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(54) Title: HUMAN ANTIBODIES THAT BIND CD70 AND USES THEREOF

(57) Abstract: The present disclosure provides isolated monoclonal antibodies that specifically bind to CD70 with high affinity, particularly human monoclonal antibodies. Preferably, the antibodies bind human CD70. In certain embodiments, the antibodies are capable of being internalized into CD70-expressing cells or are capable of mediating antigen dependent cellular cytotoxicity. Nucleic acid molecules encoding the antibodies of this disclosure, expression vectors, host cells and methods for expressing the antibodies of this disclosure are also provided. Antibody-partner molecule conjugates, bispecific molecules and pharmaceutical compositions comprising the antibodies of this disclosure are also provided. This disclosure also provides methods for detecting CD70, as well as methods for treating cancers, such as renal cancer and lymphomas, using an anti-CD70 antibody of this disclosure.

WE CLAIM:

1. An antibody-partner molecule conjugate comprising an isolated human monoclonal antibody, or an antigen-binding portion thereof, wherein the antibody binds human CD70 and exhibits at least one, two, three, four, five, or all six of the following properties:

- (a) binds to human CD70 with a K_D of 1×10^{-7} M or less; and
- (b) binds to a renal cell carcinoma tumor cell line;
- (c) binds to a lymphoma cell line;
- (d) is internalized by CD70-expressing cells;
- (e) exhibits antibody dependent cellular cytotoxicity (ADCC) against CD70-expressing cells; and
- (f) inhibits growth of CD70-expressing cells *in vivo* when conjugated to a cytotoxin, and a partner molecule, wherein the partner molecule is a therapeutic agent.

2. The antibody-partner molecule conjugate of claim 1, wherein the monoclonal antibody, or antigen binding portion thereof, binds an epitope on human CD70 recognized by a reference antibody, wherein the reference antibody comprises:

- (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:1 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:7;
- (b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:2 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:8;
- (c) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:3 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:9;
- (d) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:4 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:10;
- (e) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:5 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:11;
- (f) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:73 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:11; or
- (g) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:6 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:12, and a partner molecule, wherein the partner molecule is a therapeutic agent.

3. An antibody-partner molecule conjugate comprising an isolated monoclonal antibody, or an antigen-binding portion thereof, comprising a heavy chain variable region that is the product of or derived from a human V_H 3-30.3 gene, human V_H 3-33 gene, human V_H 4-61 gene, or human V_H 3-23 gene, and a light chain variable region that is the product of or derived from a human V_K L6 gene, human V_K L18 gene, human V_K L15 gene, human V_K L6 gene, or human V_K A27 gene, wherein the antibody specifically binds CD70, and a partner molecule, wherein the partner molecule is a therapeutic agent.

4. The antibody-partner molecule conjugate of claim 1, wherein the antibody or antigen-binding portion thereof, comprises:

- (a) a heavy chain variable region CDR1 comprising SEQ ID NO:13;
- (b) a heavy chain variable region CDR2 comprising SEQ ID NO:19;
- (c) a heavy chain variable region CDR3 comprising SEQ ID NO:25;
- (d) a light chain variable region CDR1 comprising SEQ ID NO:31;
- (e) a light chain variable region CDR2 comprising SEQ ID NO:37; and
- (f) a light chain variable region CDR3 comprising SEQ ID NO:43,

or

- (a) a heavy chain variable region CDR1 comprising SEQ ID NO:14;
- (b) a heavy chain variable region CDR2 comprising SEQ ID NO:20;
- (c) a heavy chain variable region CDR3 comprising SEQ ID NO:26;
- (d) a light chain variable region CDR1 comprising SEQ ID NO:32;
- (e) a light chain variable region CDR2 comprising SEQ ID NO:38; and
- (f) a light chain variable region CDR3 comprising SEQ ID NO:44,

or

- (a) a heavy chain variable region CDR1 comprising SEQ ID NO:15;
- (b) a heavy chain variable region CDR2 comprising SEQ ID NO:21;
- (c) a heavy chain variable region CDR3 comprising SEQ ID NO:27;
- (d) a light chain variable region CDR1 comprising SEQ ID NO:33;
- (e) a light chain variable region CDR2 comprising SEQ ID NO:39; and
- (f) a light chain variable region CDR3 comprising SEQ ID NO:45;

or

- (a) a heavy chain variable region CDR1 comprising SEQ ID NO:16;
- (b) a heavy chain variable region CDR2 comprising SEQ ID NO:22;

- (c) a heavy chain variable region CDR3 comprising SEQ ID NO:28;
- (d) a light chain variable region CDR1 comprising SEQ ID NO:34;
- (e) a light chain variable region CDR2 comprising SEQ ID NO:40; and
- (f) a light chain variable region CDR3 comprising SEQ ID NO:46;

or

- (a) a heavy chain variable region CDR1 comprising SEQ ID NO:17;
- (b) a heavy chain variable region CDR2 comprising SEQ ID NO:23;
- (c) a heavy chain variable region CDR3 comprising SEQ ID NO:29;
- (d) a light chain variable region CDR1 comprising SEQ ID NO:35;
- (e) a light chain variable region CDR2 comprising SEQ ID NO:41; and
- (f) a light chain variable region CDR3 comprising SEQ ID NO:47

or

- (a) a heavy chain variable region CDR1 comprising SEQ ID NO:17;
- (b) a heavy chain variable region CDR2 comprising SEQ ID NO:23;
- (c) a heavy chain variable region CDR3 comprising SEQ ID NO:75;
- (d) a light chain variable region CDR1 comprising SEQ ID NO:35;
- (e) a light chain variable region CDR2 comprising SEQ ID NO:41; and
- (f) a light chain variable region CDR3 comprising SEQ ID NO:47

or

- (a) a heavy chain variable region CDR1 comprising SEQ ID NO:18;
- (b) a heavy chain variable region CDR2 comprising SEQ ID NO:24;
- (c) a heavy chain variable region CDR3 comprising SEQ ID NO:30;
- (d) a light chain variable region CDR1 comprising SEQ ID NO:36;
- (e) a light chain variable region CDR2 comprising SEQ ID NO:42; and
- (f) a light chain variable region CDR3 comprising SEQ ID NO:48.

5. The antibody-partner molecule conjugate of claim 1, wherein the isolated monoclonal antibody, or antigen binding portion thereof, comprises :

(a) a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-6, and 73; and

(b) a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 7-12;

wherein the antibody specifically binds a human CD70 protein,
and a partner molecule, wherein the partner molecule is a therapeutic agent.

6. The antibody-partner molecule conjugate of claim 5, wherein the antibody or antigen-binding portion thereof, comprises:

- (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1;

and

- (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 7.

7. The antibody-partner molecule conjugate of claim 5, wherein the antibody or antigen-binding portion thereof, comprises:

- (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2;

and

- (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 8.

8. The antibody-partner molecule conjugate of claim 5, wherein the antibody or antigen-binding portion thereof, comprises:

- (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 3;

and

- (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 9.

9. The antibody-partner molecule conjugate of claim 5, wherein the antibody or antigen-binding portion thereof, comprises:

- (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 4;

and

- (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 10.

10. The antibody-partner molecule conjugate of claim 5, wherein the antibody or antigen-binding portion thereof, comprises:

- (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 5;

and

- (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 11.

11. The antibody-partner molecule conjugate of claim 5, wherein the antibody or antigen-binding portion thereof, comprises:

(a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 73; and

(b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 11.

12. The antibody-partner molecule conjugate of claim 5, wherein the antibody or antigen-binding portion thereof, comprises:

(a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 6; and

(b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 12.

13. The antibody-partner molecule conjugate of claim 1, wherein the therapeutic agent is a cytotoxin or a radioactive isotope.

14. A method of inhibiting growth of a CD70-expressing tumor cell comprising contacting the CD70-expressing tumor cell with the antibody-partner molecule conjugate of claim 1 such that growth of the CD70-expressing tumor cell is inhibited.

15. The method of claim 14, wherein the CD70-expressing tumor cell is a renal tumor cell or a lymphoma cell.

16. The method of claim 14, wherein the CD70-expressing tumor cell is from a cancer selected from the group consisting of renal cell carcinoma or lymphoma.

17. A method of treating cancer in a subject comprising administering to the subject an antibody-partner molecule of claim 1 such that the cancer is treated in the subject.

18. The method of claim 17, wherein the cancer is a renal cell carcinoma or lymphoma.

19. The method of claim 17, wherein the cancer is selected from the group consisting of: renal cell carcinomas (RCC), clear cell RCC, glioblastoma, non-Hodgkin's lymphoma

(NHL), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), Burkitt's lymphoma, anaplastic large-cell lymphomas (ALCL), multiple myeloma, cutaneous T-cell lymphomas, nodular small cleaved-cell lymphomas, lymphocytic lymphomas, peripheral T-cell lymphomas, Lennert's lymphomas, immunoblastic lymphomas, T-cell leukemia/lymphomas (ATLL), adult T-cell leukemia (T-ALL), entroblastic/centrocytic (cb/cc) follicular lymphomas cancers, diffuse large cell lymphomas of B cell lineage, angioimmunoblastic lymphadenopathy (AILD)-like T cell lymphoma, HIV associated body cavity based lymphomas, embryonal carcinomas, undifferentiated carcinomas of the rhino-pharynx, Schmincke's tumor, Castleman's disease, Kaposi's Sarcoma, multiple myeloma, Waldenstrom's macroglobulinemia and B-cell lymphomas.

