Anti-Mesothelin 3C10 VH

```
V segment:     3-33
D segment:     3-10
J segment:     JH4b
```

```
        Q   V   Y   L   V   E   S   G   G   G   V   V   Q   P   G   R   S   L
1       CAG GTG TAC CTG GTG GAG TCT GGG GGA GGC GTG GTC CAG CCC GGG AGG TCC CTG

                                                                 CDR1
                                                            ~~~~~~~~~~~~~~~~~~~
        R   L   S   C   A   A   S   G   I   T   F   S   I   Y   G   M   H   W
55      AGA CTC TCC TGT GCA GCG TCT GGA ATC ACC TTC AGT ATC TAT GGC ATG CAC TGG

                                                                     CDR2
                                                                ~~~~~~~~~~~~~~~~~~~
        V   R   Q   A   P   G   K   G   L   E   W   V   A   V   I   W   Y   D
109     GTC CGC CAG GCT CCA GGC AAG GGG CTG GAG TGG GTG GCA GTT ATA TGG TAT GAT

                        CDR2
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
        G   S   H   E   Y   Y   A   D   S   V   K   G   R   F   T   I   S   R
163     GGA AGT CAT GAA TAC TAT GCA GAC TCC GTG AAG GGC CGA TTC ACC ATC TCC AGA

        D   N   S   K   N   T   L   Y   L   L   M   N   S   L   R   A   E   D
217     GAC AAT TCC AAG AAC ACG CTG TAT CTG CTA ATG AAC AGC CTG AGA GCC GAG GAC

                                                         CDR3
                                                ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
        T   A   V   Y   Y   C   A   R   D   G   D   Y   Y   D   S   G   S   P
271     ACG GCT GTG TAT TAC TGT GCG AGA GAT GGC GAT TAT TAT GAT TCG GGG AGT CCT

          CDR3
        ~~~~~~~~~~~
        L   D   Y   W   G   Q   G   T   L   V   T   V   S   S
325     CTT GAC TAC TGG GGC CAG GGA ACC CTG GTC ACC GTC TCC TCA
```

FIGURE 1A

Anti-Mesothelin 3C10 VK

V segment: L6
J segment: JK4

```
          E   I   V   L   T   Q   S   P   A   T   L   S   L   S   P   G   E   R
1     GAA ATT GTG TTG ACA CAG TCT CCA GCC ACC CTG TCT TTG TCT CCA GGG GAA AGA

                                  CDR1
                          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
          A   T   L   S   C   R   A   S   Q   S   V   S   S   Y   L   A   W   Y
55    GCC ACC CTC TCC TGC AGG GCC AGT CAG AGT GTT AGC AGC TAC TTA GCC TGG TAC

                                                                CDR2
                                                        ~~~~~~~~~~~~~~~~~~~~
          Q   Q   K   P   G   Q   A   P   R   L   L   I   Y   D   A   S   N   R
109   CAA CAG AAA CCT GGC CAG GCT CCC AGG CTC CTC ATC TAT GAT GCA TCC AAC AGG

          CDR2
          ~~~~~~~~
          A   T   G   I   P   A   R   F   S   G   S   G   S   G   T   D   F   T
163   GCC ACT GGC ATC CCA GCC AGG TTC AGT GGC AGT GGG TCT GGG ACA GAC TTC ACT

                                                                        CDR3
                                                                        ~~~~~~~~
          L   T   I   S   S   L   E   P   E   D   F   A   V   Y   Y   C   Q   Q
217   CTC ACC ATC AGC AGC CTA GAG CCT GAA GAT TTT GCA GTT TAT TAC TGT CAG CAG

                  CDR3
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~
          R   S   N   W   P   L   T   F   G   G   G   T   K   V   E   I   K
271   CGT AGC AAC TGG CCG CTC ACT TTC GGC GGA GGG ACC AAG GTG GAG ATC AAA
```

FIGURE 1B

Anti-Mesothelin 6A4 VH

```
V segment:    3-33
D segment:    3-10
J segment:    JH4b
```

```
        Q   V   H   L   V   E   S   G   G   G   V   V   Q   P   G   R   S   L
1       CAG GTG CAC CTG GTG GAG TCT GGG GGA GGC GTG GTC CAG CCT GGG AGG TCC CTG

                                                            CDR1
                                                        ~~~~~~~~~~~~~~~~~~~
        R   L   S   C   V   A   S   G   I   T   F   R   I   Y   G   M   H   W
55      AGA CTC TCC TGT GTA GCG TCT GGA ATC ACC TTC AGG ATC TAT GGC ATG CAC TGG

                                                                CDR2
                                                            ~~~~~~~~~~~~~~~~~~~
        V   R   Q   A   P   G   K   G   L   E   W   V   A   V   L   W   Y   D
109     GTC CGC CAG GCT CCA GGC AAG GGG CTG GAG TGG GTG GCA GTT TTA TGG TAT GAT

                    CDR2
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
        G   S   H   E   Y   Y   A   D   S   V   K   G   R   F   T   I   S   R
163     GGA AGT CAT GAA TAC TAT GCA GAC TCC GTG AAG GGC CGA TTC ACC ATC TCC AGA

        D   N   S   K   N   T   L   Y   L   Q   M   N   S   L   R   A   E   D
217     GAC AAT TCC AAG AAC ACG CTA TAT CTG CAA ATG AAC AGC CTG AGA GCC GAG GAC

                                                    CDR3
                                        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
        T   A   I   Y   Y   C   A   R   D   G   D   Y   Y   D   S   G   S   P
271     ACG GCT ATA TAT TAC TGT GCG AGA GAT GGC GAT TAC TAT GAT TCG GGG AGT CCT

          CDR3
        ~~~~~~~~~~
        L   D   Y   W   G   Q   G   T   L   V   T   V   S   S
325     CTT GAC TAC TGG GGC CAG GGA ACC CTG GTC ACC GTC TCC TCA
```

