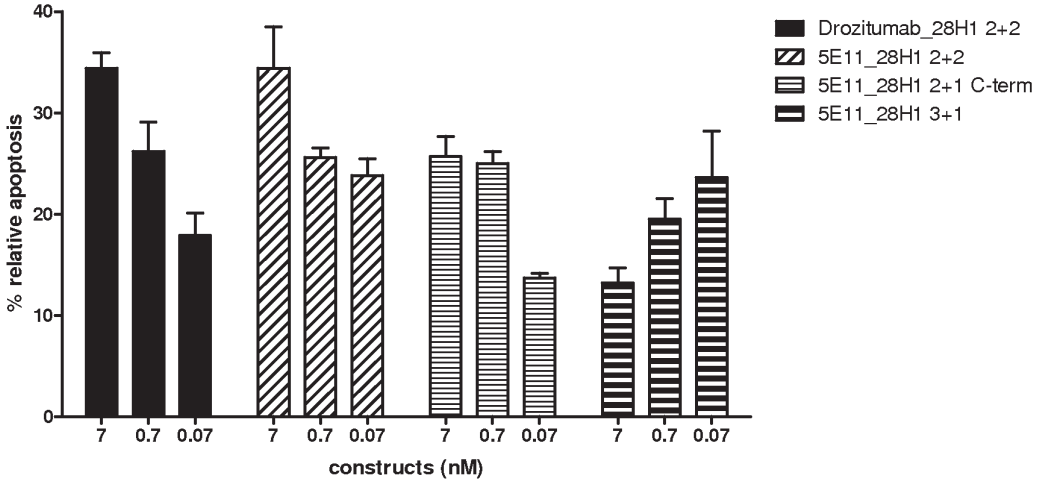
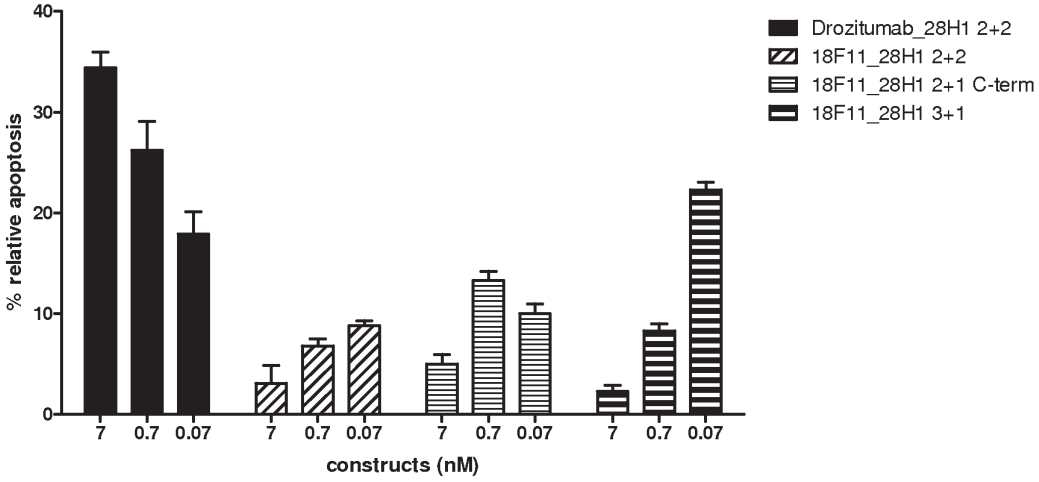
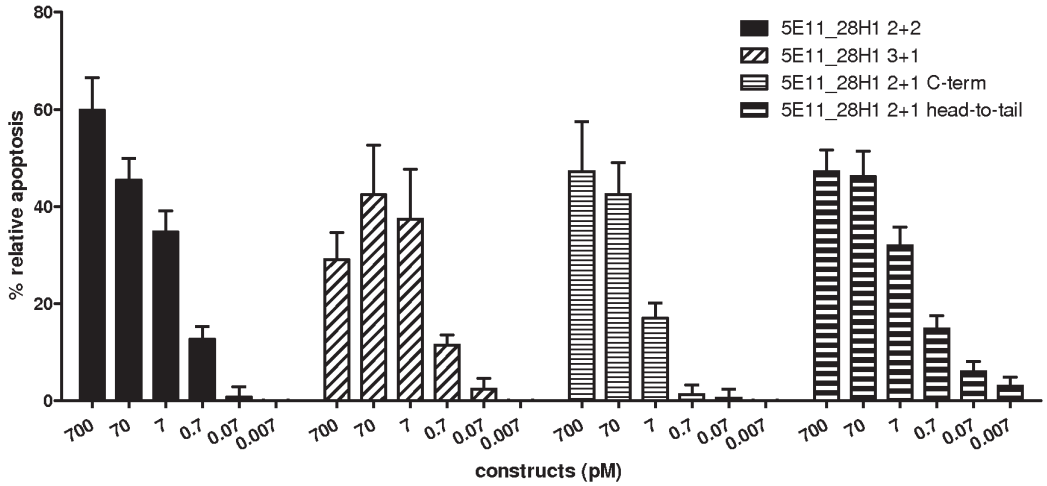



Fig. 26b



# Fig. 27


5E11_28H1 2+2
5E11_28H1 3+1
5E11_28H1 2+1 C-term
5E11_28H1 2+1 head-to-tail
% relative apoptosis
0
20
40
60
80
700
70
7
0.7
0.07
0.007
constructs (pM)

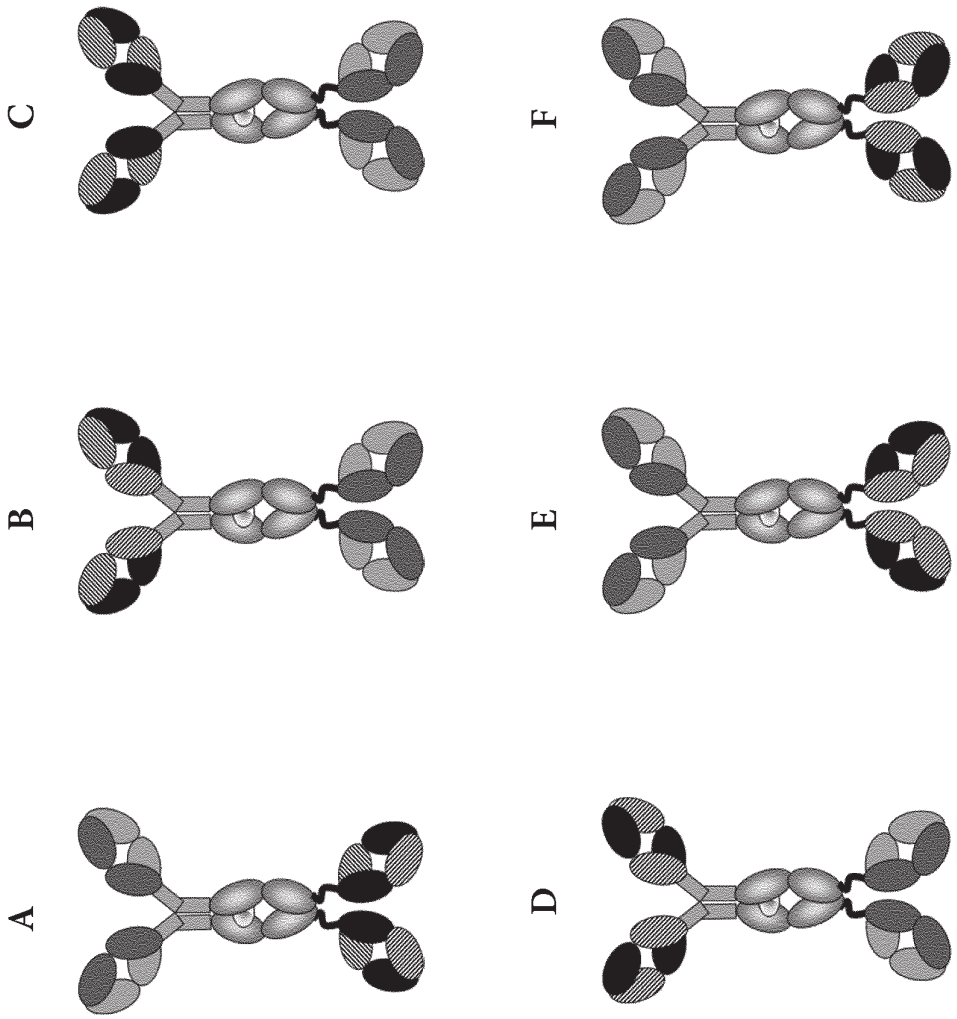



Fig. 28

Fig. 29

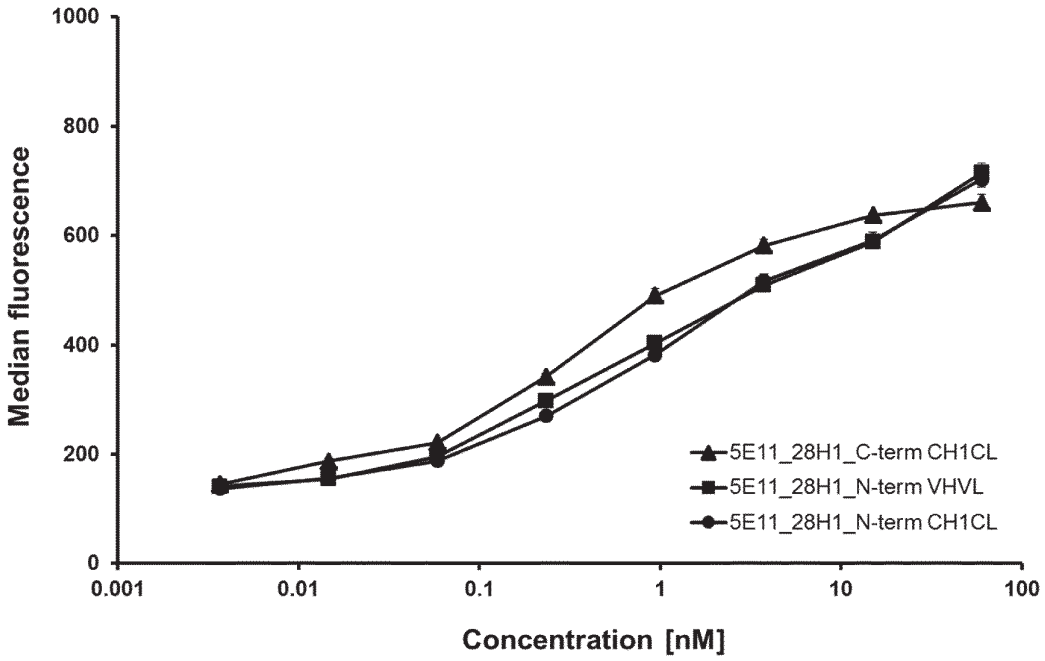

1000
800
600
400
200
0
Median fluorescence
0.001
0.01
0.1
1
10
100
Concentration [nM]
5E11_28H1_C-term CH1CL
5E11_28H1_N-term VHVL
5E11_28H1_N-term CH1CL