20. A method of treating or preventing an autoimmune disease in a subject comprising administering to the subject an antibody-partner molecule of claim 1 whereby the autoimmune disease is treated or prevented in the subject.

21. A method of treating or preventing inflammation in a subject comprising administering to the subject an antibody-partner molecule of claim 1 such that the inflammation is treated or prevented in the subject.

22. A method of treating a viral infection in a subject comprising administering to the subject an antibody-partner molecule of claim 1 such that the viral infection is treated in the subject.

23. The antibody-partner molecule conjugate of claim 1, wherein the partner molecule is conjugated to the antibody by a chemical linker.

24. The antibody-partner molecule conjugate of claim 23, wherein the chemical linker is selected from the group consisting of peptidyl linkers, hydrazine linkers, and disulfide linkers.

25. The antibody-partner molecule conjugate of claim 1, wherein the antibody, or antigen binding portion thereof, is nonfucosylated.

26. An isolated monoclonal antibody, or an antigen-binding portion thereof, comprising: a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 6 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 12.

27. An isolated monoclonal antibody, or an antigen binding portion thereof, which binds an epitope on the human CD70 protein recognized by an antibody comprising: a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 6 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 12.

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Anti-CD70 2H5 VH Regions

V segment: 3-30.3 '
D segment:undetermined
J segment: JH4b

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

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

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

                                CDR2
                                ~~~~~
      G R N K Y Y A D S V K G R F T I S R
163 GGA AGA AAC AAA TAC TAC 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 CTG TAT CTG CAA ATG AAC AGC CTG AGA GCT GAG GAC

                                CDR3
                                ~~~~~
      T A V Y Y C A R D T D G Y D F D Y W
271 ACG GCT GTG TAT TAC TGT GCG AGA GAT ACG GAT GGC TAC GAT TTT GAC TAC TGG
                                |
                                JH4b

      G Q G T L V T V S S
325 GGC CAG GGA ACC CTG GTC ACC GTC TCC TCA
```

Fig. 1A

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Anti-CD70 2H5 VK Regions

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 P 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 T N W P L T F G G G T K V E I K
271  CGT ACC AAC TGG CCG CTC ACT TTC GGC GGA GGG ACC AAG GTG GAG ATC AAA
      |
      |→ JK4
```

Fig. 1B

3/101

Anti-CD70 10B4 VH Regions

V segment: 3-30.3
 D segment: 4-11
 J segment: JH4b

```

      Q   I   Q   L   V   E   S   G   G   G   V   V   Q   P   G   R   S   L
1  CAA ATA CAA CTG GTG GAG TCT GGG GGA GGC GTG GTC CAG CCT GGG AGG TCC CTG

                                     CDR1
                                     -----
      R   L   S   C   A   A   S   G   F   T   F   G   Y   Y   A   M   H   W
55 AGA CTC TCC TGT GCA GCC TCT GGA TTC ACC TTC GGT TAC TAT GCT ATG CAC TGG

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

      CDR2
      -----
      G   S   I   K   Y   Y   A   D   S   V   K   G   R   F   T   I   S   R
163 GGA AGC ATT AAA TAC TAC 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 CTG TAT CTG CAA ATG AAC AGC CTG AGA GCT GAG GAC

                                     CDR3
                                     -----
      T   A   V   Y   Y   C   A   R   E   G   P   Y   S   N   Y   L   D   Y
271 ACG GCT GTG TAT TAC TGT GCG AGA GAG GGC CCT TAC AGT AAC TAC CTT GAC TAC

                                     JH4b
                                     -----
      W   G   Q   G   T   L   V   T   V   S   S
325 TGG GGC CAG GGA ACC CTG GTC ACC GTC TCC TCA
  
```

Fig. 2A

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Anti-CD70 10B4 VK Regions

V segment: L18
J segment: JK3

```
      A I Q L T Q S P S S L S A S V G D R
1  GCC ATC CAG TTG ACC CAG TCT CCA TCC TCC CTG TCT GCA TCT GTA GGA GAC AGA

      CDR1
      ~~~~~
      V T I T C R A S Q G I S S A L A W Y
55  GTC ACC ATC ACT TGC CGG GCA AGT CAG GGC ATT AGC AGT GCT TTA GCC TGG TAT

      CDR2
      ~~~~~
      Q Q K P G K A P K F L I Y D A S S L
109 CAG CAG AAA CCA GGG AAA GCT CCT AAG TTC TTG ATC TAT GAT GCC TCC AGT TTG

      CDR2
      ~~~~~
      E S G V P S R F S G S G S G T D F T
163 GAA AGT GGG GTC CCA TCA AGG TTC AGC GGC AGT GGA TCT GGG ACA GAT TTC ACT

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

      CDR3
      ~~~~~
      F N S Y P F T F G P G T K V D I K
271 TTT AAT AGT TAC CCA TTC ACT TTC GGC CCT GGG ACC AAA GTG GAT ATC AAA
      |
      JK3
```

Fig. 2B

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Anti-CD70 8B5 VH Regions

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

```

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

                                CDR1
                                ~~~~~
      R  L  S  C  A  T  S  G  F  T  F  S  D  Y  G  M  H  W
55 AGA CTC TCC TGT GCG ACG TCT GGA TTC ACC TTC AGT GAC 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  N  K  Y  Y  A  D  S  V  K  G  R  F  T  I  S  R
163 GGA AGT AAT AAA TAC TAT GCA GAC TCC GTG AAG GGC CGA TTC ACC ATC TCC AGA

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

                                CDR3
                                ~~~~~
      T  A  V  Y  Y  C  A  R  D  S  I  M  V  R  G  D  Y  W
271 ACG GCT GTG TAT TAC TGT GCG AGA GAT TCT ATT ATG GTT CGG GGG GAC TAC TGG

                                JH4b
                                ~~~~~
      G  Q  G  T  L  V  T  V  S  S
325 GGC CAG GGA ACC CTG GTC ACC GTC TCC TCA
  
```

Fig. 3A

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Anti-CD70 8B5 VK Regions

V segment: L15
J segment: JK4

```

      D   I   Q   M   T   Q   S   P   S   S   L   S   A   S   V   G   D   R
1  GAC ATC CAG ATG ACC CAG TCT CCA TCC TCA CTG TCT GCA TCT GTA GGA GAC AGA

                                CDR1
                                ~~~~~
      V   T   I   T   C   R   A   S   Q   G   I   S   S   W   L   A   W   Y
55  GTC ACC ATC ACT TGT CGG GCG AGT CAG GGT ATT AGC AGC TGG TTA GCC TGG TAT

                                CDR2
                                ~~~~~
      Q   Q   K   P   E   K   A   P   K   S   L   I   Y   A   A   S   S   L
109 CAG CAG AAA CCA GAG AAA GCC CCT AAG TCC CTG ATC TAT GCT GCA TCC AGT TTG

      CDR2
      ~~~~~
      Q   S   G   V   P   S   R   F   S   G   S   G   S   G   T   D   F   T
163 CAA AGT GGG GTC CCA TCA AGG TTC AGC GGC AGT GGA TCT GGG ACA GAT TTC ACT

                                CDR3
                                ~~~~~
      L   T   I   S   S   L   Q   P   E   D   F   A   T   Y   Y   C   Q   Q
217 CTC ACC ATC AGC AGC CTG CAG CCT GAA GAT TTT GCA ACT TAT TAC TGC CAA CAG

      CDR3
      ~~~~~
      Y   N   S   Y   P   L   T   F   G   G   G   T   K   V   E   I   K
271 TAT AAT AGT TAC CCG CTC ACT TTC GGC GGA GGG ACC AAG GTG GAG ATC AAA
      |
      ↓
      JK4

```

Fig. 3B

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Anti-CD70 18E7 VH Regions

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

```

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

                                CDR1
                                ~~~~~
      R  L  S  C  A  A  S  G  F  T  F  S  D  H  G  M  H  W
55 AGA CTC TCC TGT GCA GCG TCT GGA TTC ACC TTC AGC GAC CAT 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  N  K  Y  Y  A  D  S  V  K  G  R  F  T  I  S  R
153 GGA AGT AAT AAA 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 CTG TAT CTG CAA ATG AAC AGC CTG AGA GCC GAG GAC

                                CDR3
                                ~~~~~
      T  A  V  Y  Y  C  A  R  D  S  I  M  V  R  G  D  Y  W
271 ACG GCT GTG TAT TAC TGT GCG AGA GAT TCT ATT ATG GTT CCG GGG GAC TAC TGG
                                |
                                → JH4b

      G  Q  G  T  L  V  T  V  S  S
325 GGC CAG GGA ACC CTG GTC ACC GTC TCC TCA