FIGURE 2A

Anti-Mesothelin 6A4 VK

V segment: L6
J segment: JK4

```
          E   I   V   L   T   Q   S   P   A   T   L   S   L   S   P   G   E   R
1     GAA ATT GTG TTG ACA CAG TCT CCA GCC ACC CTG TCT TTG TCT CCA GGG GAA AGA

                                  CDR1
                          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
          A   T   L   S   C   R   A   S   Q   S   V   S   S   Y   L   A   W   Y
55    GCC ACC CTC TCC TGC AGG GCC AGT CAG AGT GTT AGC AGC TAC TTA GCC TGG TAC

                                                                CDR2
                                                        ~~~~~~~~~~~~~~~~~~~~
          Q   Q   K   P   G   Q   A   P   R   L   L   I   Y   D   A   S   N   R
109   CAA CAG AAA CCT GGC CAG GCT CCC AGG CTC CTC ATC TAT GAT GCA TCC AAC AGG

          CDR2
          ~~~~~~~
          A   T   G   I   P   A   R   F   S   G   S   G   S   G   T   D   F   T
163   GCC ACT GGC ATC CCA GCC AGG TTC AGT GGC AGT GGG TCT GGG ACA GAC TTC ACT

                                                                    CDR3
                                                                    ~~~~~~~
          L   T   I   S   S   L   E   P   E   D   F   A   V   Y   Y   C   Q   Q
217   CTC ACC ATC AGC AGC CTA GAG CCT GAA GAT TTT GCA GTT TAT TAC TGT CAG CAG

                  CDR3
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~
          R   S   N   W   P   L   T   F   G   G   G   T   K   V   E   I   K
271   CGT AGC AAC TGG CCG CTC ACT TTC GGC GGA GGG ACC AAG GTG GAG ATC AAA
```

FIGURE 2B

Anti-Mesothelin 7B1 VH

V segment: 3-7
D segment: 3-10
J segment: JH6b

```
          E   V   H   L   V   E   S   G   G   G   L   V   Q   P   G   G   S   L
1         GAG GTT CAC CTG GTG GAG TCT GGG GGA GGC TTG GTC CAG CCT GGG GGG TCC CTG

                                                          CDR1
                                                  ~~~~~~~~~~~~~~~~~~~
          R   L   S   C   A   A   S   G   F   T   F   S   R   Y   W   M   S   W
55        AGA CTC TCC TGT GCA GCC TCT GGA TTC ACC TTT AGT AGA TAC TGG ATG AGC TGG

                                                              CDR2
                                                      ~~~~~~~~~~~~~~~~~~~
          V   R   Q   A   Q   G   K   G   L   E   W   V   A   S   I   K   Q   A
109       GTC CGC CAG GCT CAA GGG AAA GGG CTG GAG TGG GTG GCC AGC ATA AAG CAA GCT

                        CDR2
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
          G   S   E   K   T   Y   V   D   S   V   K   G   R   F   T   I   S   R
163       GGA AGT GAG AAA ACC TAT GTG GAC TCT GTG AAG GGC CGA TTC ACC ATC TCC AGA

          D   N   A   K   N   S   L   S   L   Q   M   N   S   L   R   A   E   D
217       GAC AAC GCC AAG AAC TCA CTG TCT CTG CAA ATG AAC AGC CTG AGA GCC GAG GAC

                                                      CDR3
                                              ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
          T   A   V   Y   Y   C   A   R   E   G   A   Y   Y   Y   D   S   A   S
271       ACG GCT GTT TAT TAC TGT GCG AGG GAG GGG GCA TAT TAC TAT GAT TCG GCG AGT

                        CDR3
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
          Y   Y   P   Y   Y   Y   Y   Y   S   M   D   V   W   G   Q   G   T   T
325       TAT TAC CCT TAC TAC TAC TAC TAC AGT ATG GAC GTC TGG GGC CAA GGG ACC ACG

          V   T   V   S   S
379       GTC ACC GTC TCC TCA
```