Fig. 30 a

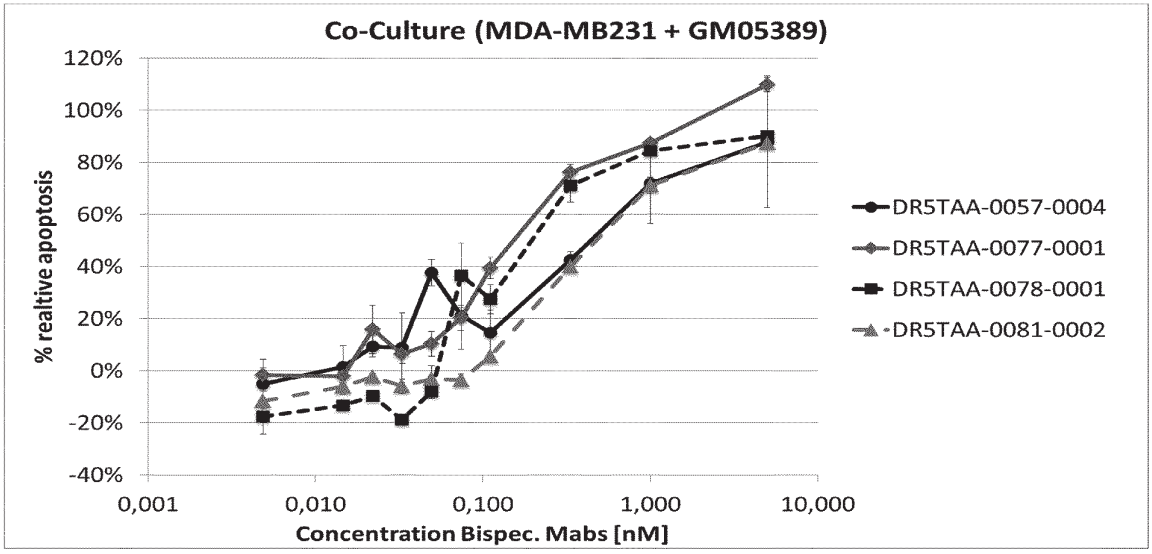
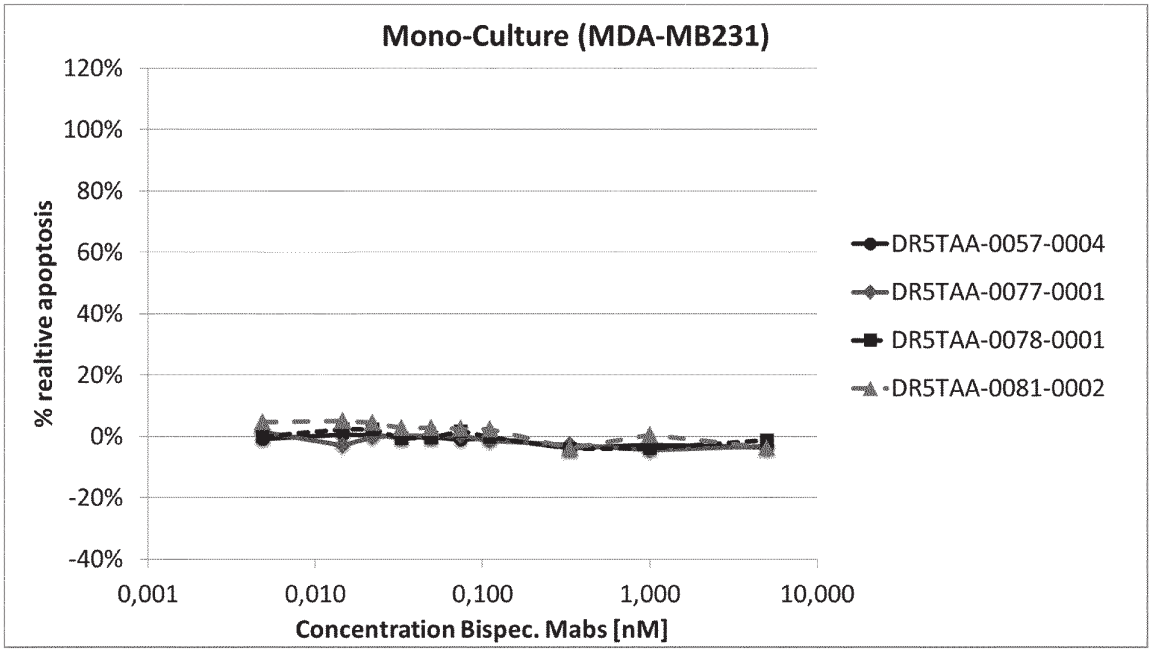



Fig. 30 b



# Fig. 30 c

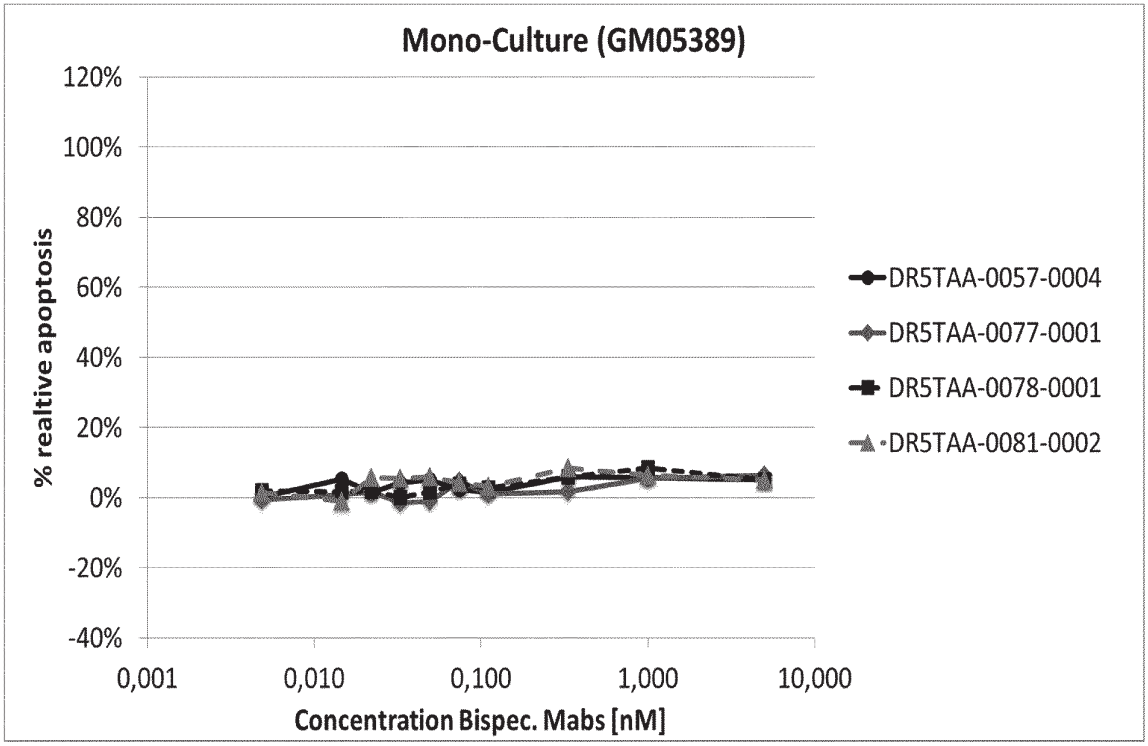
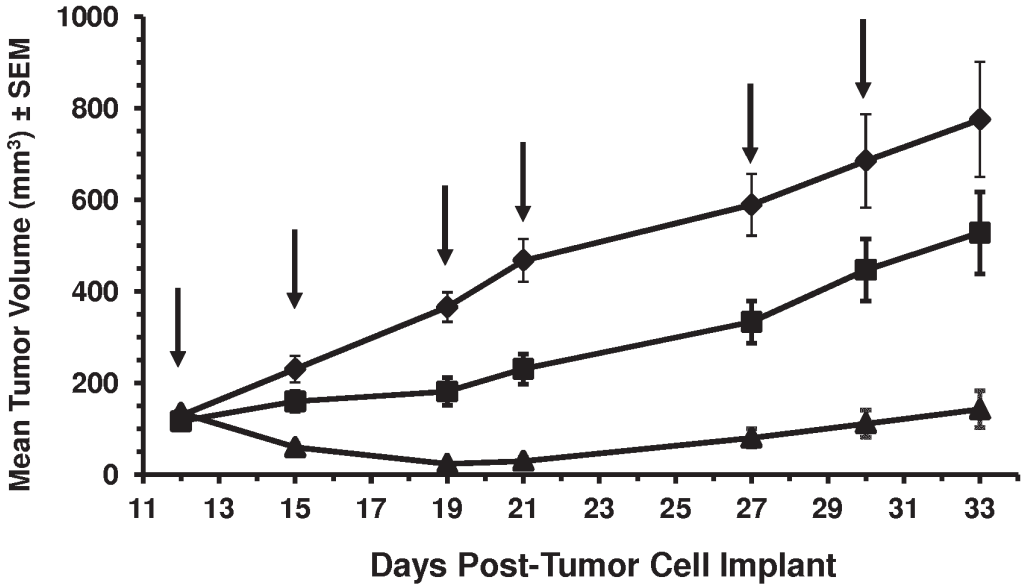
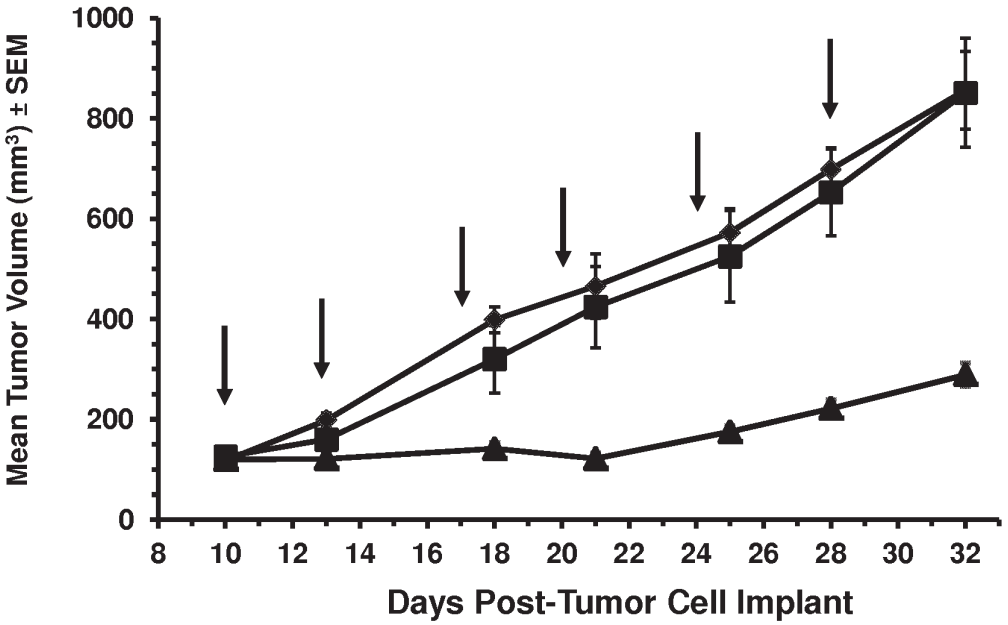

Mono-Culture (GM05389)
120%
100%
80%
60%
40%
20%
0%
-20%
-40%
% realtive apoptosis
0,001
0,010
0,100
1,000
10,000
Concentration Bispec. Mabs [nM]
DR5TAA-0057-0004
DR5TAA-0077-0001
DR5TAA-0078-0001
DR5TAA-0081-0002

Fig. 31

A


Mean Tumor Volume (mm3) ± SEM
1000
800
600
400
200
0
11
13
15
17
19
21
23
25
27
29
31
33
Days Post-Tumor Cell Implant

B


Mean Tumor Volume (mm3) ± SEM
1000
800
600
400
200
0
8
10
12
14
16
18
20
22
24
26
28
30
32
Days Post-Tumor Cell Implant