```

Fig. 4A

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Anti-CD70 18E7 VK Regions

V segment: L15
J segment: JK4

```

      D I Q M T Q S P S S L S A S V G D R
1  GAC ATC CAG ATG ACC CAG TCT CCA TCC TCA CTG TCT GCA TCT GTA GGA GAC AGA

      CDR1
      ~~~~~
      V T I T C R A S Q G I S S W L A W Y
55 GTC ACC ATC ACT TGT CGG GCG AGT CAG GGT ATT AGC AGC TGG TTA GCC TGG TAT

      CDR2
      ~~~~~
      Q Q K P E K A P K S L I Y A A S S L
109 CAG CAG AAA CCA GAG AAA GCC CCT AAG TCC CTG ATC TAT GCT GCA TCC AGT TTG

      CDR2
      ~~~~~
      Q S G V P S R F S G S G S G T D F T
163 CAA AGT GGG GTC CCA TCA AGG TTC AGC GGC AGT GGA TCT GGG ACA GAT TTC ACT

      CDR3
      ~~~~~
      L T I S S L Q P E D F A T Y Y C Q Q
217 CTC ACC ATC AGC AGC CTG CAG CCT GAA GAT TTT GCA ACT TAT TAC TGC CAA CAG

      CDR3
      ~~~~~
      Y N S Y P L T F G G G T K V E I K
271 TAT AAT AGT TAC CCG CTC ACT TTC GGC GGA GGG ACC AAG GTG GAG ATC AAA

      |
      |→ JK4

```

Fig. 4B

9/101

Anti-CD70 69A7 VH

V segment: 4-61
 D segment: 4-23
 J segment: JH4b

```

1      Q V Q L Q E S G P G L V K P S E T L
      CAG GTG CAG CTG CAG GAG TCG GGC CCA GGA CTG GTG AAG CCT TCG GAG ACC CTG

                                         CDR1
                                         ~~~~~~
55     S L T C T V S G G S V S S D Y Y Y W
      TCC CTC ACC TGC ACT GTC TCT GGT GGC TCC GTC AGC AGT GAT TAT TAC TAC TGG

      CDR1                                CDR2
      ~~~~                                ~~~~~~
109    S W I R Q P P G K G L E W L G Y I Y
      AGC TGG ATC CGG CAG CCC CCA GGG AAG GGA CTG GAG TGG CTT GGG TAT ATC TAT

                                         CDR2
                                         ~~~~~~
163    Y S G S T N Y N P S L K S R V T I S
      TAC AGT GGG AGC ACC AAC TAC AAC CCC TCC CTC AAG AGT CGA GTC ACC ATA TCA

      V D T S K N Q F S L K L R S V T T A
217    GTA GAC ACG TCC AAG AAC CAG TTC TCC CTG AAG CTG AGG TCT GTG ACC ACT GCG

                                         CDR3
                                         ~~~~~~
271    D T A V Y Y C A R G D G D Y G G N C
      GAC ACG GCC GTG TAT TAC TGT GCG AGA GGG GAT GGG GAC TAC GGT GGT AAC TGT

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

Fig. 5A

10/101

Anti-CD70 69A7 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 F D A S N R
109  CAA CAG AAA CCT GGC CAG GCT CCC AGG CTC CTC ATC TTT 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 CAA

      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
```

Fig. 5B

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Anti- CD70 1F4 VH Regions

V segment: 3-23
 D segment: 4-4
 J segment: JH4b

```

      E V Q L L E S G G G L V Q P G G S L
1 GAG GTG CAG CTG TTG GAG TCT GGG GGA GGC TTG GTA CAG CCT GGG GGG TCC CTG

                                CDR 1
                                ~~~~~
      R L S C A A S G F T F S I Y A M S W
55 AGA CTC TCC TGT GCA GCC TCT GGA TTC ACC TTT AGC ATC TAT GCC ATG AGC TGG

                                CDR 2
                                ~~~~~
      V R Q A P G K G L E W V S A I S D S
109 GTC CGC CAG GCT CCA GGG AAG GGG CTG GAG TGG GTC TCA GCT ATT AGT GAT AGT

                                CDR 2
                                ~~~~~
      G G R T Y F A D S V R G R F T I S R
163 GGT GGT CGC ACA TAC TTC GCA GAC TCC GTG AGG GGC CGG TTC ACC ATC TCC AGA

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

                                CDR 3
                                ~~~~~
      T A V Y Y C A K V D Y S N Y L F F D
271 ACG GCC GTA TAT TAC TGT GCG AAG GTC GAC TAC AGT AAC TAC CTA TTC TTT GAC

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

```

Fig. 6A

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Anti- CD70 1F4 VK Regions

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

                                CDR 1
                                ~~~~~
      A T L S C R A S Q S I S S S Y L A W
55 GCC ACC CTC TCC TGC AGG GCC AGT CAG AGT ATT AGC AGC AGC TAC TTA GCC TGG

                                CDR 2
                                ~~~~~
      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

      CDR 2
      ~~~~~
      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 ICT GGG ACA GAC TTC

                                CDR
                                ~~~
      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