FIGURE 3A

Anti-Mesothelin 7B1 VK

V segment: A27
J segment: JK2

```
          E   I   V   L   T   Q   S   P   G   T   L   S   L   S   P   G   E   R
1       GAA ATT GTG TTG ACG CAG TCT CCA GGC ACC CTG TCT TTG TCT CCA GGG GAA AGA

                                    CDR1
                        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
          A   T   L   S   C   R   A   S   Q   S   V   S   S   S   Y   L   A   W
55      GCC ACC CTC TCC TGC AGG GCC AGT CAG AGT GTT AGC AGC AGC TAC TTA GCC TGG

                                                                CDR2
                                                            ~~~~~~~~~~~~~~~~
          Y   Q   Q   K   P   G   Q   A   P   R   L   L   I   Y   G   A   S   S
109     TAC CAG CAG AAA CCT GGC CAG GCT CCC AGG CTC CTC ATC TAT GGT GCA TCC AGC

          CDR2
        ~~~~~~~~~~~
          R   A   T   G   I   P   D   R   F   S   G   S   G   S   G   T   D   F
163     AGG GCC ACT GGC ATC CCA GAC AGG TTC AGT GGC AGT GGG TCT GGG ACA GAC TTC

                                                                        CDR3
                                                                        ~~~
          T   L   T   I   S   R   L   E   P   E   D   F   A   V   Y   Y   C   Q
217     ACT CTC ACC ATC AGC AGA CTG GAG CCT GAA GAT TTT GCA GTG TAT TAC TGT CAG

                    CDR3
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
          Q   Y   G   S   S   Q   Y   T   F   G   Q   G   T   K   L   E   I   K
271     CAG TAT GGT AGC TCA CAG TAC ACT TTT GGC CAG GGG ACC AAG CTG GAG ATC AAA
```

FIGURE 3B

Anti-Mesothelin 3C10 and 6A4 VH regions

```
                                                                                   ___CDR1___
3-33 germline     Q V Q L V E S G G G V V Q P G R S L R L S C A A S G F T F S S Y G M H W
3C10 VH           - - Y - - - - - - - - - - - - - - - - - - - - - - - I - - - I - - - - -
6A4 VH            - - H - - - - - - - - - - - - - - - - - - - - - V - - I - - R I - - - - -

                                              _______CDR2___________________
3-33 germline     V R Q A P G K G L E W V A V I W Y D G S N K Y Y A D S V K G R F T I S R
3C10 VH           - - - - - - - - - - - - - - - - - - - - H E - - - - - - - - - - - - - -
6A4 VH            - - - - - - - - - - - - - - L - - - - - H E - - - - - - - - - - - - - -

                                                                        _____CDR3_____
3-33 germline     D N S K N T L Y L Q M N S L R A E D T A V Y Y C A R
3C10 VH           - - - - - - - - - L - - - - - - - - - - - - - - - - D G D Y Y D S G S P
6A4 VH            - - - - - - - - - - - - - - - - - - - - I - - - - - D G D Y Y D S G S P

                  ___
JH4b germline       D Y W G Q G T L V T V S S
3C10 VH           L - - - - - - - - - - - - -     (JH4b)
6A4 VH            L - - - - - - - - - - - - -     (JH4b)
```

FIGURE 4

Anti-Mesothelin 3C10 and 6A4 VK regions

																						CDR1									
L6 germline	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C	R	A	S	Q	S	V	S	S
3C10 VK	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6A4 VK	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

																			CDR2												
L6 germline	Y	L	A	W	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	D	A	S	N	R	A	T	G	I	P	A	R	F
3C10 VK	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6A4 VK	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

																											CDR3				
L6 germline	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	E	P	E	D	F	A	V	Y	Y	C	Q	Q	R	S	N
3C10 VK	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6A4 VK	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

L6 germline	W	P																													
JK4 germline			L	T	F	G	G	G	T	K	V	E	I	K																	
3C10 VK	-	-	-	-	-	-	-	-	-	-	-	-	-	-	(JK4)																
6A4 VK	-	-	-	-	-	-	-	-	-	-	-	-	-	-	(JK4)																

FIGURE 5

Anti-Mesothelin 7B1 VH region



FIGURE 6

Anti-Mesothelin 7B1 VK region

```
                                                                  ____CDR1_____
A27 germline    E I V L T Q S P G T L S L S P G E R A T L S C R A S Q S V S S
7B1 VK          - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -

                _CDR1__                                 ____CDR2_____
A27 germline    S Y L A W Y Q Q K P G Q A P R L L I Y G A S S R A T G I P D R
7B1 VK          - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -

                                                                  _CDR3__
A27 germline    F S G S G S G T D F T L T I S R L E P E D F A V Y Y C Q Q Y G
7B1 VK          - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -

                __CDR3___
A27 germline    S S
JK2 germline          Y T F G Q G T K L E I K
7B1 VK          - - Q - - - - - - - - - - - -    (JK2)
```