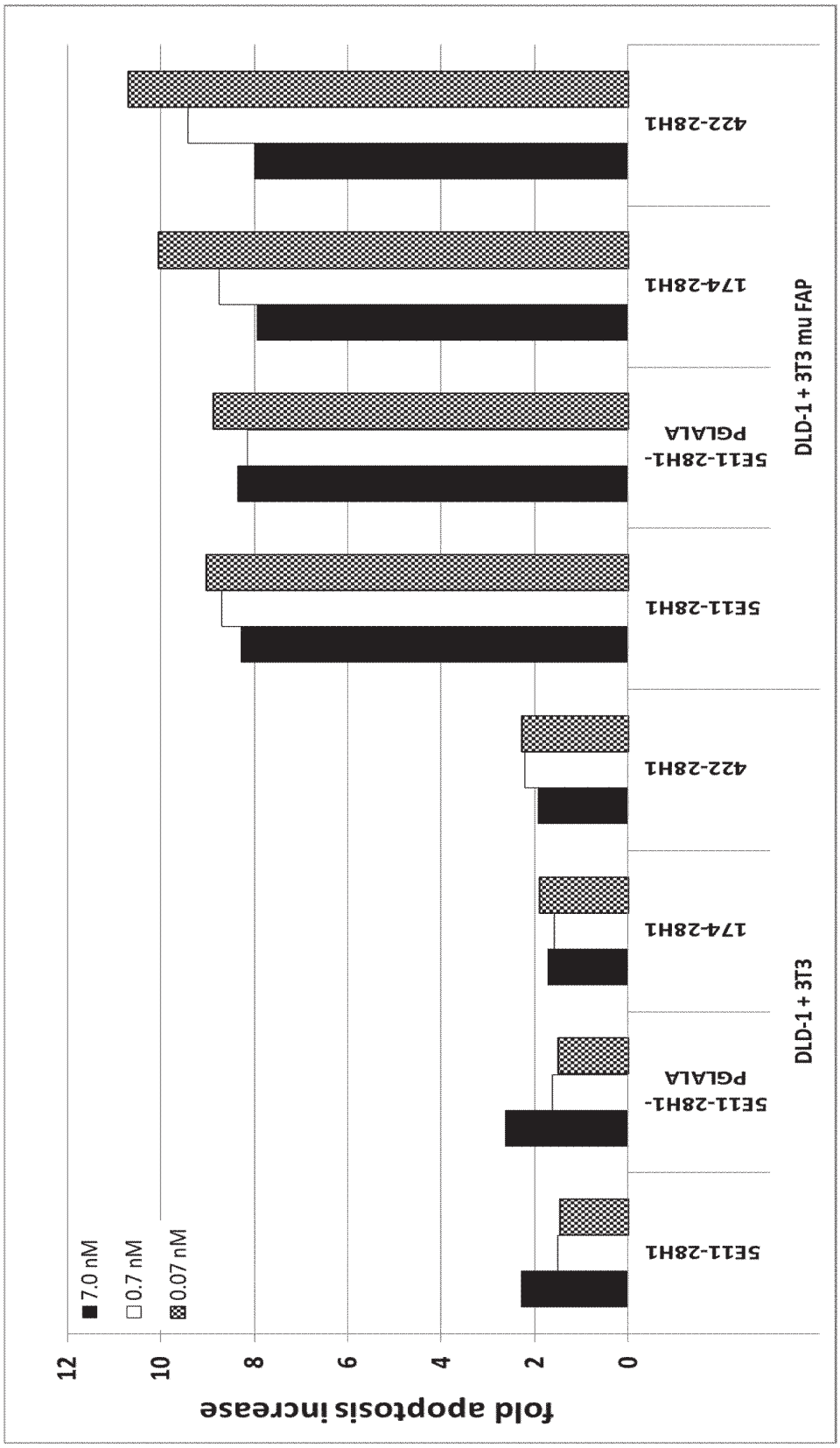

fold apoptosis increase
0
2
4
6
8
10
12
7.0 nM
0.7 nM
0.07 nM
5E11-28H1
5E11-28H1-PGLALA
174-28H1
422-28H1
DLD-1 + 3T3
5E11-28H1
5E11-28H1-PGLALA
174-28H1
422-28H1
DLD-1 + 3T3 mu FAP

Fig. 32

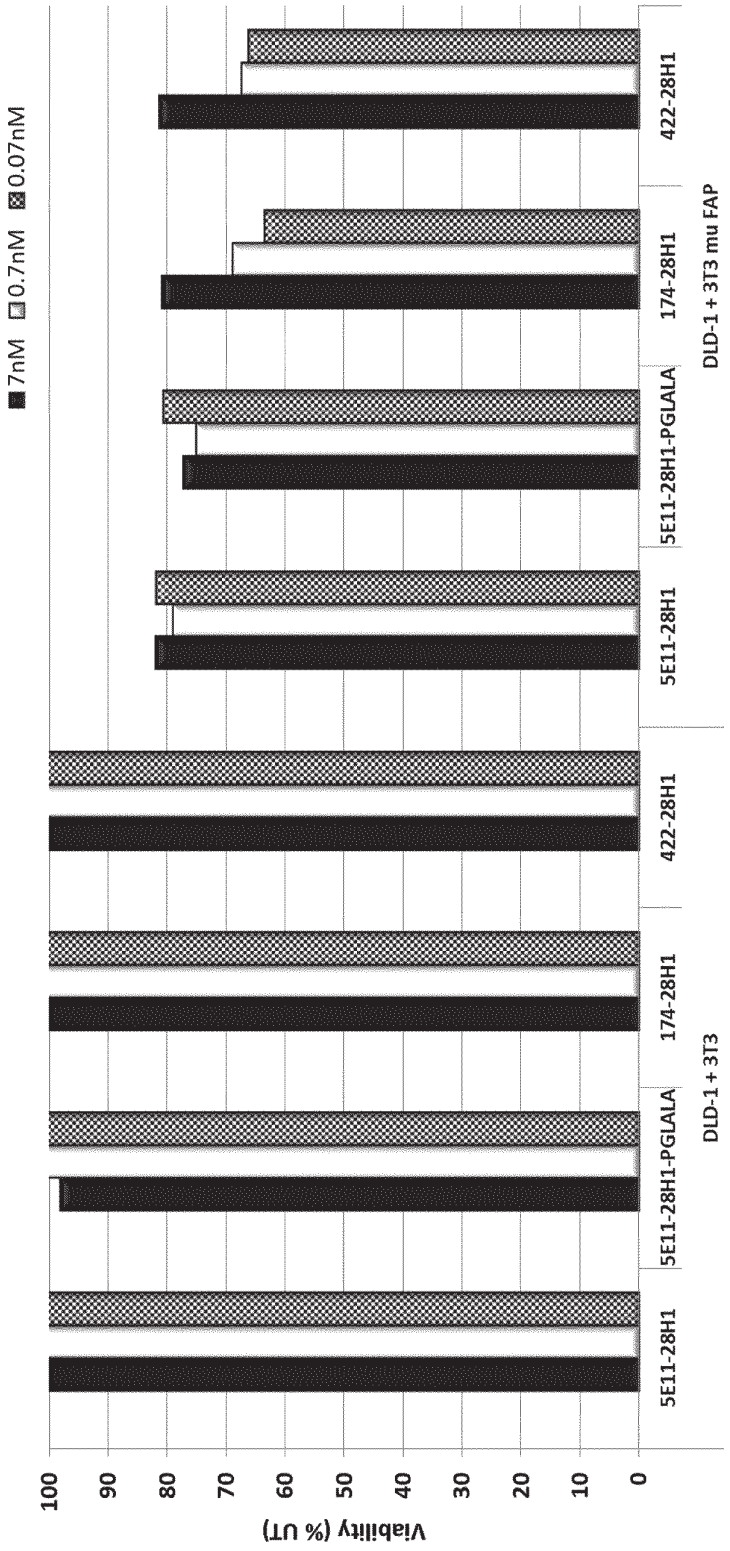
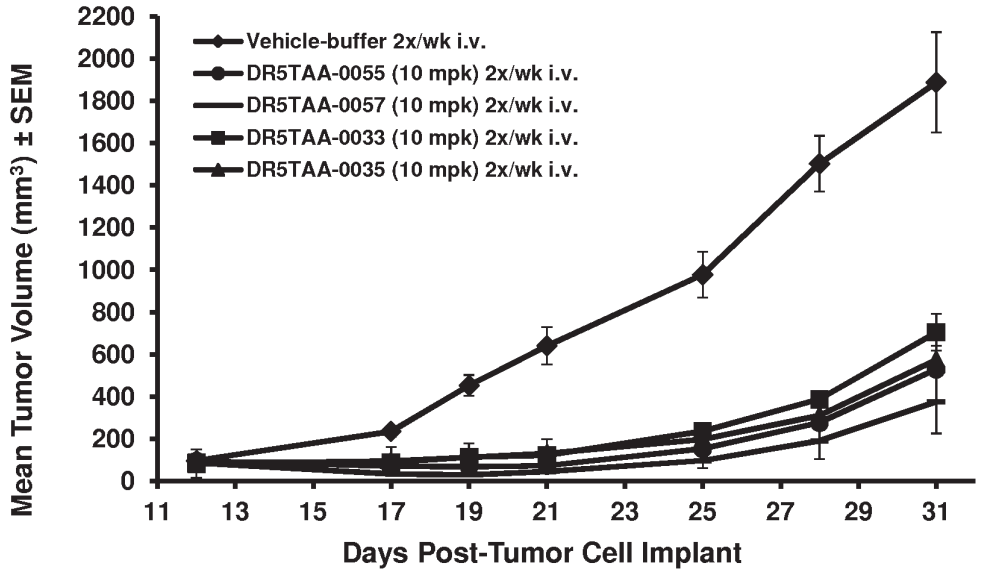

7nM
0.7nM
0.07nM
Viability (% UT)
100
90
80
70
60
50
40
30
20
10
0
5E11-28H1
5E11-28H1-PGLALA
174-28H1
422-28H1
DLD-1 + 3T3
5E11-28H1
5E11-28H1-PGLALA
174-28H1
422-28H1
DLD-1 + 3T3 mu FAP

Fig. 33

Fig. 34

A


Vehicle-buffer 2x/wk i.v.
DR5TAA-0055 (10 mpk) 2x/wk i.v.
DR5TAA-0057 (10 mpk) 2x/wk i.v.
DR5TAA-0033 (10 mpk) 2x/wk i.v.
DR5TAA-0035 (10 mpk) 2x/wk i.v.
Mean Tumor Volume (mm3) ± SEM
Days Post-Tumor Cell Implant
0
200
400
600
800
1000
1200
1400
1600
1800
2000
2200
11
13
15
17
19
21
23
25
27
29
31

B

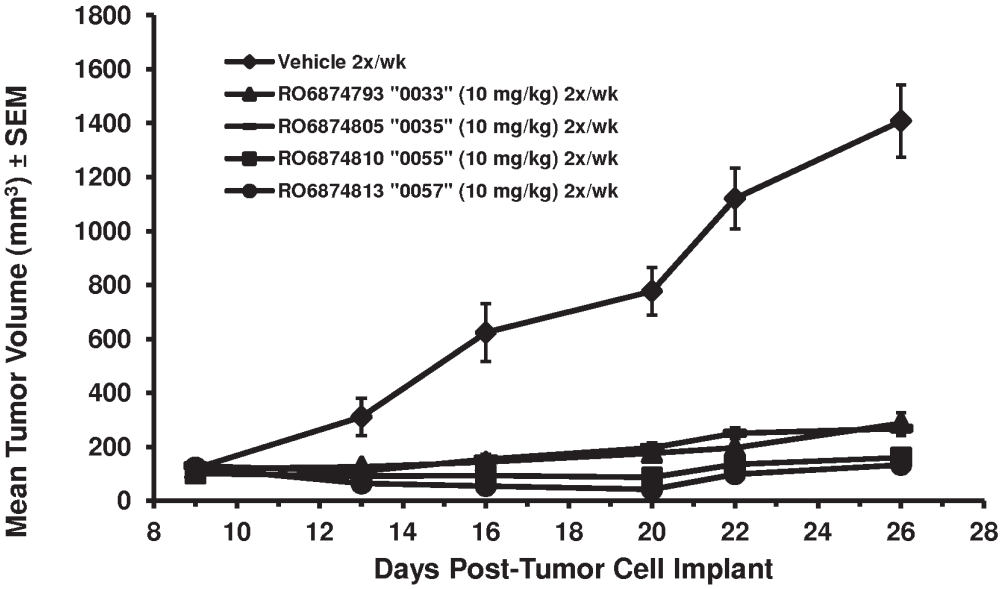
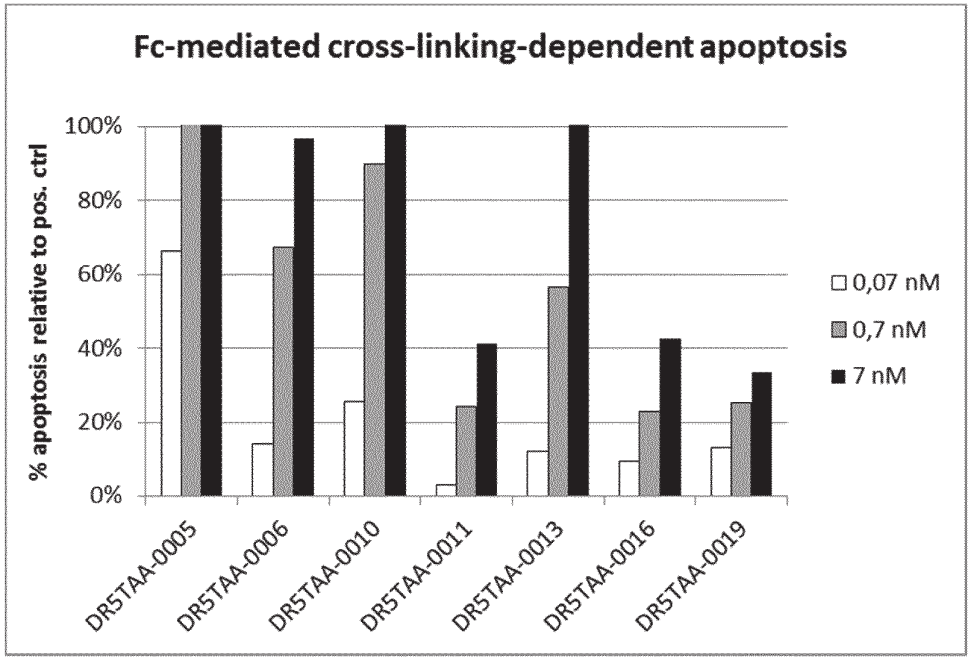