      CDR 3
      ~~~~~
      Q Y G S S P Y T F G Q G T K L E I K
271 CAG TAT GGT AGC TCA CCG TAC ACT TTT GGC CAG GGG ACC AAG CTG GAG ATC AAA

```

Fig. 6B

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Anti-CD70 2H5 and 10B4 V_H Regions

3-30.3 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 A M H W V R Q	CDR1
2H5 VH:	- - - - -	- - - - -
10B4 VH:	- I - - - - -	- - - - - G Y - - - - -
3-30.3 Germline:	A P G K G L E W V A V I S Y D G S N K Y Y A D S V K G R F T I S R D N S K N T	CDR2
2H5 VH:	- - - - -	- - - - -
10B4 VH:	- - - - -	- - - - -
3-30.3 Germline:	L Y L Q M N S L R A E D T A V Y Y C A R	CDR3
JH4b Germline:	- - - - -	- - - - -
2H5 VH:	- - - - -	- - - - -
10B4 VH:	- - - - -	- - - - -
JH4b Germline:	V T V S S	- - - - -
2H5 VH:	- - - - -	- - - - -
10B4 VH:	- - - - -	- - - - -

Y F D Y W G Q G T L
D T D G Y D
E G P Y S N - L

"," Indicates there is no residue at this position for this clone

Fig. 7

Anti-CD70 8B5 and 18E7 V_H regions

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 V R Q	CDR1
8B5 VH:	- - - - -	- - - - -
18E7 VH:	- - - - -	- - - - -
3-33 Germline:	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 D N S K N T	CDR2
8B5 VH:	- - - - -	- - - - -
18E7 VH:	- - - - -	- - - - -
3-33 Germline:	L Y L Q M N S L R A E D T A V Y Y C A R	CDR3
D 3-10 Germline:	- - - - -	- - - - -
JH4b Germline:	- - - - -	- - - - -
8B5 VH:	- S - - - - -	- - - - -
18E7 VH:	- - - - -	- - - - -

Fig. 8