FIGURE 7

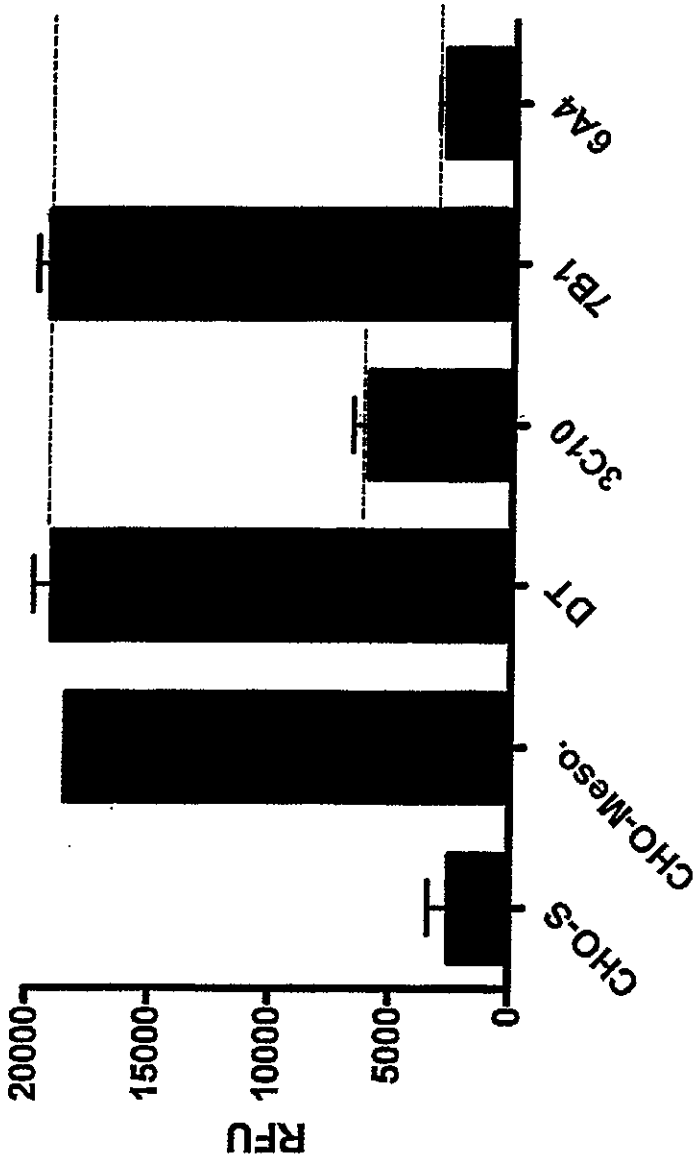


FIGURE 8

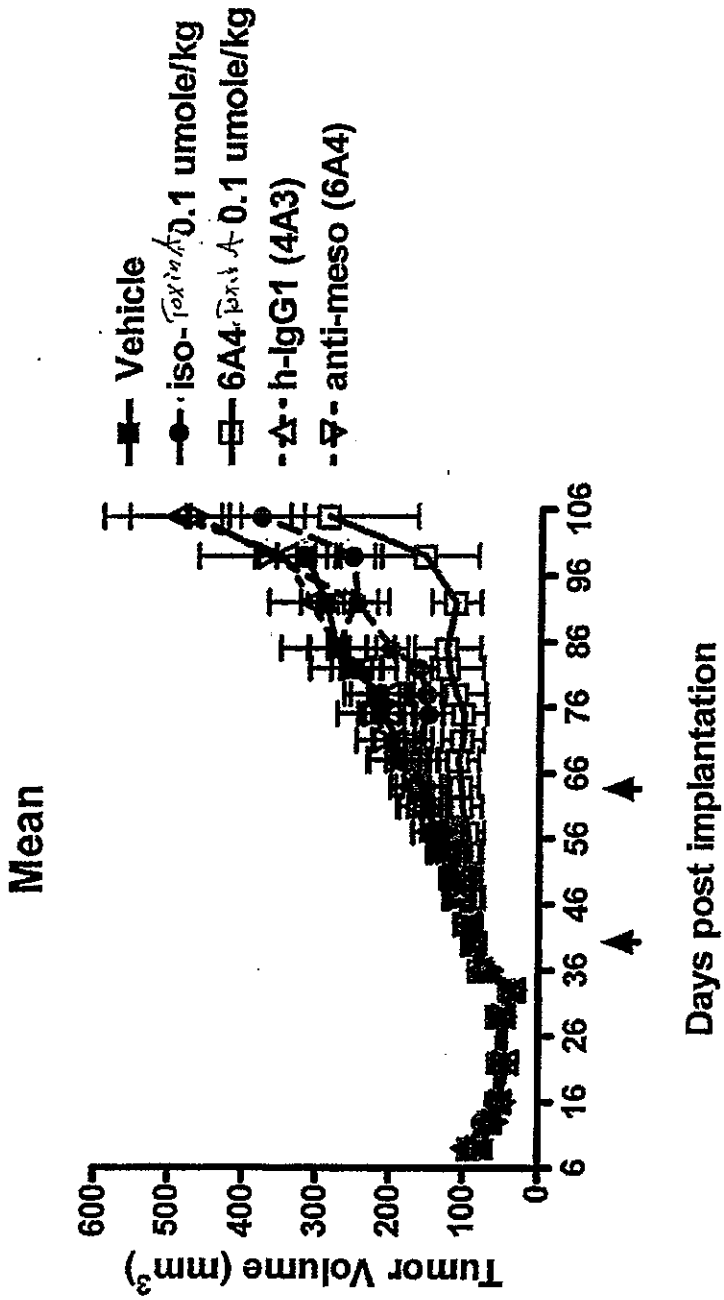

Mean
Vehicle
iso-Toxin A 0.1 umole/kg
6A4-Toxin A 0.1 umole/kg
h-IgG1 (4A3)
anti-meso (6A4)
Tumor Volume (mm3)
600
500
400
300
200
100
0
6
16
26
36
46
56
66
76
86
96
106
Days post implantation