Vehicle 2x/wk
RO6874793 "0033" (10 mg/kg) 2x/wk
RO6874805 "0035" (10 mg/kg) 2x/wk
RO6874810 "0055" (10 mg/kg) 2x/wk
RO6874813 "0057" (10 mg/kg) 2x/wk
Mean Tumor Volume (mm3) ± SEM
Days Post-Tumor Cell Implant
0
200
400
600
800
1000
1200
1400
1600
1800
8
10
12
14
16
18
20
22
24
26
28

Fig. 35


Fc-mediated cross-linking-dependent apoptosis
% apoptosis relative to pos. ctrl
100%
80%
60%
40%
20%
0%
DR5TAA-0005
DR5TAA-0006
DR5TAA-0010
DR5TAA-0011
DR5TAA-0013
DR5TAA-0016
DR5TAA-0019
0,07 nM
0,7 nM
7 nM

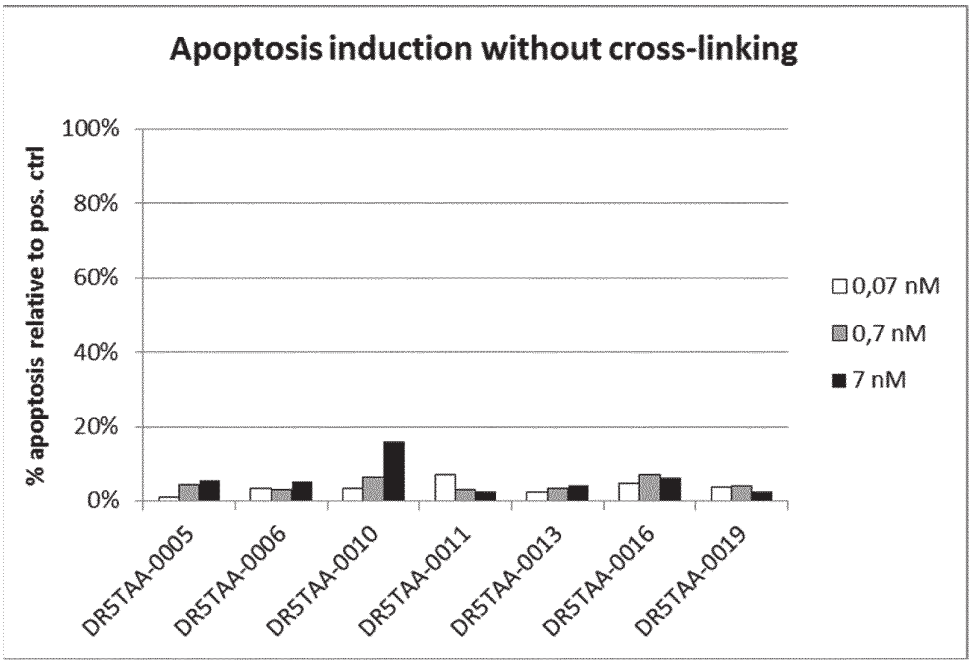
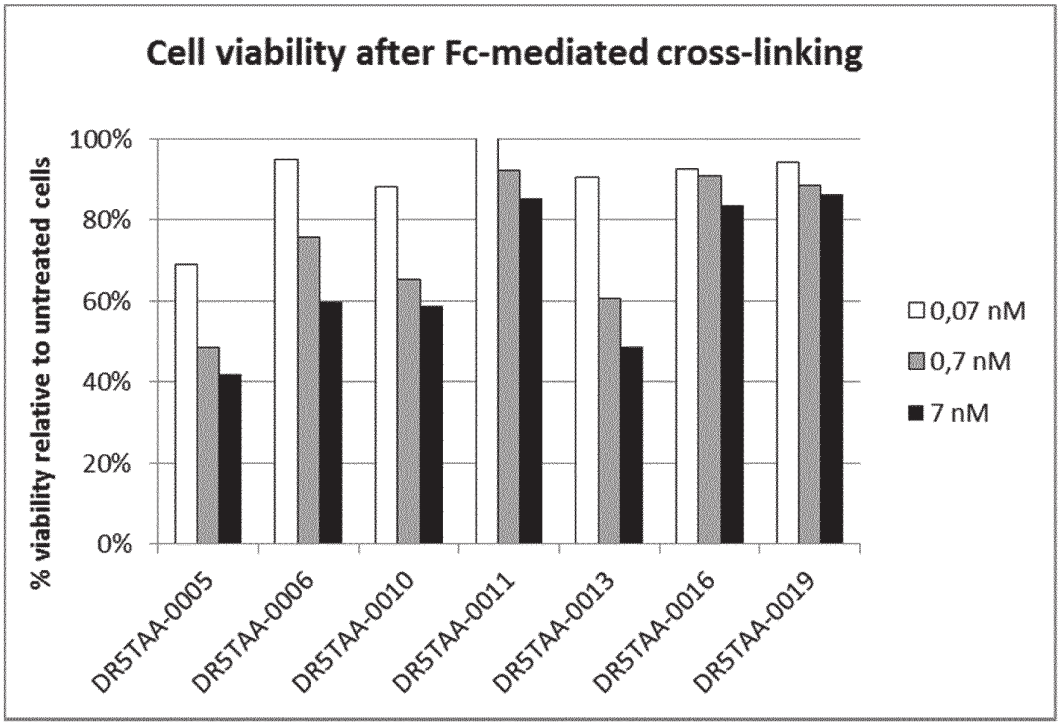

Apoptosis induction without cross-linking
% apoptosis relative to pos. ctrl
100%
80%
60%
40%
20%
0%
DR5TAA-0005
DR5TAA-0006
DR5TAA-0010
DR5TAA-0011
DR5TAA-0013
DR5TAA-0016
DR5TAA-0019
0,07 nM
0,7 nM
7 nM

Fig. 36


Cell viability after Fc-mediated cross-linking
% viability relative to untreated cells
100%
80%
60%
40%
20%
0%
DR5TAA-0005
DR5TAA-0006
DR5TAA-0010
DR5TAA-0011
DR5TAA-0013
DR5TAA-0016
DR5TAA-0019
0,07 nM
0,7 nM
7 nM

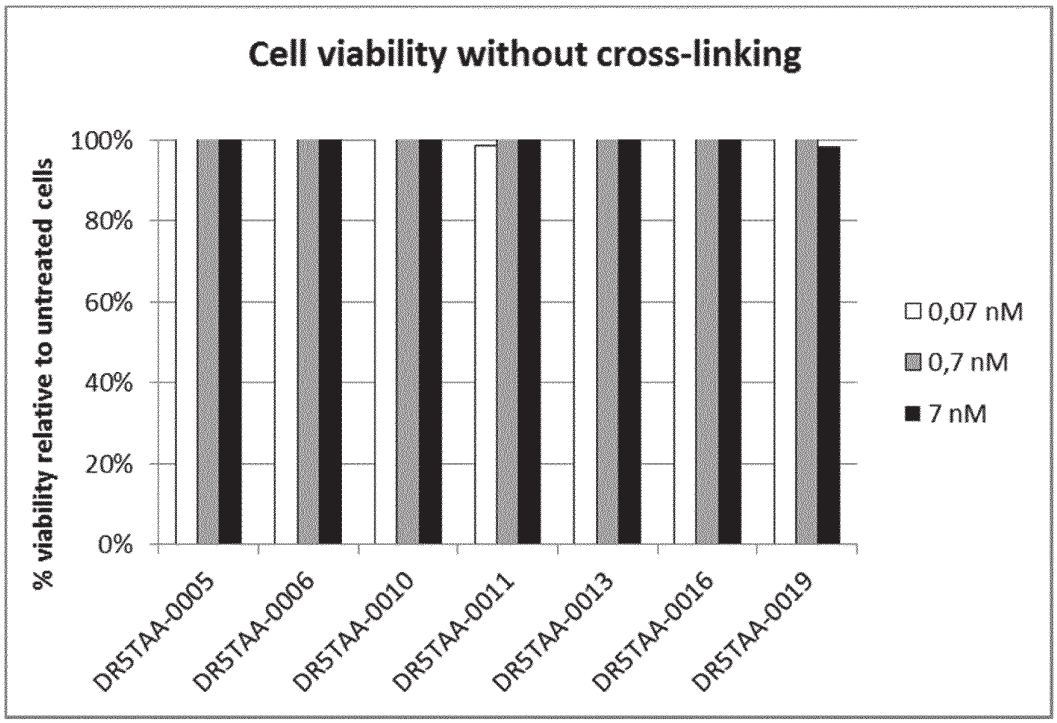

Cell viability without cross-linking
% viability relative to untreated cells
100%
80%
60%
40%
20%
0%
DR5TAA-0005
DR5TAA-0006
DR5TAA-0010
DR5TAA-0011
DR5TAA-0013
DR5TAA-0016
DR5TAA-0019
0,07 nM
0,7 nM
7 nM

Fig. 37

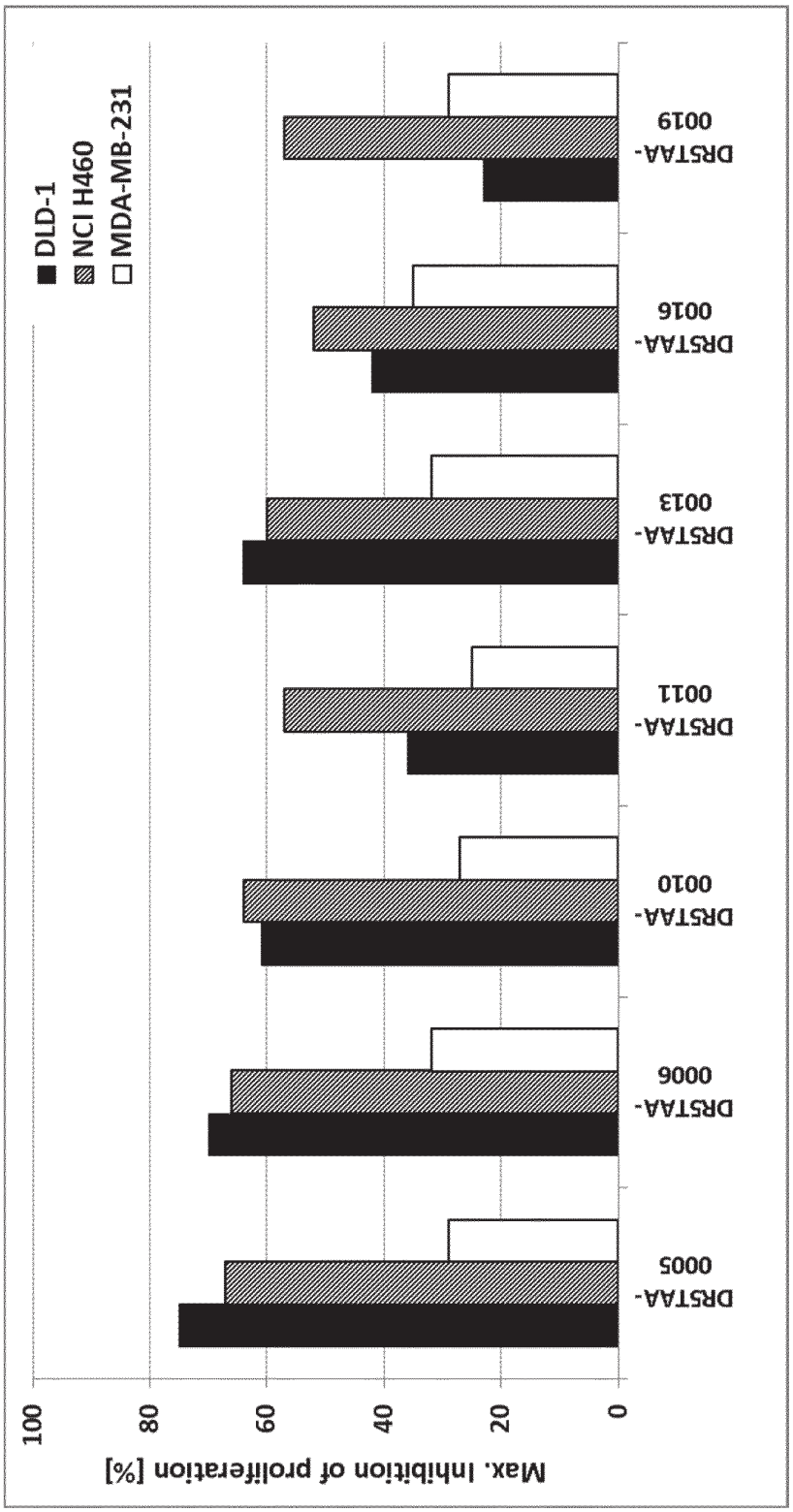

DLD-1
NCI H460
MDA-MB-231
Max. Inhibition of proliferation [%]
0
20
40
60
80
100
DR5TAA-0005
DR5TAA-0006
DR5TAA-0010
DR5TAA-0011
DR5TAA-0013
DR5TAA-0016
DR5TAA-0019