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Anti-CD70 69A7 VH region

4-61 germline 69A7 VH	Q V Q L Q E S G P G L V K P S E T L S L T C T V S G G S V S S G S Y Y W ----- CDR1 ----- D Y - -
4-61 germline 69A7 VH	S W I R Q P P G K G L E W I G Y I Y Y S G S T N Y N P S L K S R V T I S ----- CDR2 ----- I - - - -
4-61 germline JH4b germline 69A7 VH	V D T S K N Q F S L K L S S V T A A D T A V Y Y C A R ----- CDR3 ----- Y - - - - - R - - - - - G D G D Y G G N C
JH4b germline 69A7 VH	F D Y W G Q G T L V T V S S ----- (JH4b)

Fig. 9

Anti- CD70 1F4 VH Region

[illegible]

Fig. 10

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Anti-CD70 mAb1 2H5 VK Region

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 Y L A	CDR1
2H5 VK #1:	- - - - -	- - - - -

L6 Germline:	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 S G S G S G	CDR2
2H5 VK #1:	- - - - -	- - - - -

L6 Germline:	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 W	CDR3
JK4 Germline:	- - - - -	- - - - -
2H5 VK #1:	- - - - -	- - - - -

JK4 Germline:	K V E I K
2H5 VK #1:	- - - - - (JK4)

Fig. 11

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Anti-CD70 mAb3 10B4 VK Regions

L18 Germline:	A I Q L T Q S P S S L S A S V G D R V T I T C R A S Q G I S S A L A	CDR1
10B4 VK:	- - - - -	- - - - -
L18 Germline:	W Y Q Q K P G K A P K L L I Y D A S S L E S G V P S R F S G S G S G	CDR2
10B4 VK:	- - - - - F - - - - -	- - - - -
L18 Germline:	T D F T L T I S S L Q P E D F A T Y Y C Q Q F N S Y P	CDR3