FIGURE 9A

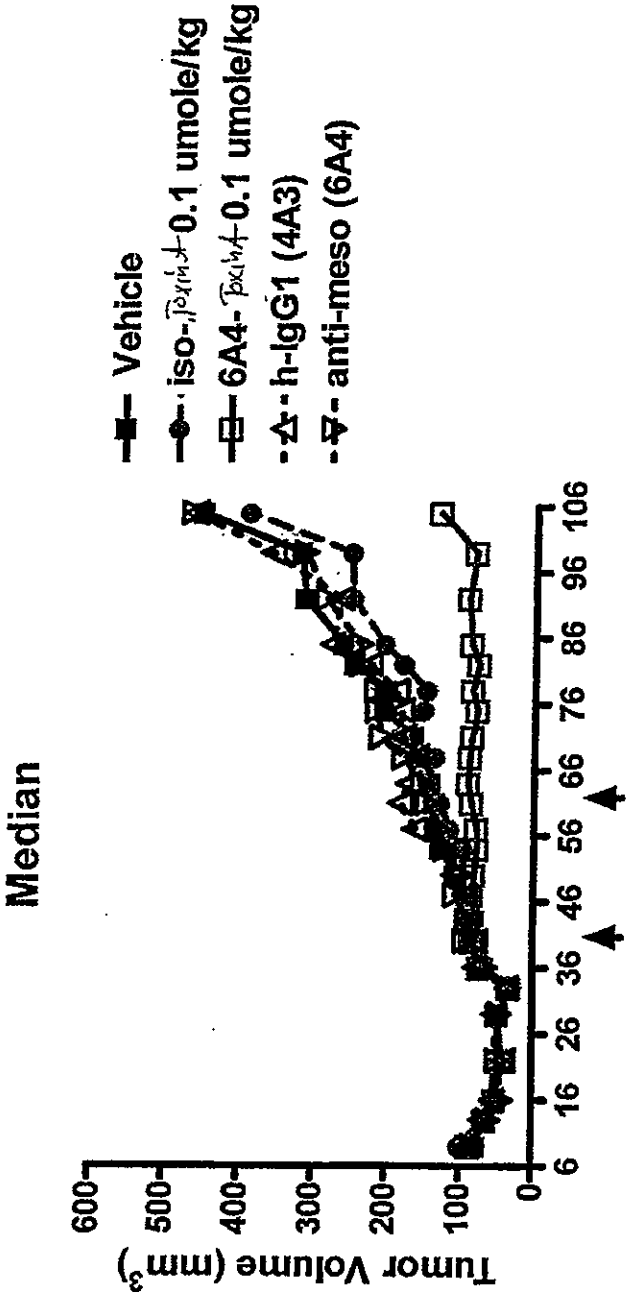

Median
Vehicle
iso-[illegible]-0.1 umole/kg
6A4-[illegible]-0.1 umole/kg
h-IgG1 (4A3)
anti-meso (6A4)
Tumor Volume (mm3)
600
500
400
300
200
100
0
6
16
26
36
46
56
66
76
86
96
106
Days post implantation