Fig. 38

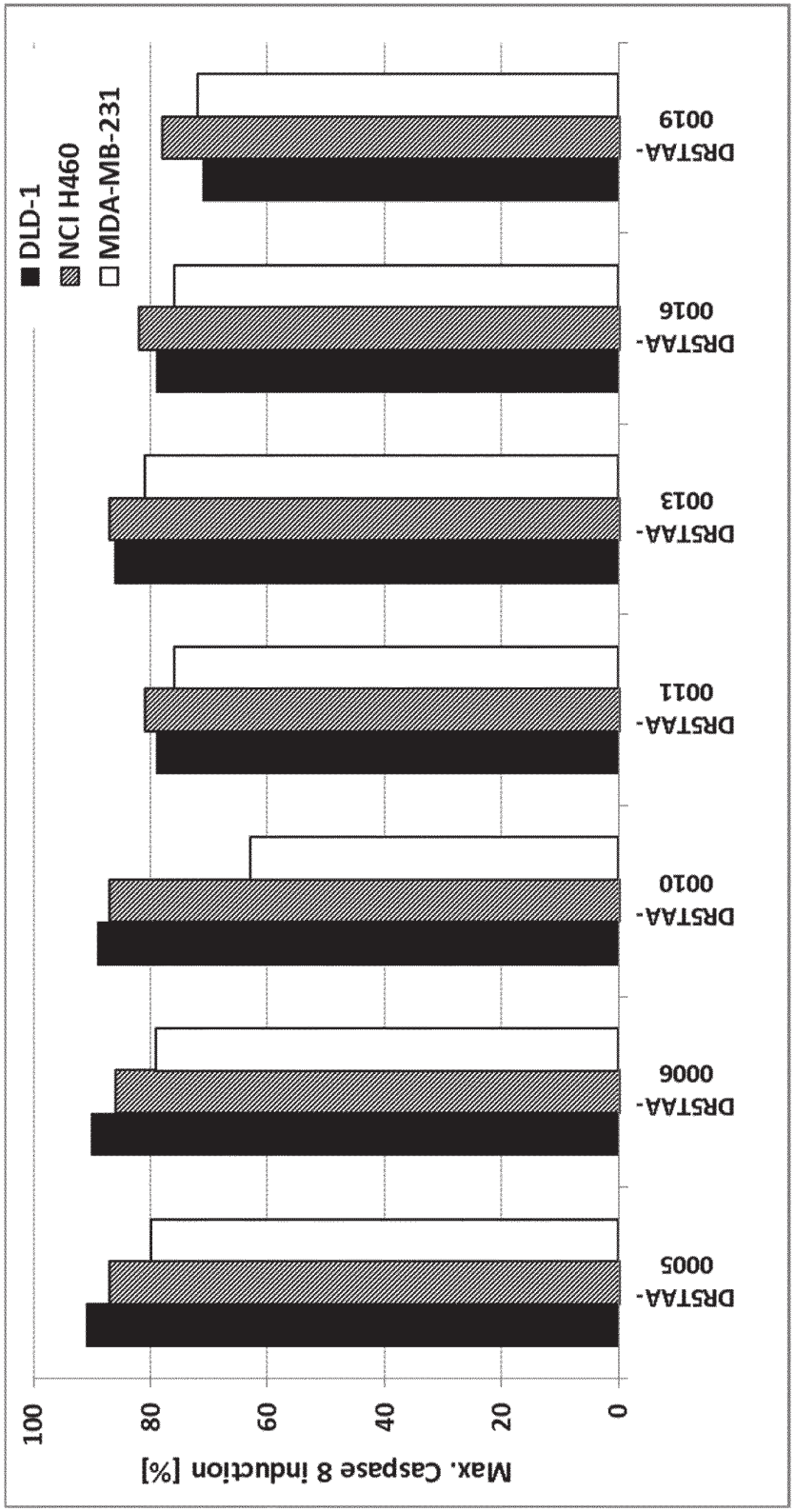

DLD-1
NCI H460
MDA-MB-231
DR5TAA-0019
DR5TAA-0016
DR5TAA-0013
DR5TAA-0011
DR5TAA-0010
DR5TAA-0006
DR5TAA-0005
100
80
60
40
20
0
Max. Caspase 8 induction [%]

Fig. 39

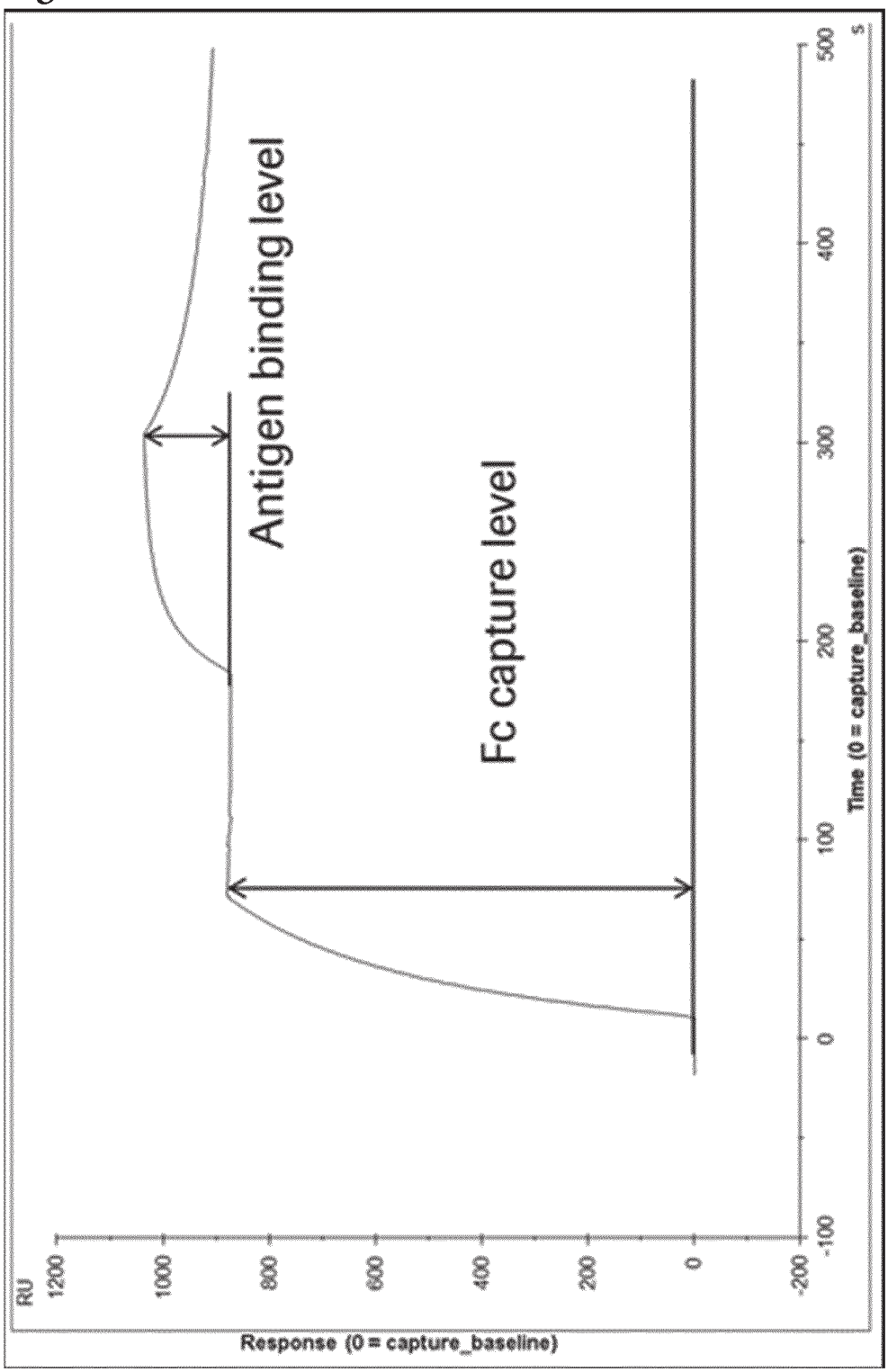

Antigen binding level
Fc capture level
RU
1200
1000
800
600
400
200
0
-200
Response (0 = capture_baseline)
-100
0
100
200
300
400
500
s
Time (0 = capture_baseline)

Fig.40

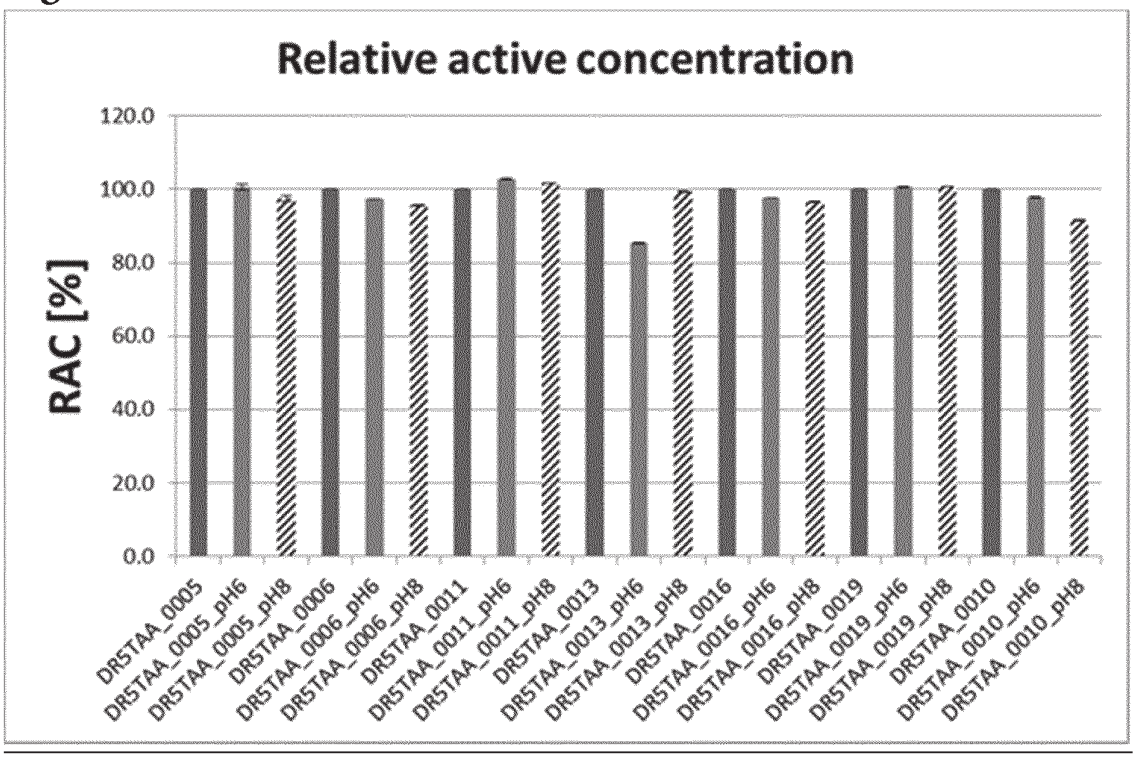

Relative active concentration
RAC [%]
120.0
100.0
80.0
60.0
40.0
20.0
0.0
DR5TAA_0005
DR5TAA_0005_pH6
DR5TAA_0005_pH8
DR5TAA_0006
DR5TAA_0006_pH6
DR5TAA_0006_pH8
DR5TAA_0011
DR5TAA_0011_pH6
DR5TAA_0011_pH8
DR5TAA_0013
DR5TAA_0013_pH6
DR5TAA_0013_pH8
DR5TAA_0016
DR5TAA_0016_pH6
DR5TAA_0016_pH8
DR5TAA_0019
DR5TAA_0019_pH6
DR5TAA_0019_pH8
DR5TAA_0010
DR5TAA_0010_pH6
DR5TAA_0010_pH8