JK3 Germline:	- - - - -	- - - - -
10B4 VK:	- - - - -	F T F G P G T - - - - -
JK3 Germline:	K V D I K	
10B4 VK:	- - - - - (JK3)	

Fig. 12

Anti-CD70 8B5 and 18E7 VK Regions

L15 Germline: 8B5 VK: 18E7 VK:	D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q G I S S W L A	CDR1
L15 Germline: 8B5 VK: 18E7 VK #1:	W Y Q Q K P E K A P K S L I Y A A S S L Q S G V P S R R P S G S G	CDR2
L15 Germline: JK4 Germline: 8B5 VK: 18E7 VK #1:	T D P T L T I S S L Q P E D F A T Y Y C Q Q Y N S Y P	CDR3
JK4 Germline: 8B5 VK: 18E7 VK #1:	T K V E I K	

Fig. 13

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Anti-CD70 69A7 VK region

L6 germline 69A7 VK	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	CDR1
------------------------	---	------

L6 germline 69A7 VK	Y L A W Y Q Q K P G Q A P R L L I Y D A S N R R A T G I P A R F	CDR2
------------------------	---	------

L6 germline 69A7 VK	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	CDR3
------------------------	---	------

L6 germline JK4 germline 69A7 VK	W P L T F G G G T K V E I K	(JK4)
--	-----------------------------	-------

Fig. 14

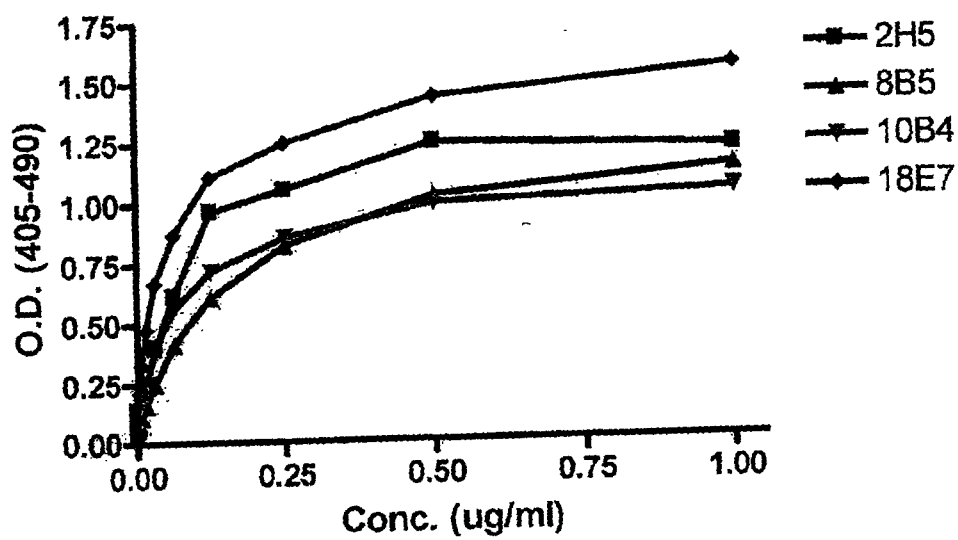
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Anti - CD70 IF4 VK Region

A27 germline 1F4 VK	E I V L T Q S P G T L S L S P G E R
A27 germline 1F4 VK	CDR1 A T L S C R A S Q S V S S S Y L A W
A27 germline 1F4 VK	CDR 2 Y Q Q K P G Q A P R L L I Y G A S S
A27 germline 1F4 VK	R A T G I P D R F S G S G S G T D F