FIGURE 9B

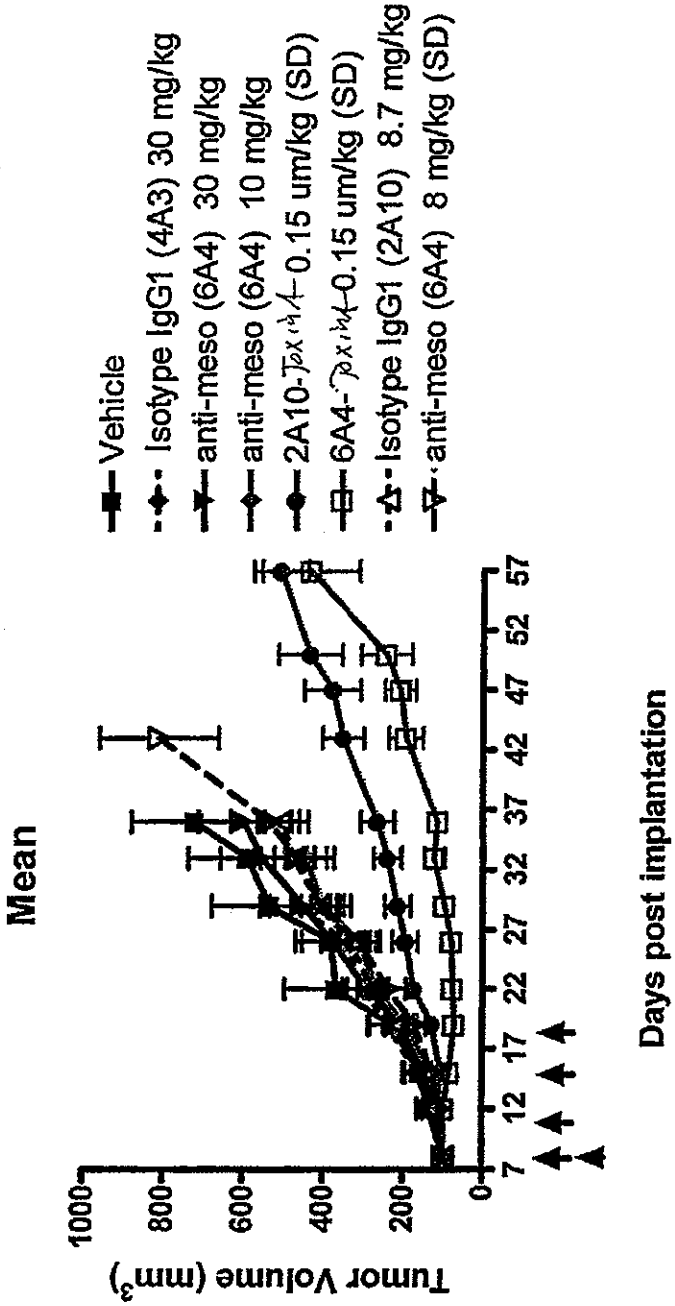

Mean
Tumor Volume (mm3)
1000
800
600
400
200
0
7
12
17
22
27
32
37
42
47
52
57
Days post implantation
Vehicle
Isotype IgG1 (4A3) 30 mg/kg
anti-meso (6A4) 30 mg/kg
anti-meso (6A4) 10 mg/kg
2A10-Taxol 0.15 um/kg (SD)
6A4-Taxol 0.15 um/kg (SD)
Isotype IgG1 (2A10) 8.7 mg/kg
anti-meso (6A4) 8 mg/kg (SD)

FIGURE 10A

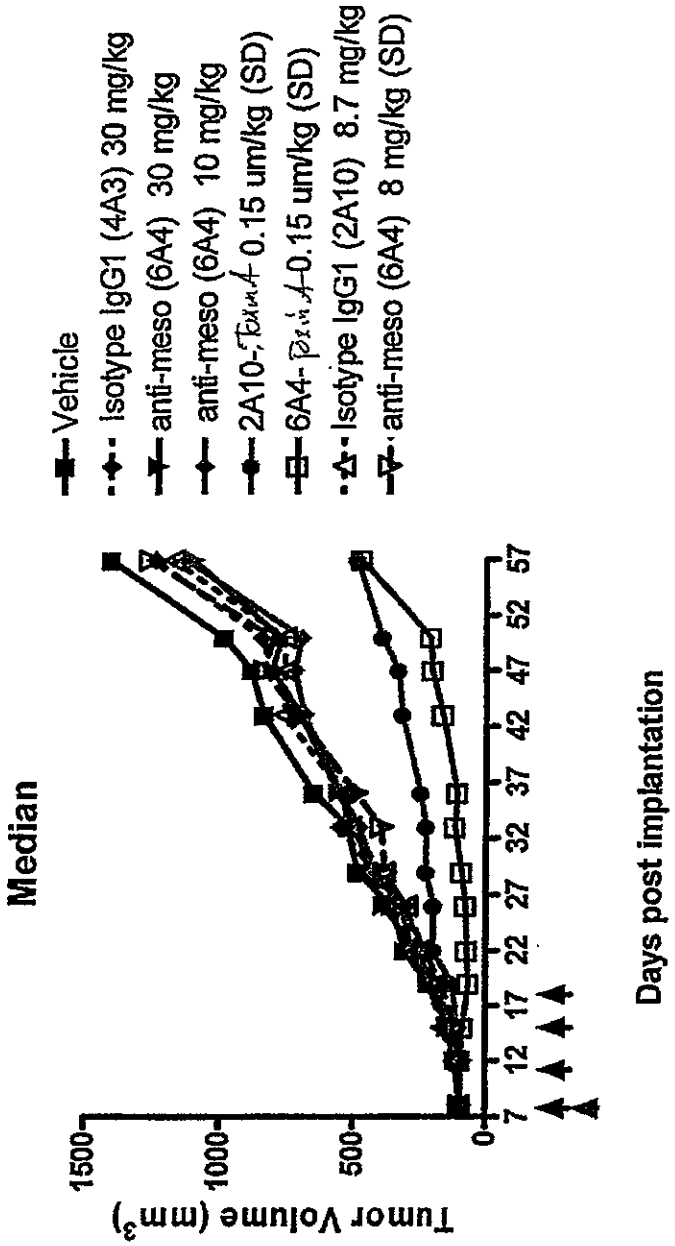

Median
Vehicle
Isotype IgG1 (4A3) 30 mg/kg
anti-meso (6A4) 30 mg/kg
anti-meso (6A4) 10 mg/kg
2A10-Taxol 0.15 um/kg (SD)
6A4-Taxol 0.15 um/kg (SD)
Isotype IgG1 (2A10) 8.7 mg/kg
anti-meso (6A4) 8 mg/kg (SD)
Tumor Volume (mm3)
1500
1000
500
0
7
12
17
22
27
32
37
42
47
52
57
Days post implantation