Fig.41

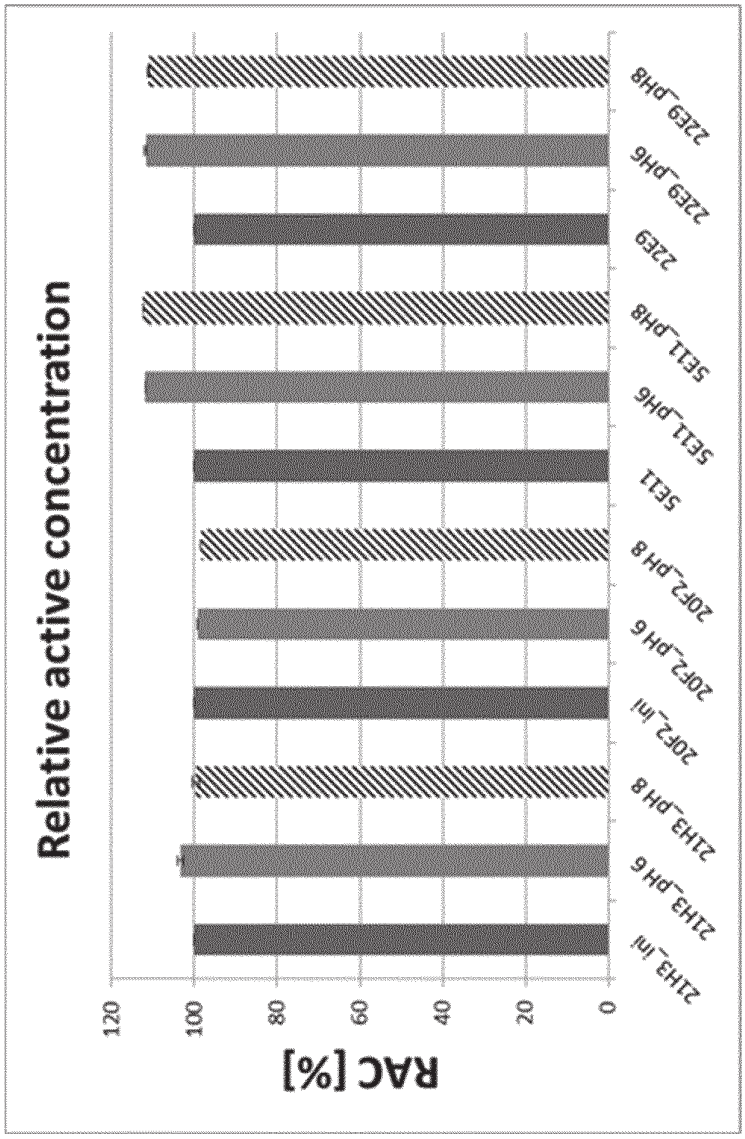
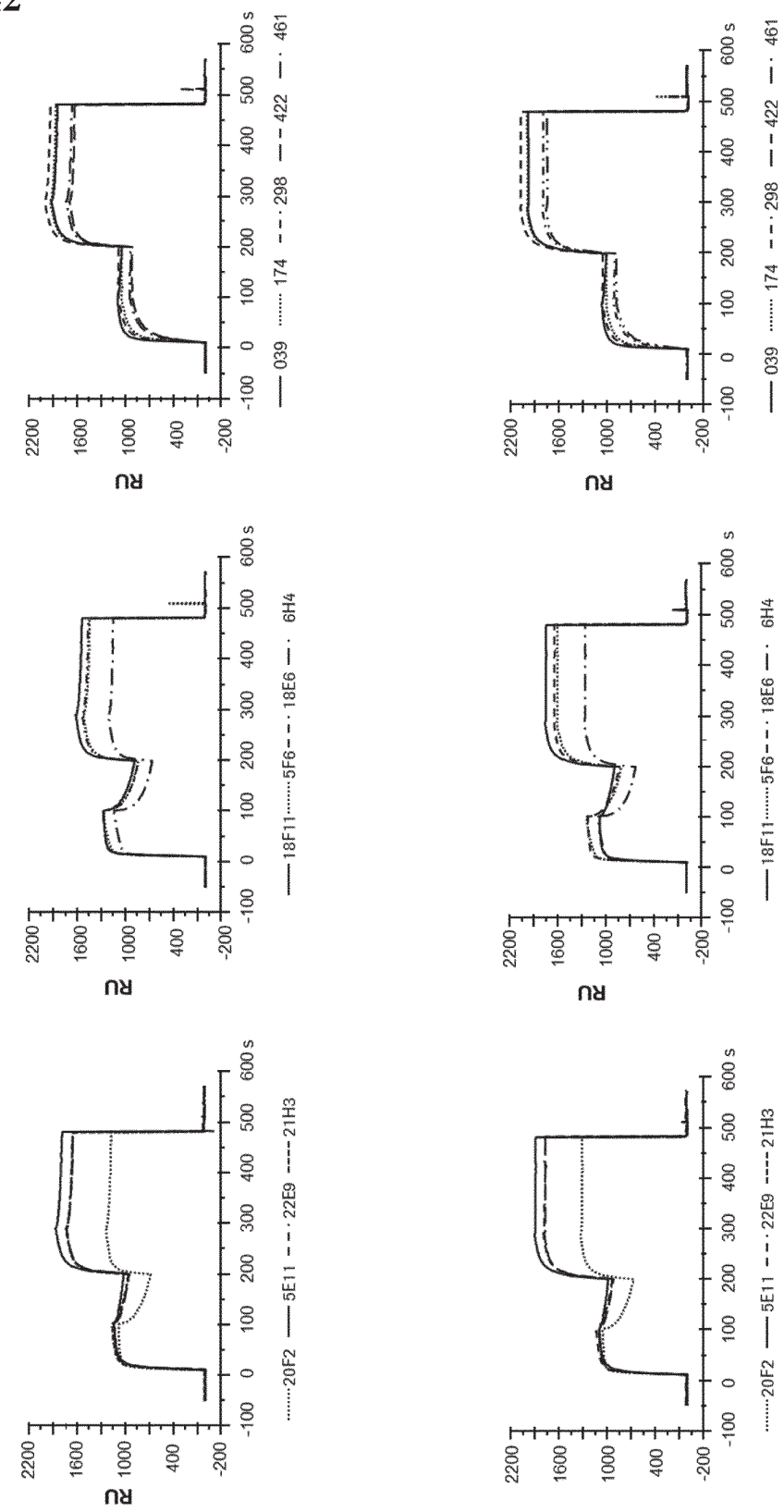
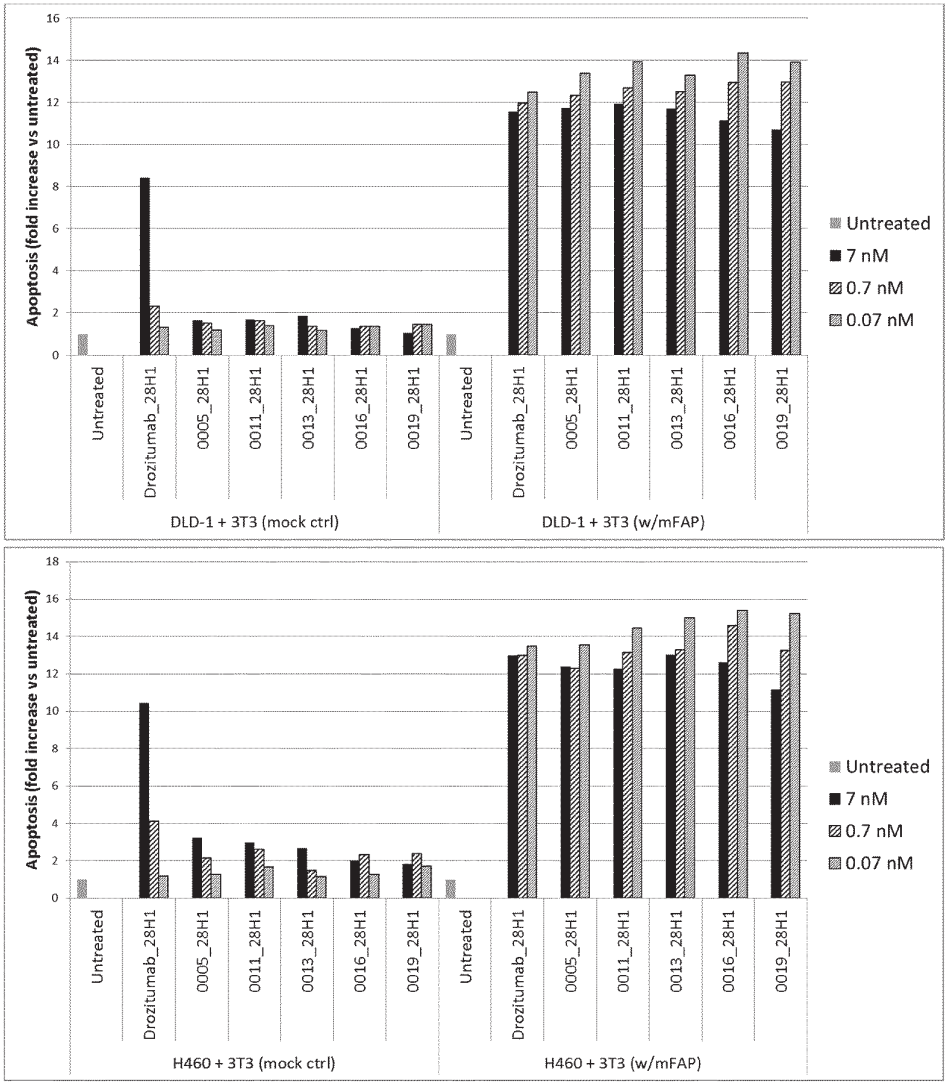

Relative active concentration
RAC [%]
120
100
80
60
40
20
0
21H3_ini
21H3_pH6
21H3_pH8
20F2_ini
20F2_pH6
20F2_pH8
5E11
5E11_pH6
5E11_pH8
22E9
22E9_pH6
22E9_pH8