A27 germline 1F4 VK	T L T I S R L E P E D F A V Y Y C Q
A27 germline JK2 germline 1F4 VK	CDR3 Q Y G S S P Y T F G Q G T K L E I K

Fig. 15

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*Fig. 16*

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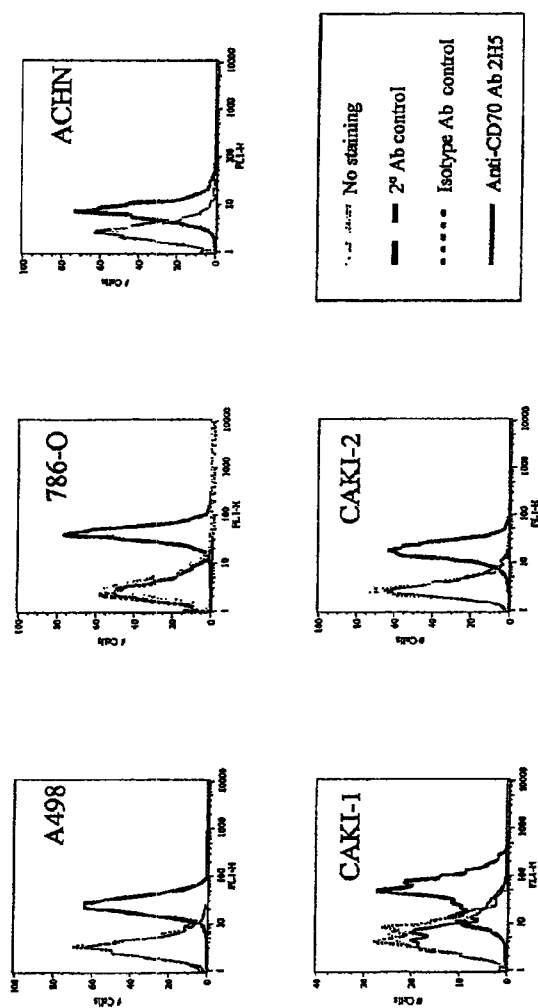
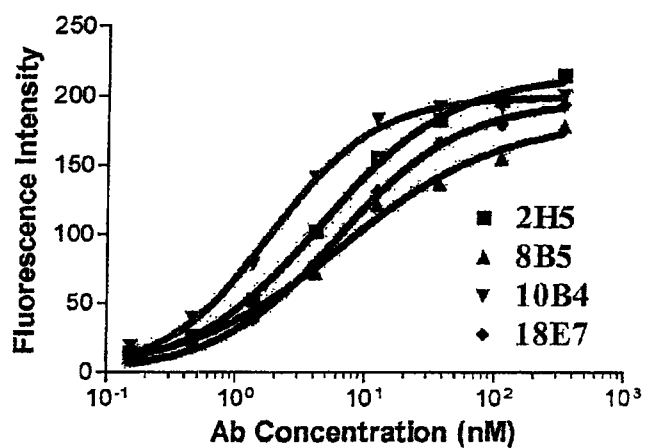
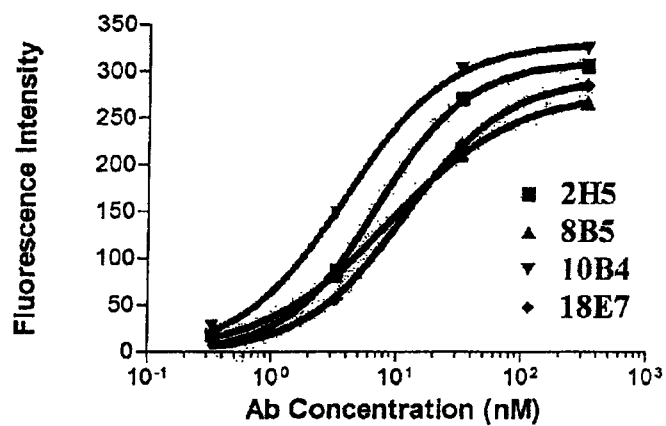


Fig. 17

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786-O FACS Titration*Fig. 18A***A498 FACS Titration***Fig. 18B*

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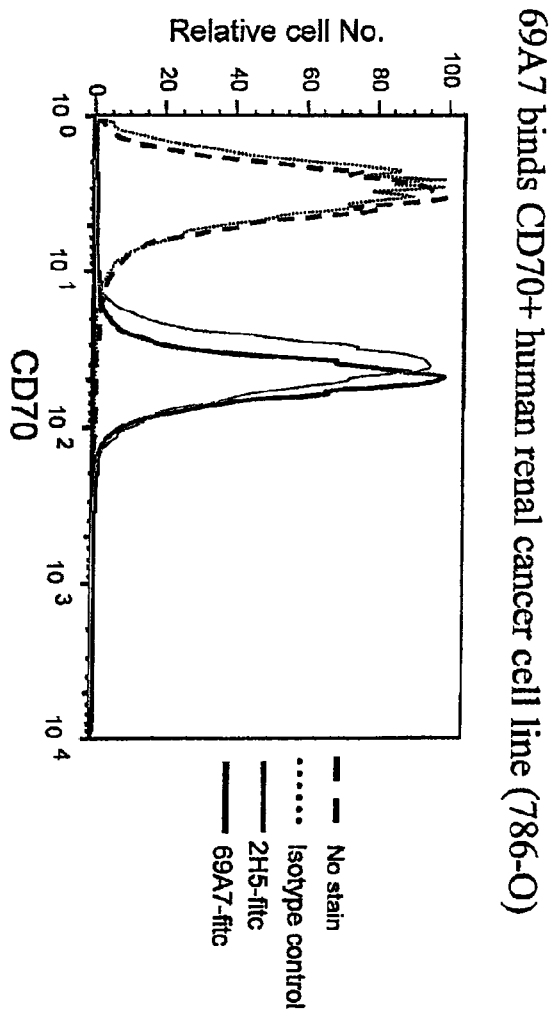
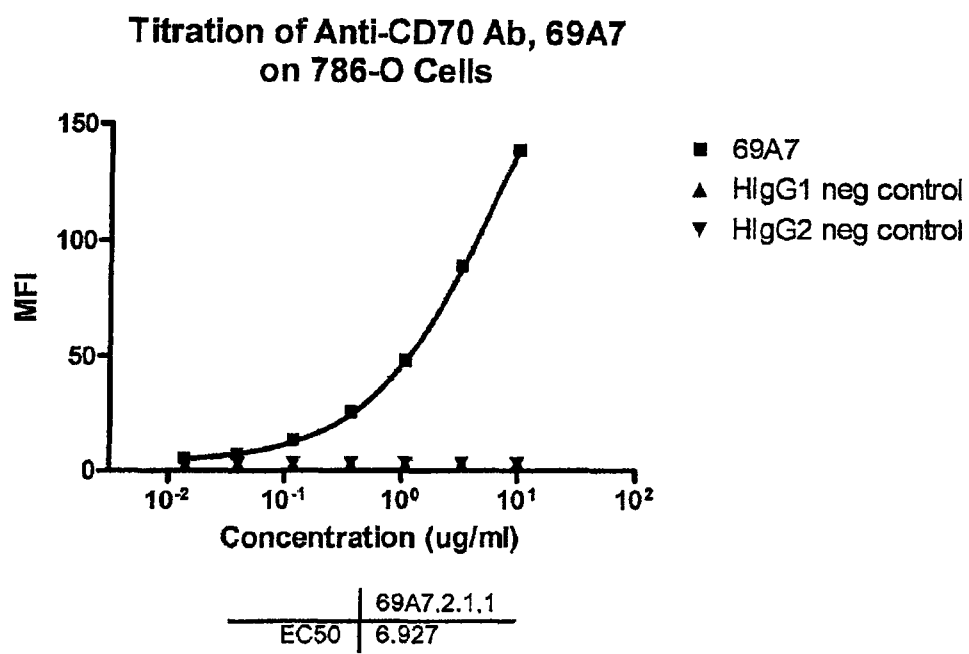


Fig. 18C

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*Fig. 18D*

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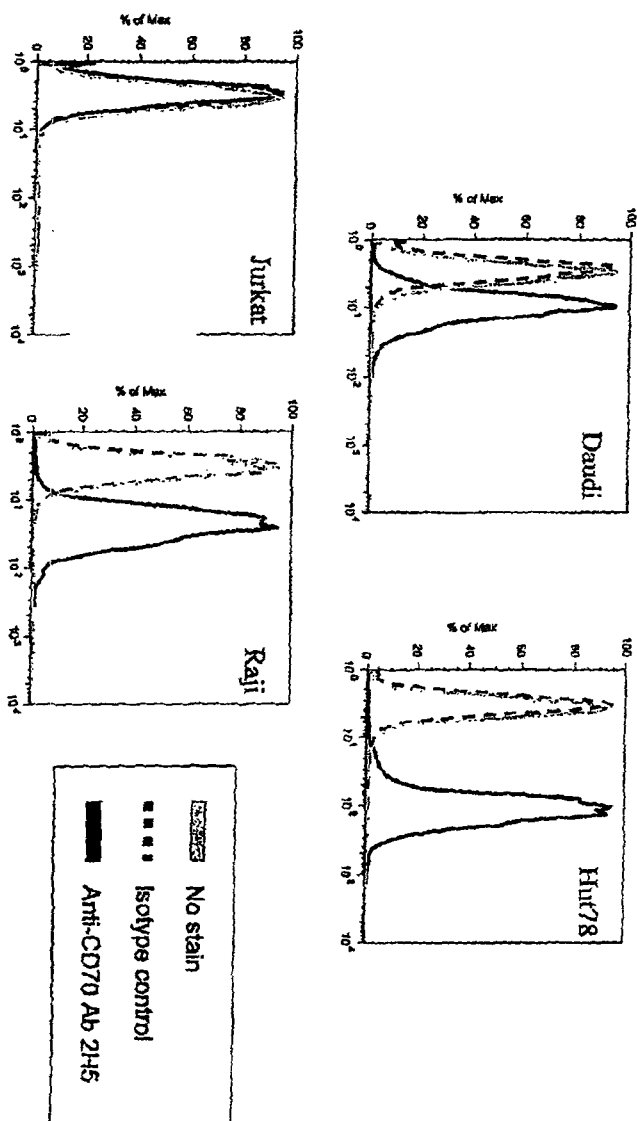
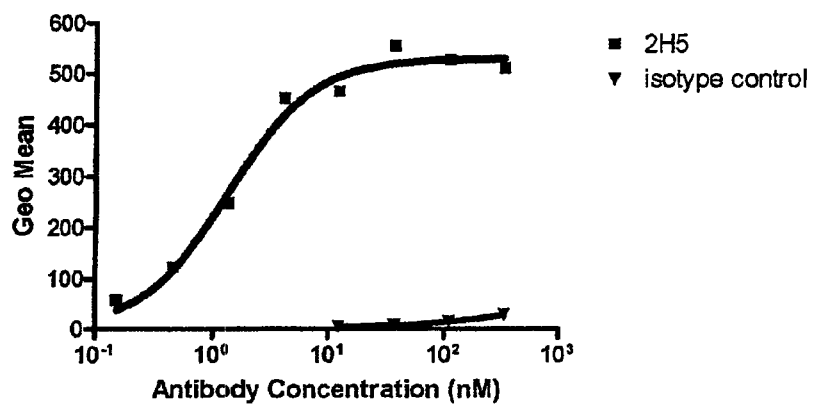


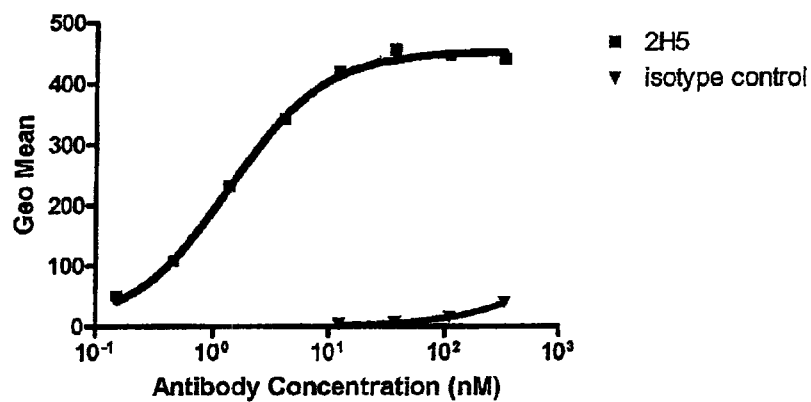
Fig. 19

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FACS on Raji Cells

*Fig. 20A*

FACS on Granta-519 Cells

*Fig. 20B*

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69A7 binds CD70+ human B lymphoma cell line (Raji cells)

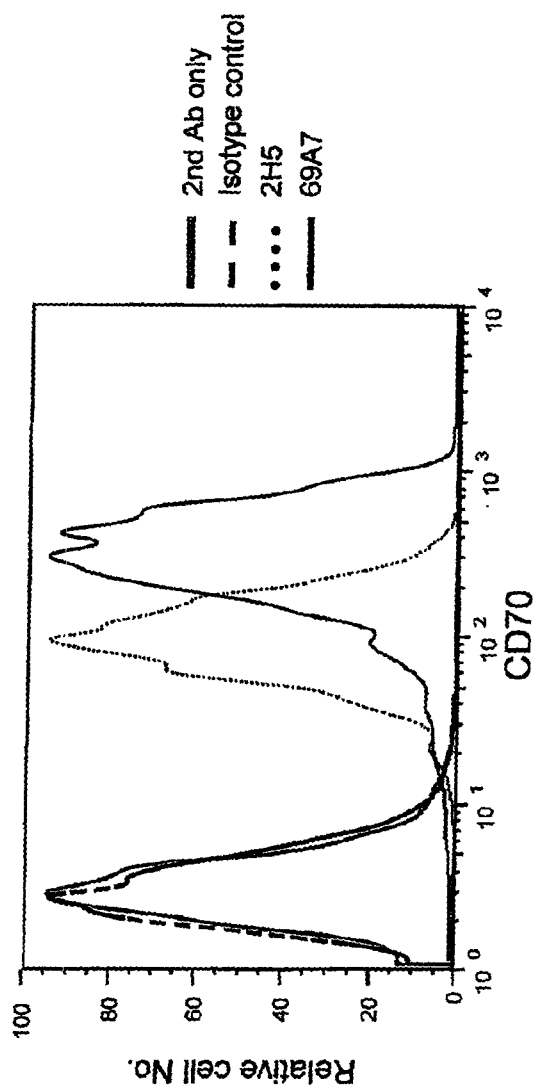


Fig. 20C

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69A7 and 2H5 react with a similar epitope of CD70 in Raji cells

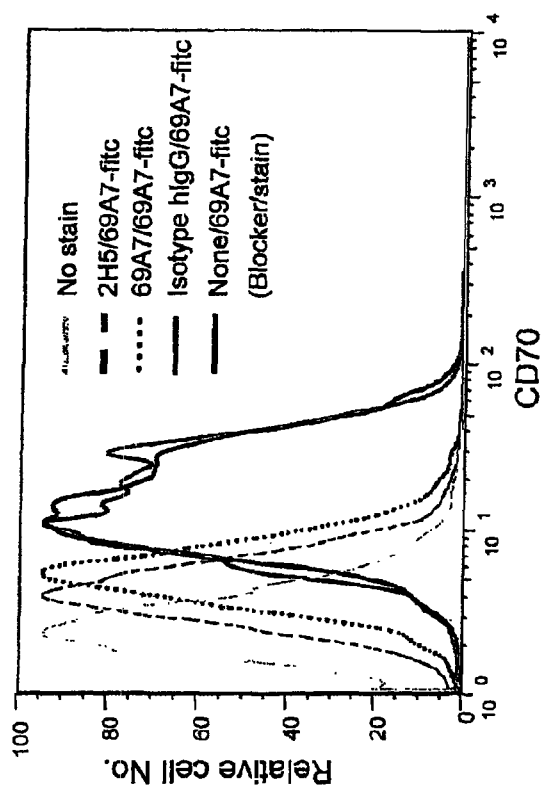
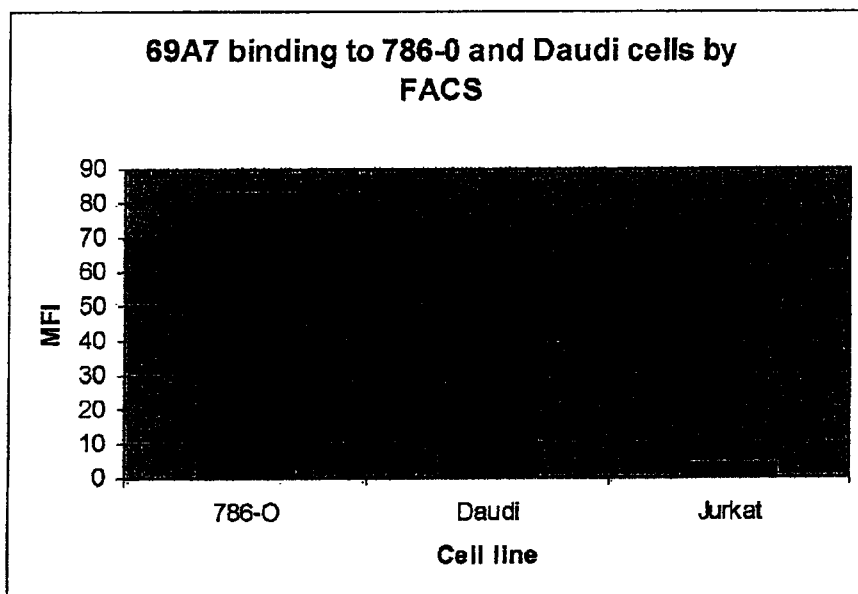
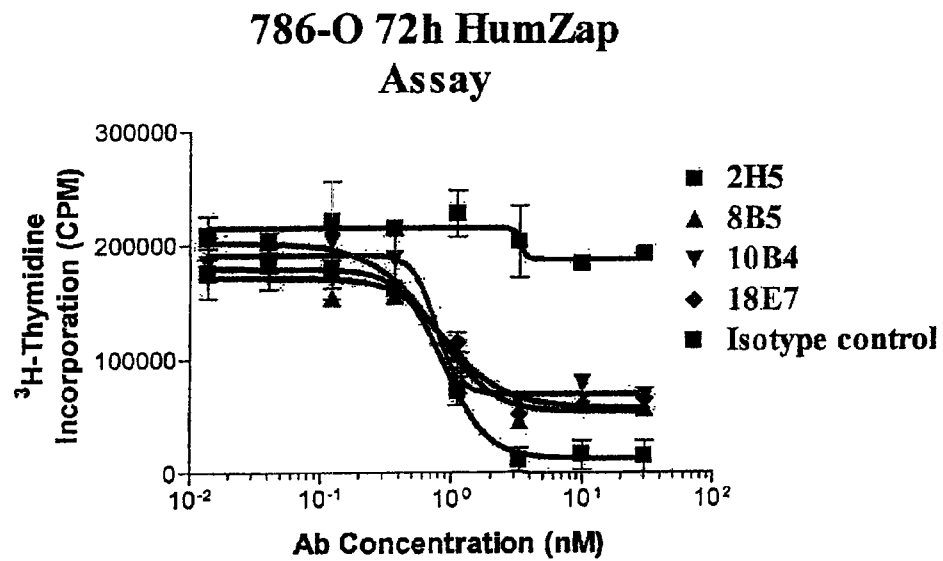