FIGURE 10B

Figure 11

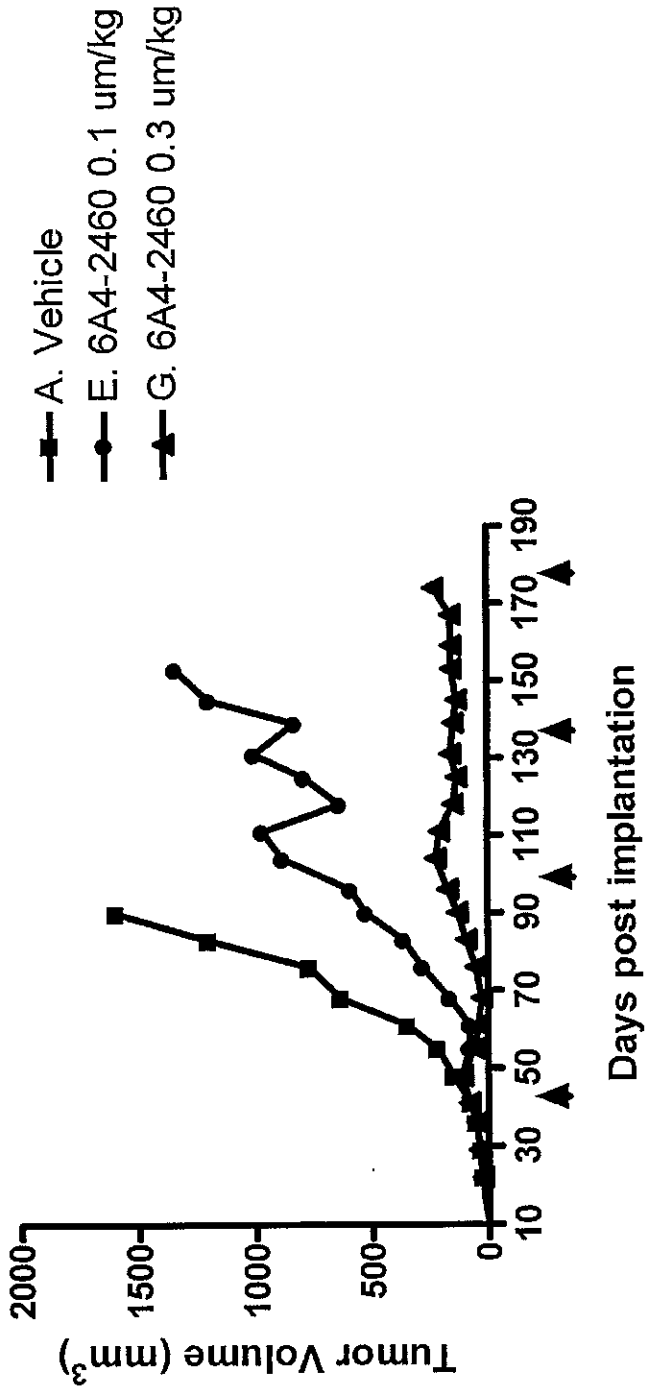

A. Vehicle
E. 6A4-2460 0.1 um/kg
G. 6A4-2460 0.3 um/kg
Tumor Volume (mm3)
2000
1500
1000
500
0
10
30
50
70
90
110
130
150
170
190
Days post implantation