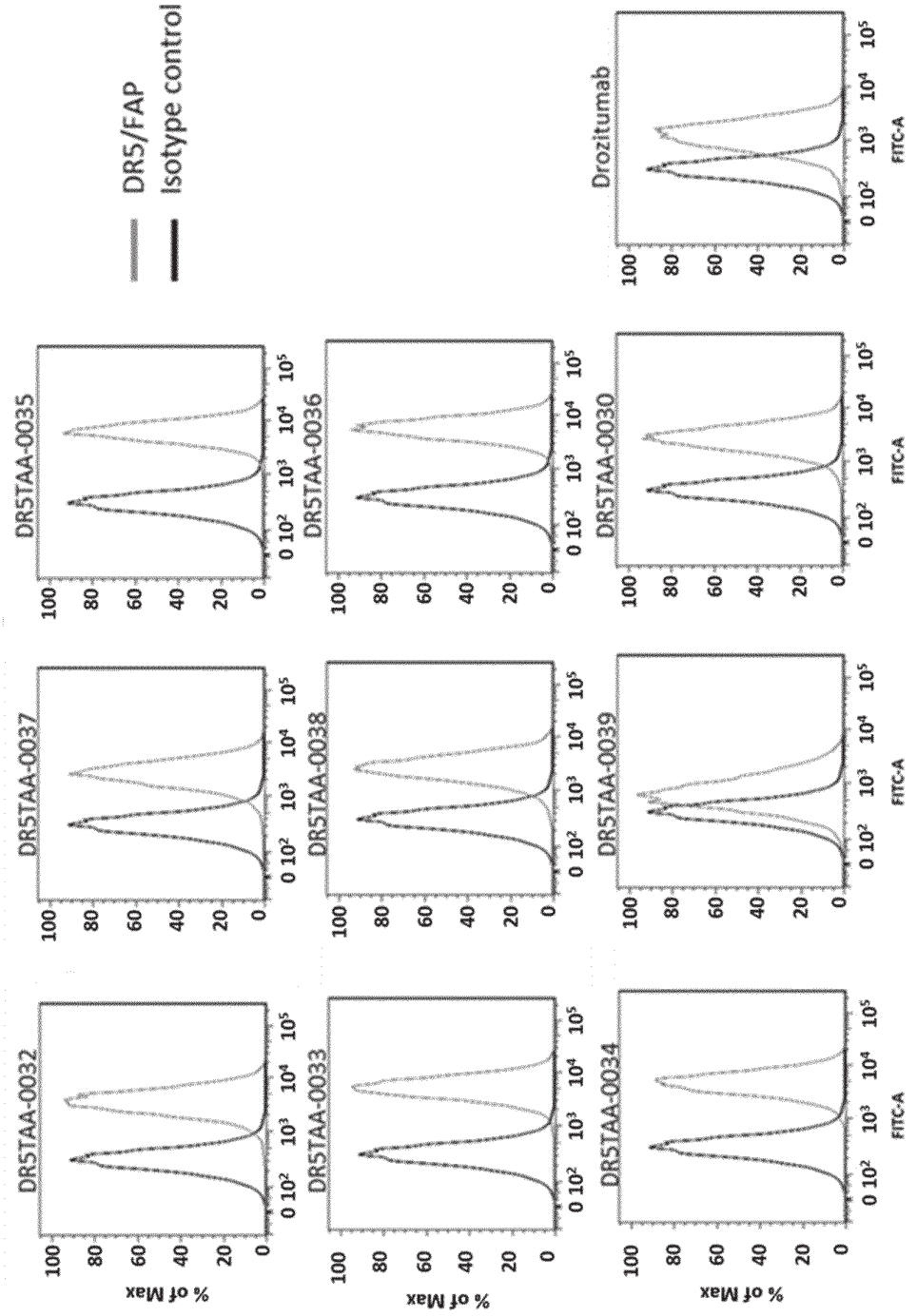
Fig. 42


RU
2200
1600
1000
400
-200
-100 0 100 200 300 400 500 600 s
039 174 298 422 461
18F11 5F6 18E6 6H4
20F2 5E11 22E9 21H3

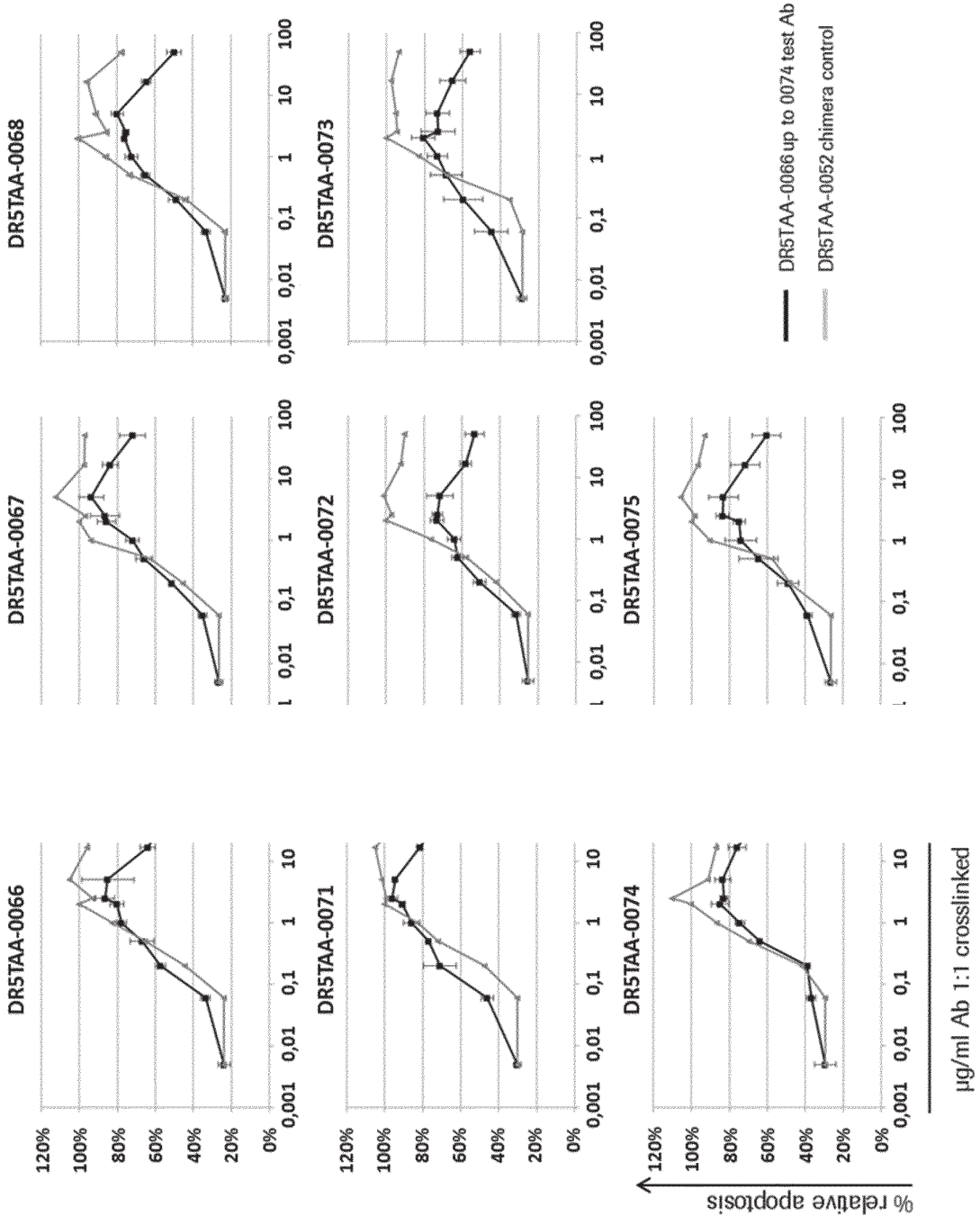
# Fig.43


Apoptosis (fold increase vs untreated)
16
14
12
10
8
6
4
2
0
Untreated
Drozitumab_28H1
0005_28H1
0011_28H1
0013_28H1
0016_28H1
0019_28H1
DLD-1 + 3T3 (mock ctrl)
DLD-1 + 3T3 (w/mFAP)
Untreated
7 nM
0.7 nM
0.07 nM
Apoptosis (fold increase vs untreated)
18
16
14
12
10
8
6
4
2
0
H460 + 3T3 (mock ctrl)
H460 + 3T3 (w/mFAP)
Untreated
7 nM
0.7 nM
0.07 nM

# Fig. 44


DR5/FAP
Isotype control
DR5TAA-0032
DR5TAA-0033
DR5TAA-0034
DR5TAA-0035
DR5TAA-0036
DR5TAA-0037
DR5TAA-0038
DR5TAA-0039
DR5TAA-0030
Drozitumab
% of Max
FITC-A

# Fig. 45 a


DR5TAA-0066
DR5TAA-0067
DR5TAA-0068
DR5TAA-0071
DR5TAA-0072
DR5TAA-0073
DR5TAA-0074
DR5TAA-0075
DR5TAA-0066 up to 0074 test Ab
DR5TAA-0052 chimera control
% relative apoptosis
µg/ml Ab 1:1 crosslinked

# Fig. 45 b

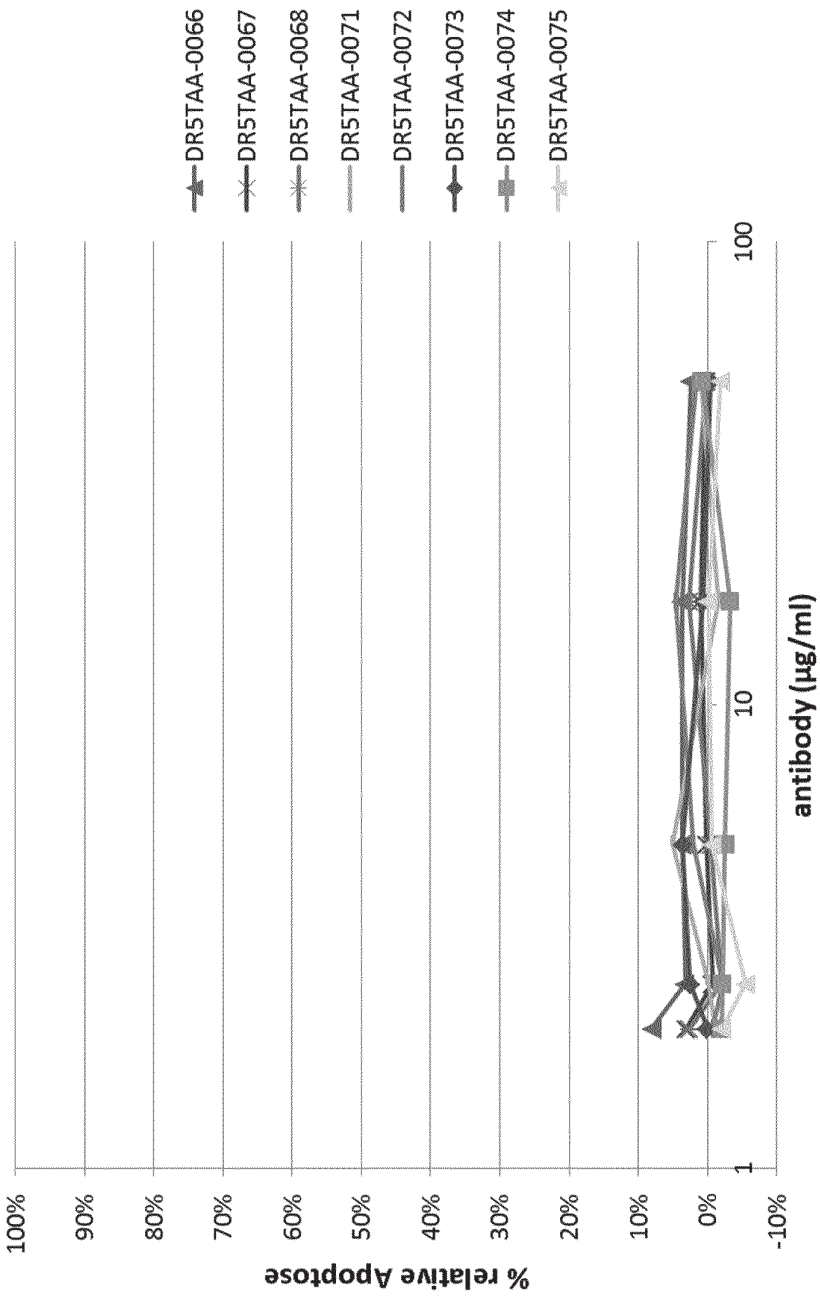
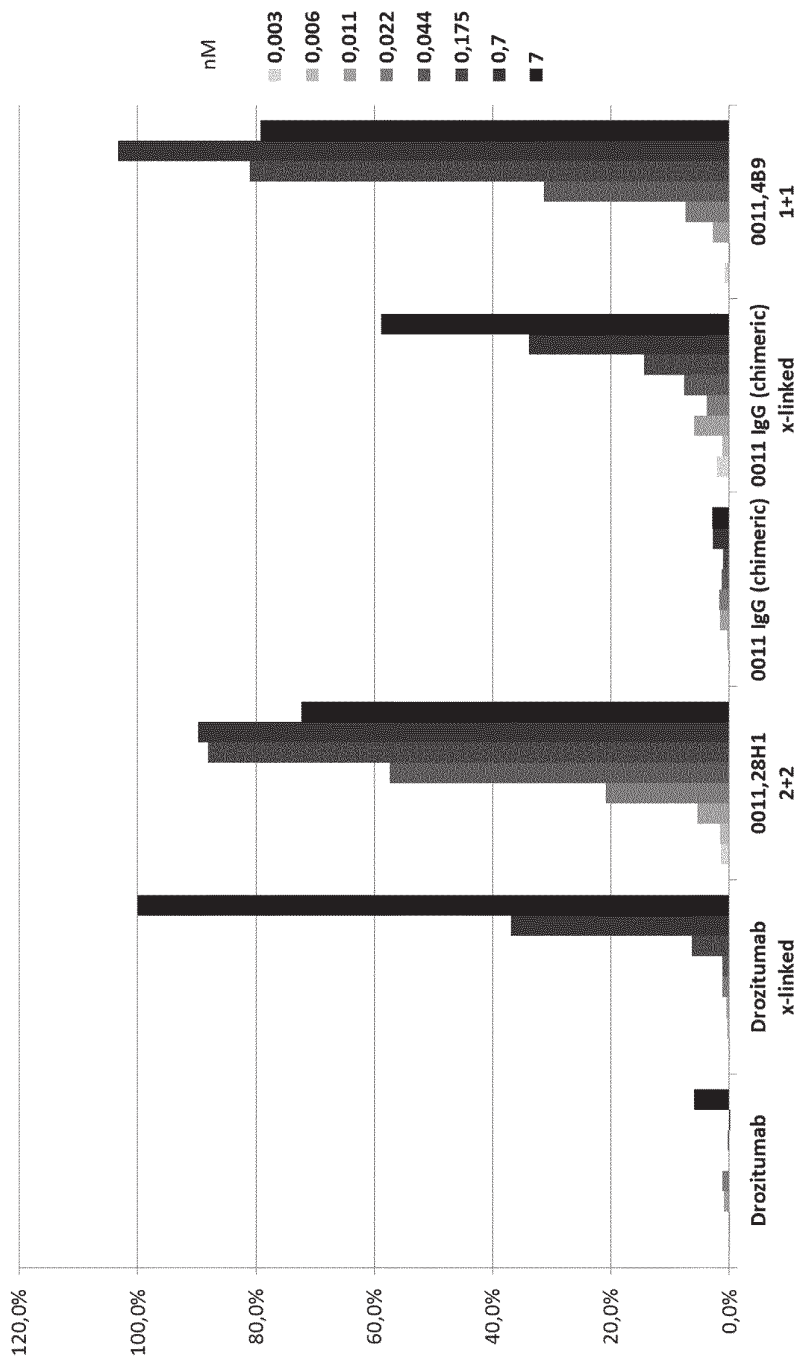