FIGURE 12a

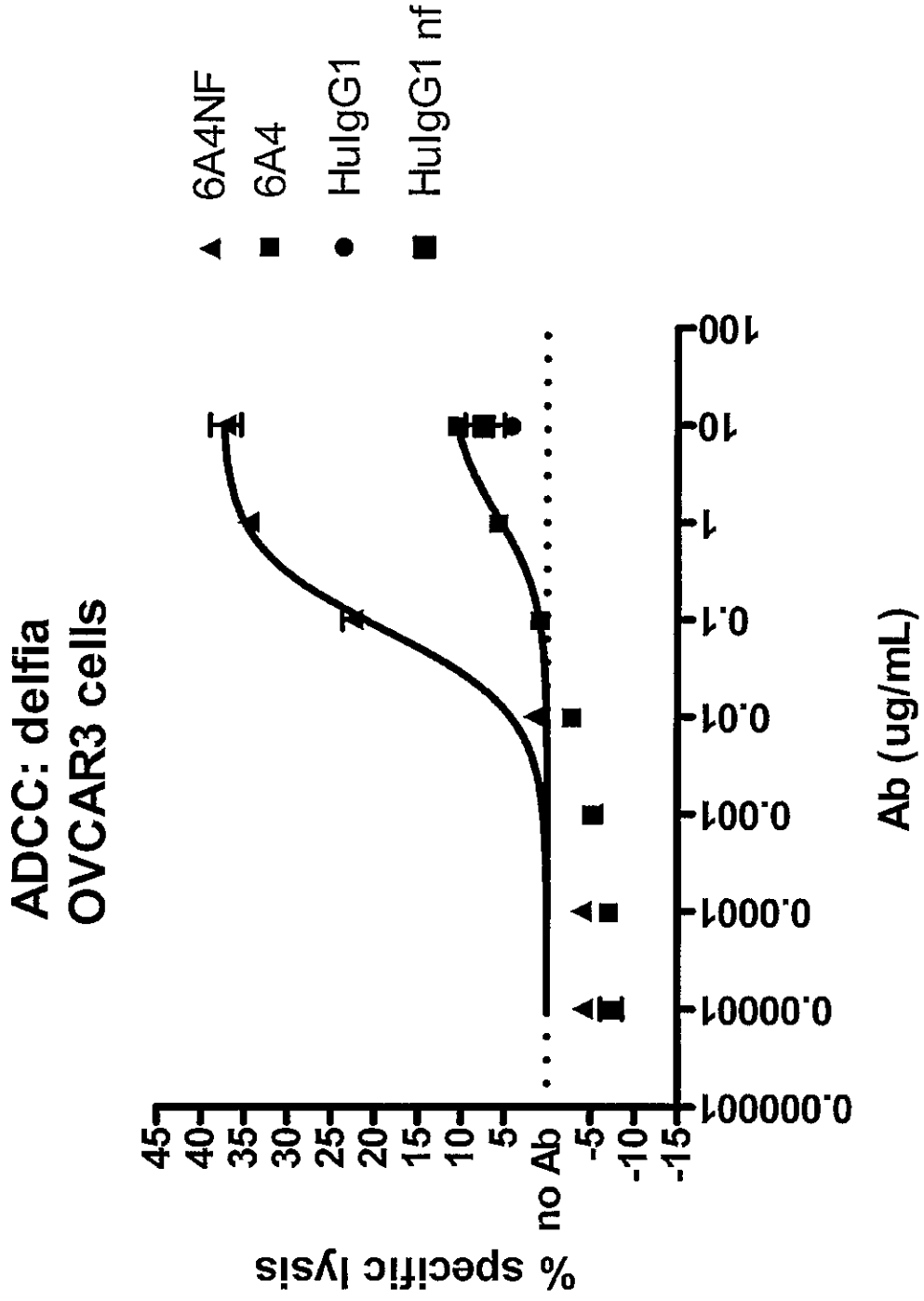
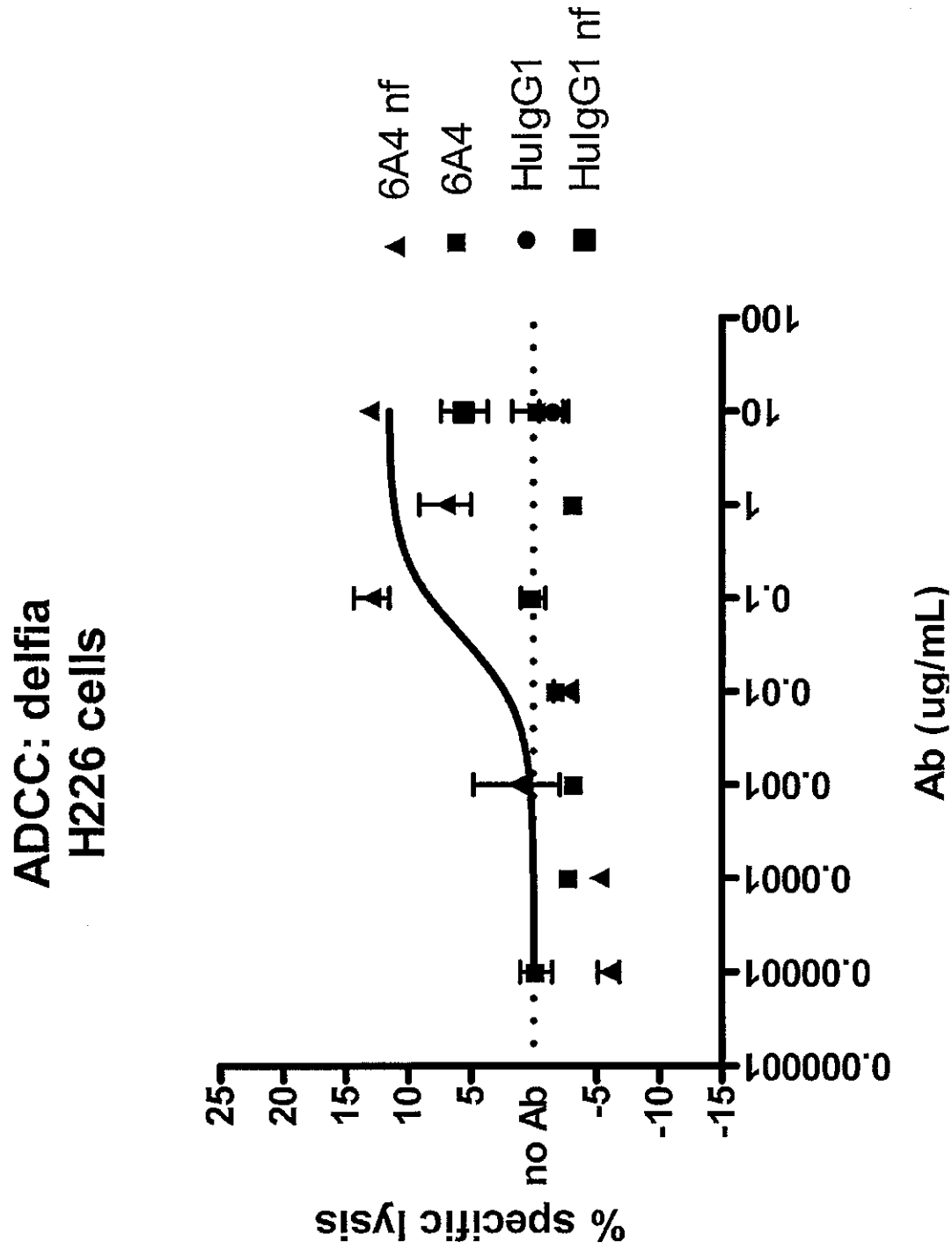

ADCC: delfia
OVCAR3 cells
6A4NF
6A4
HulgG1
HulgG1 nf
% specific lysis
45
40
35
30
25
20
15
10
5
no Ab
-5
-10
-15
100
10
1
0.1
0.01
0.001
0.0001
0.00001
0.000001
Ab (ug/mL)

FIGURE 12B


ADCC: delfia
H226 cells
6A4 nf
6A4
HuIgG1
HuIgG1 nf
% specific lysis
25
20
15
10
5
no Ab
-5
-10
-15
100
10
1
0.1
0.01
0.001
0.0001
0.00001
0.000001
Ab (ug/mL)