DR5TAA-0066
DR5TAA-0067
DR5TAA-0068
DR5TAA-0071
DR5TAA-0072
DR5TAA-0073
DR5TAA-0074
DR5TAA-0075
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
-10%
% relative Apoptose
1
10
100
antibody (µg/ml)

Fig. 46


CDDE 24h: Co-Culture MDA-MB-231 & GM05389
% relative apoptosis as compared to Drozitumab 7nM crosslinked
nM
0,003
0,006
0,011
0,022
0,044
0,175
0,7
7
120,0%
100,0%
80,0%
60,0%
40,0%
20,0%
0,0%
Drozitumab
Drozitumab x-linked
0011,28H1 2+2
0011 IgG (chimeric)
0011 IgG (chimeric) x-linked
0011,4B9 1+1

# Fig. 47

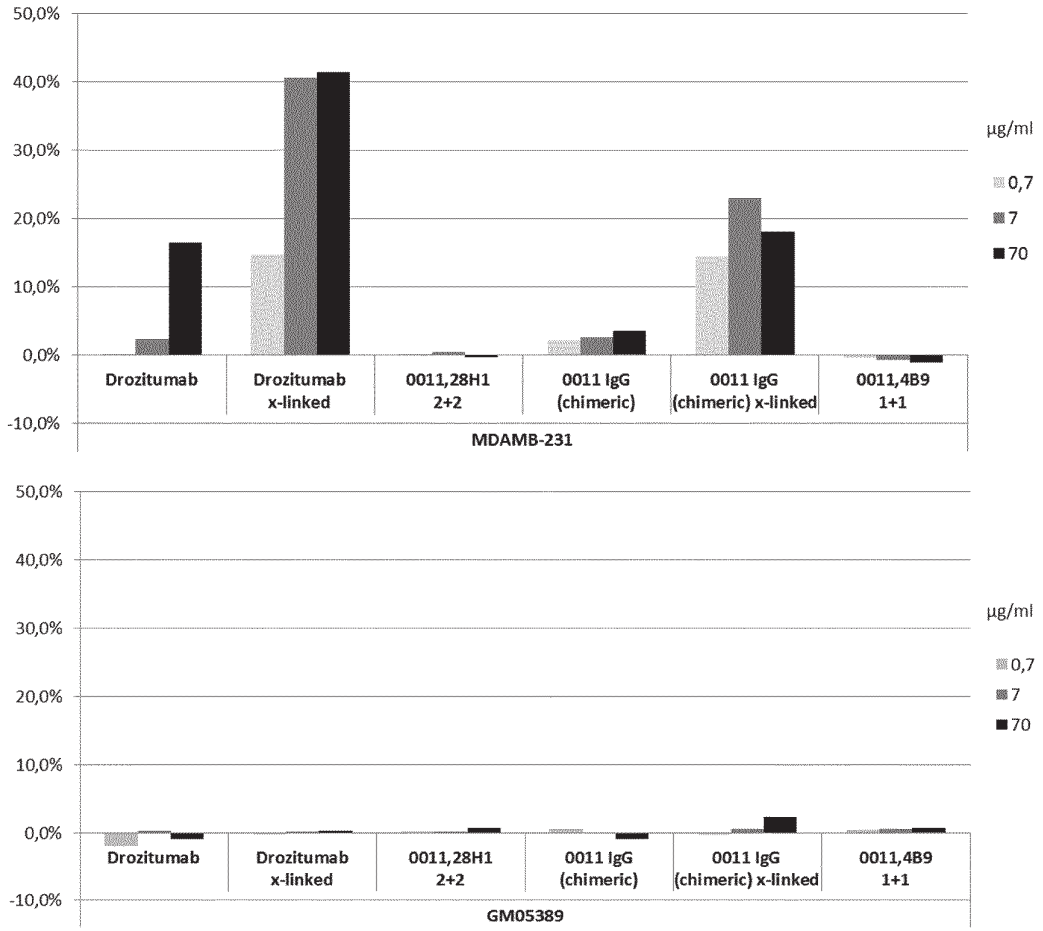

50,0%
40,0%
30,0%
20,0%
10,0%
0,0%
-10,0%
µg/ml
0,7
7
70
Drozitumab
Drozitumab x-linked
0011,28H1 2+2
0011 IgG (chimeric)
0011 IgG (chimeric) x-linked
0011,4B9 1+1
MDAMB-231
GM05389

Fig. 48

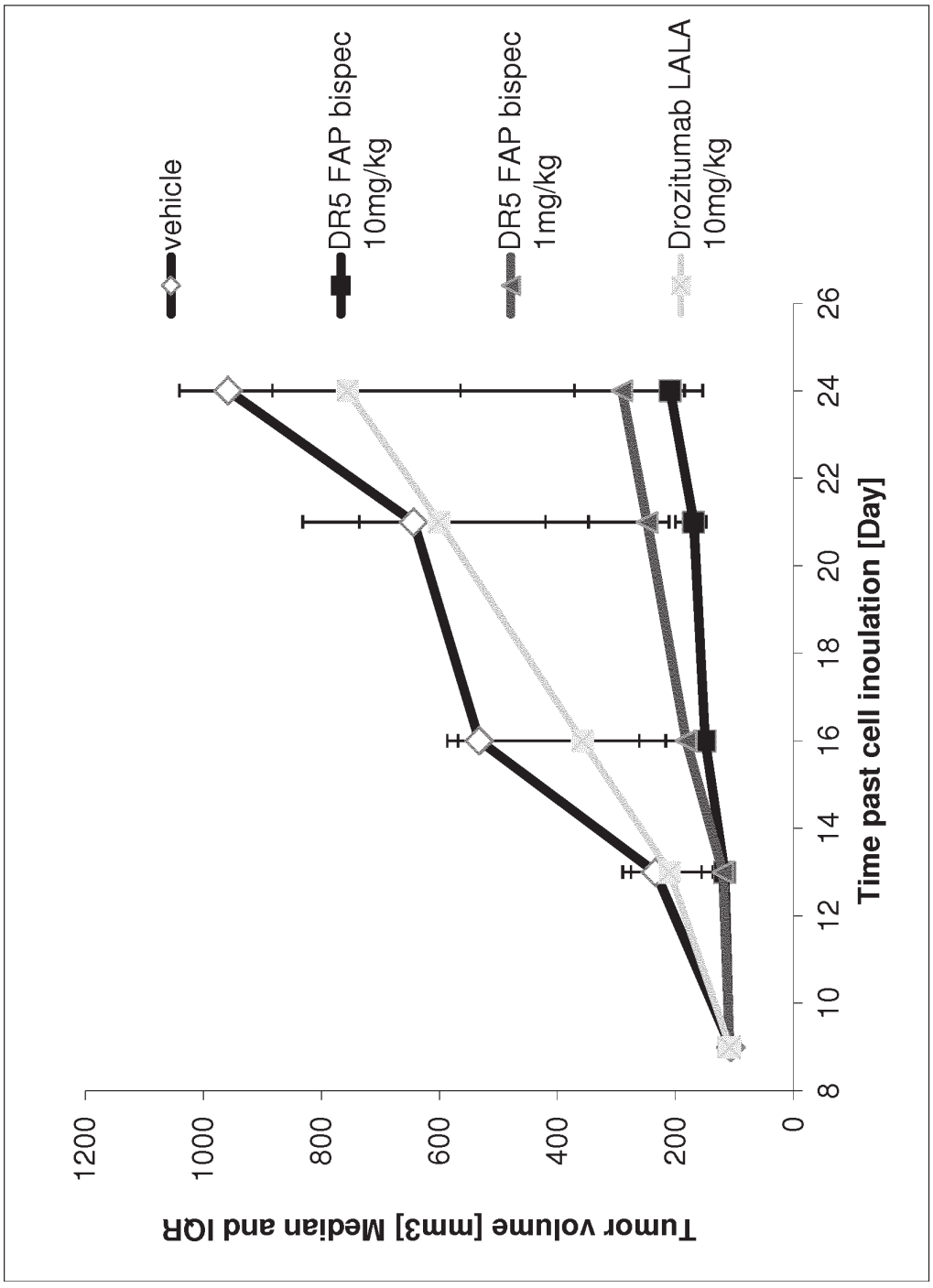
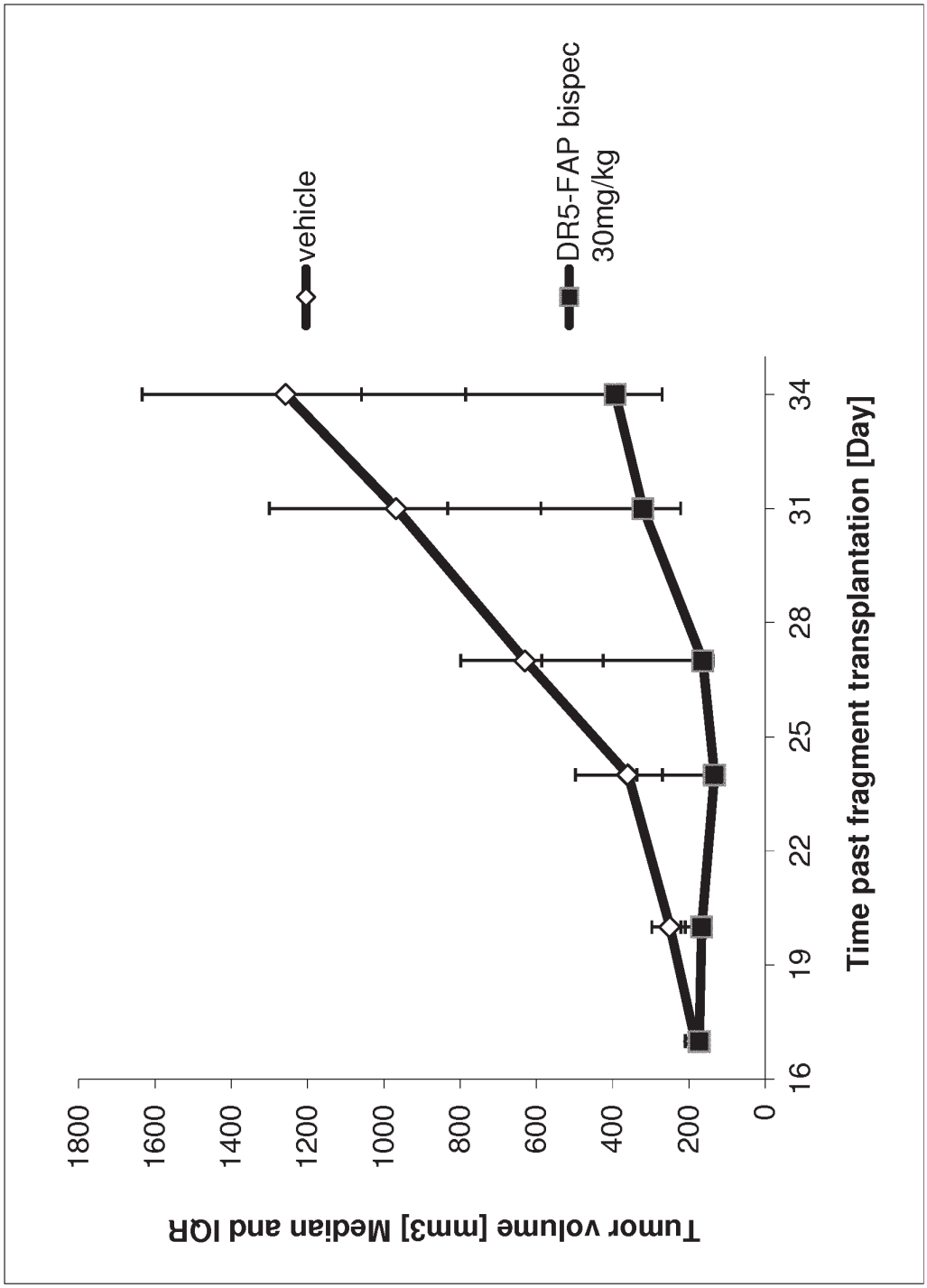

vehicle
DR5 FAP bispec 10mg/kg
DR5 FAP bispec 1mg/kg
Drozitumab LALA 10mg/kg
Tumor volume [mm3] Median and IQR
Time past cell inoulation [Day]
0
200
400
600
800
1000
1200
8
10
12
14
16
18
20
22
24
26

Fig. 49


vehicle
DR5-FAP bispec
30mg/kg
Tumor volume [mm3] Median and IQR
1800
1600
1400
1200
1000
800
600
400
200
0
16
19
22
25
28
31
34
Time past fragment transplantation [Day]