Fig. 20D

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*Fig. 20E*

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*Fig. 21*

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CAKI-2 72h Assay

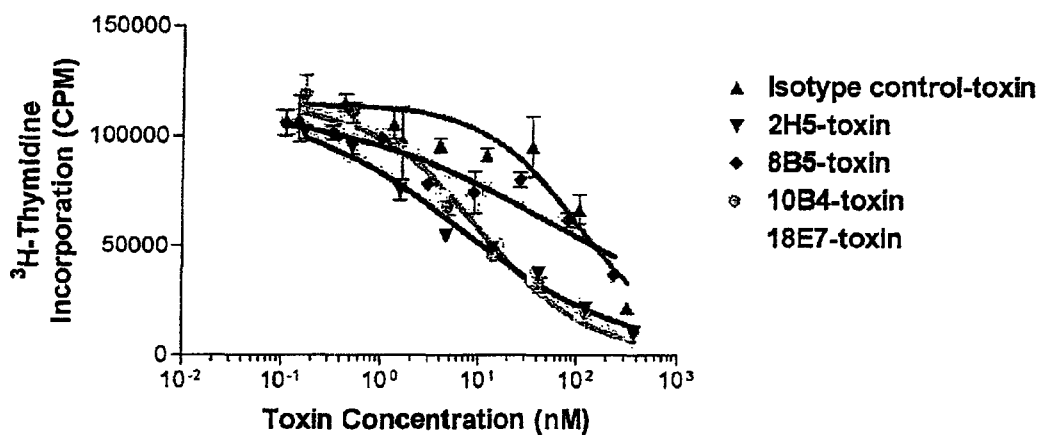


Fig. 22A

786-O 72h Assay

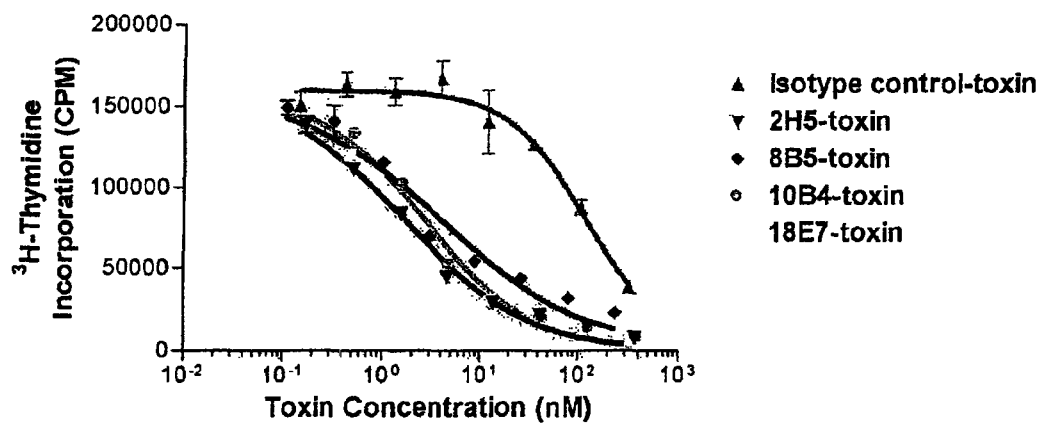
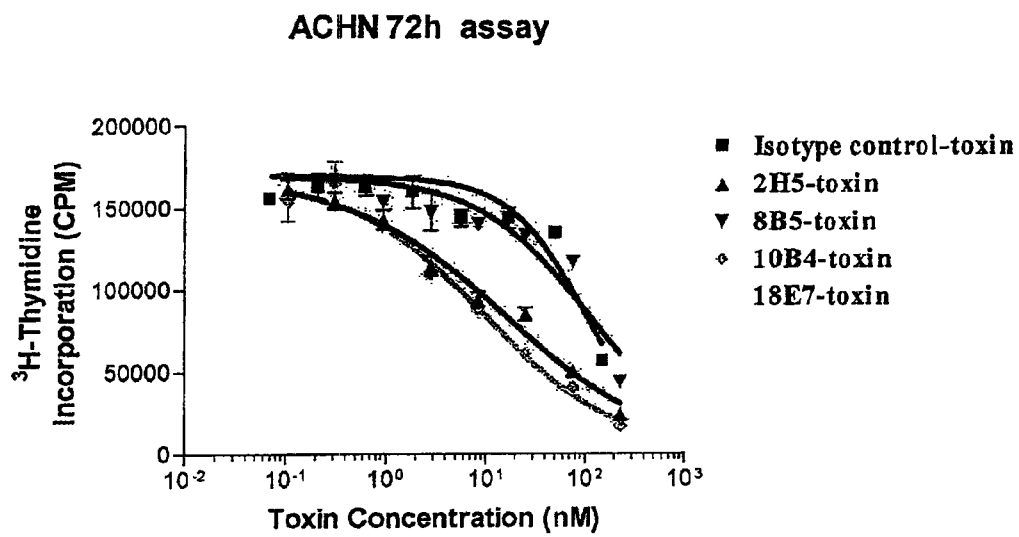
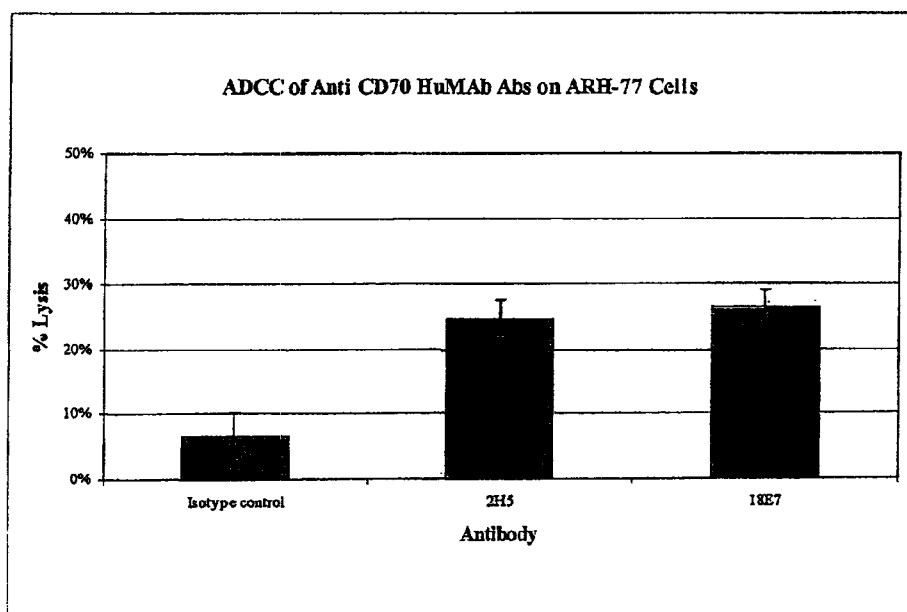
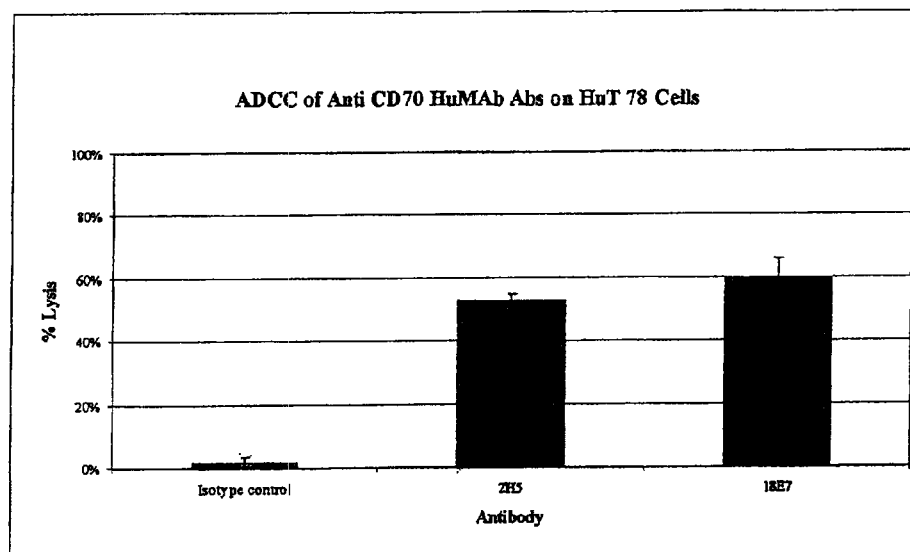


Fig. 22B

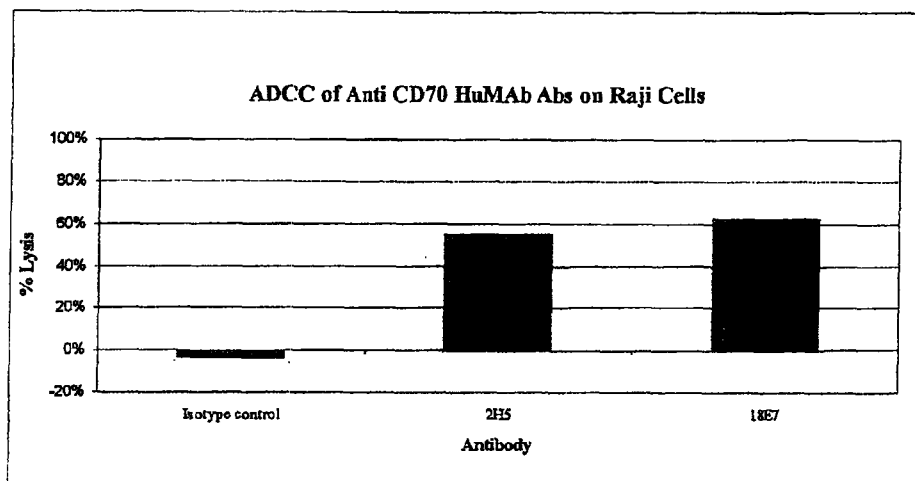
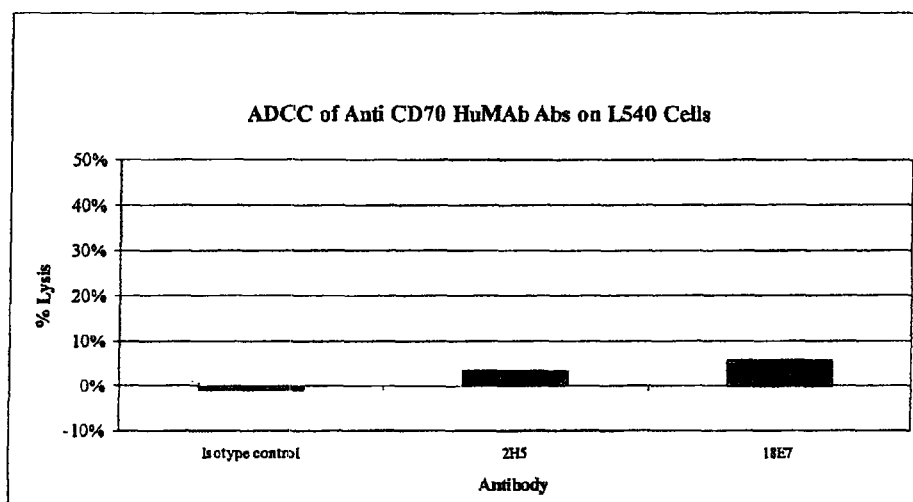
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*Fig. 22C*

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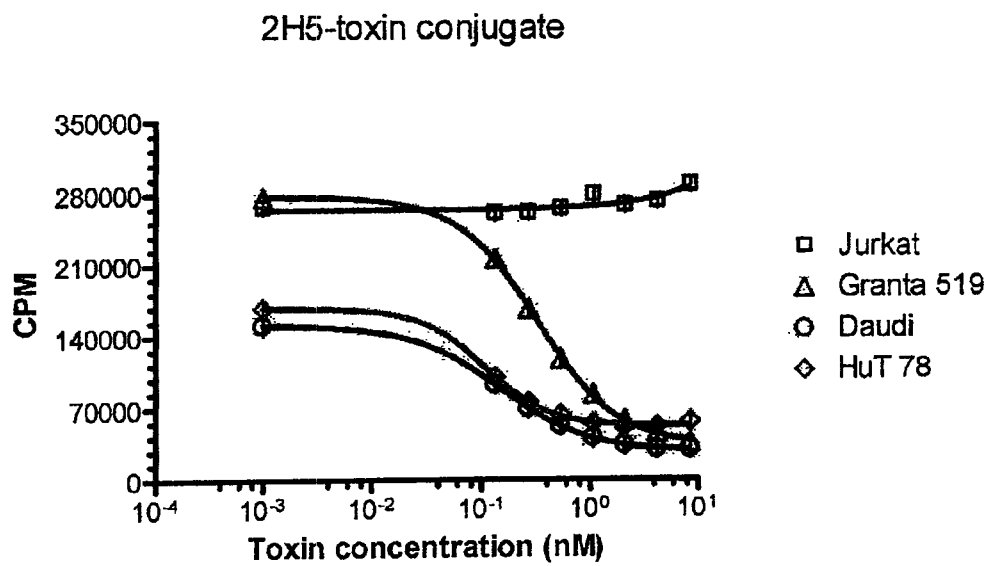
*Fig. 23A**Fig. 23B*

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*Fig. 23C**Fig. 23D*

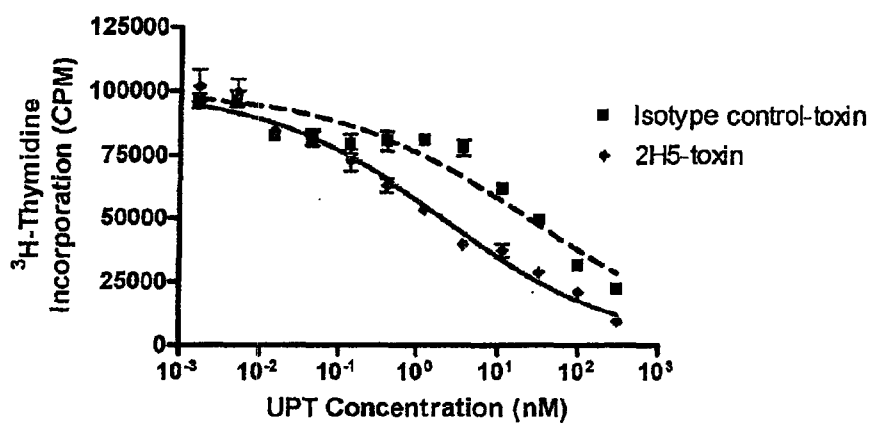
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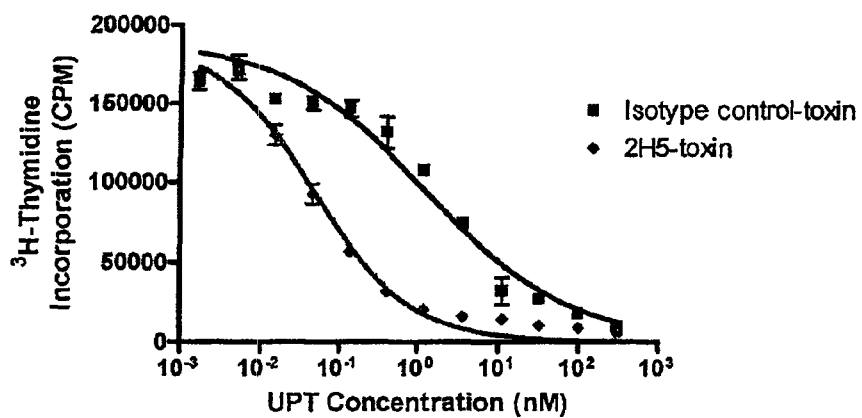
*Fig. 24*

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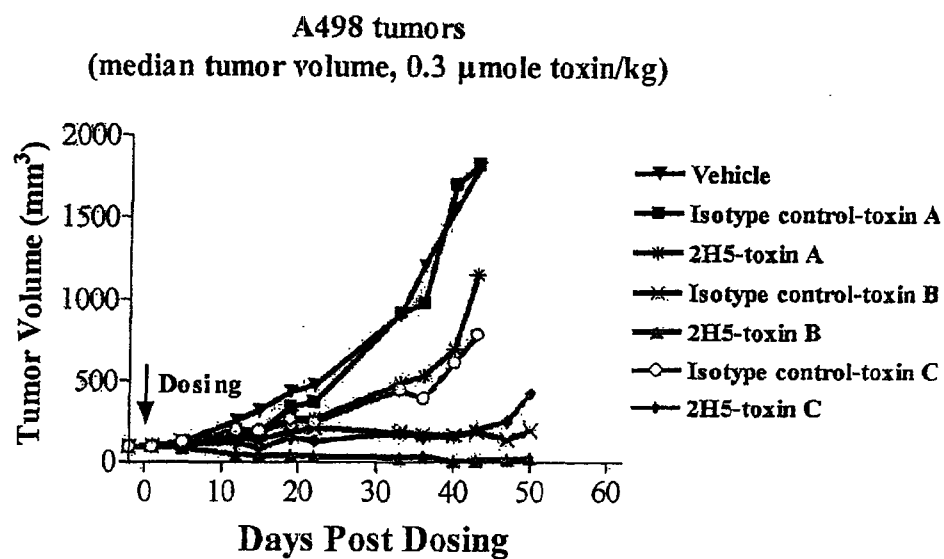
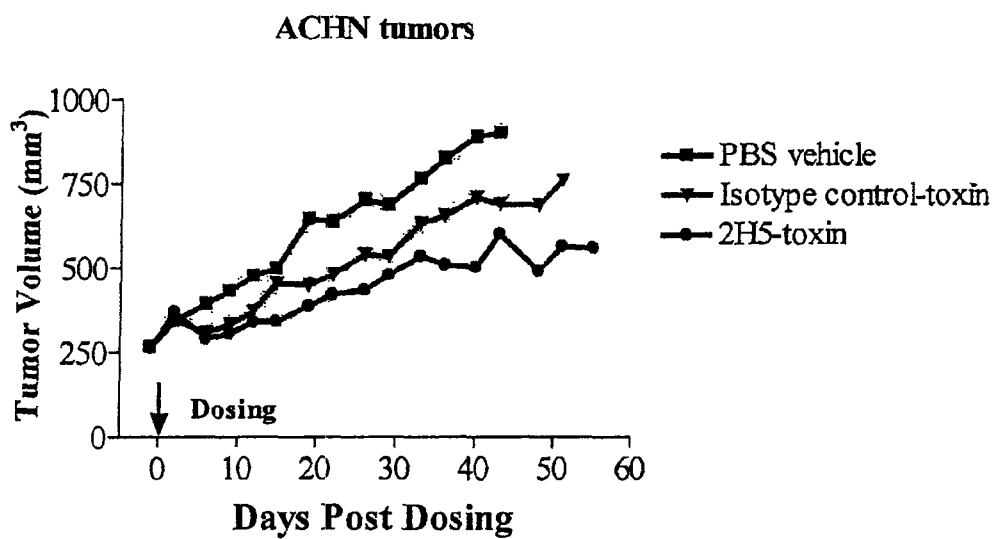
Raji 3h Wash 72h Assay

*Fig. 25A*

Raji Continuous 72h Assay

*Fig. 25B*

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*Fig. 26A**Fig. 26B*

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ADCC on ARH77 cells

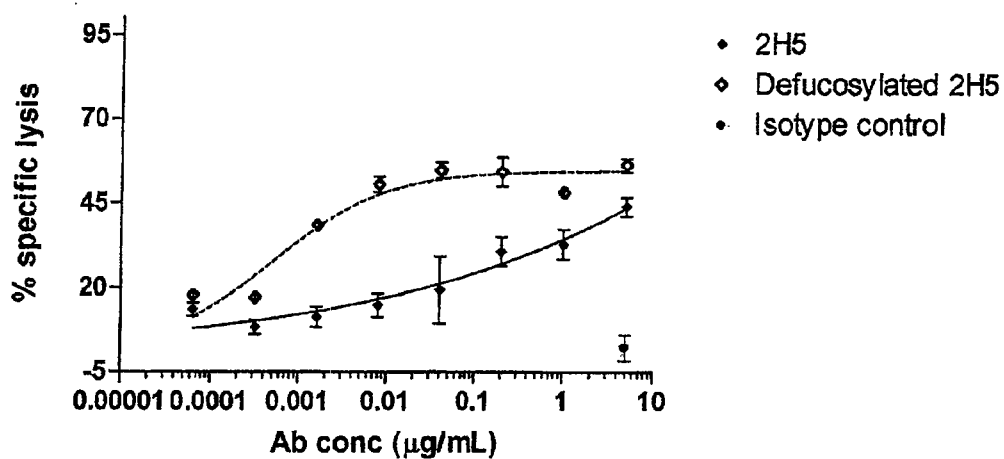


Fig. 27A

ADCC on MEC-1 Cells

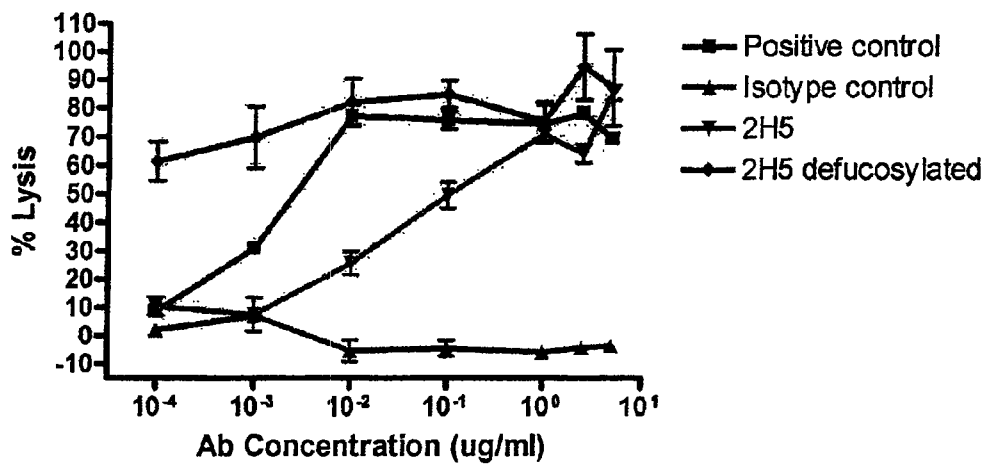
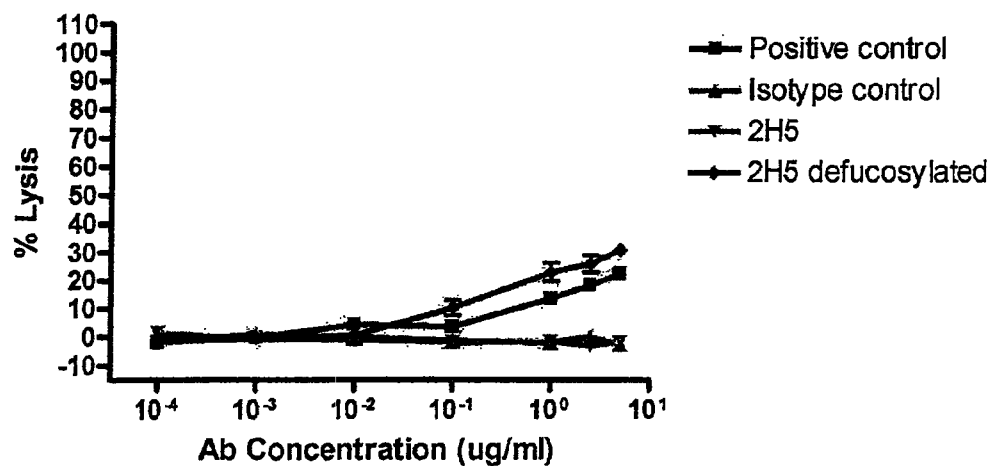
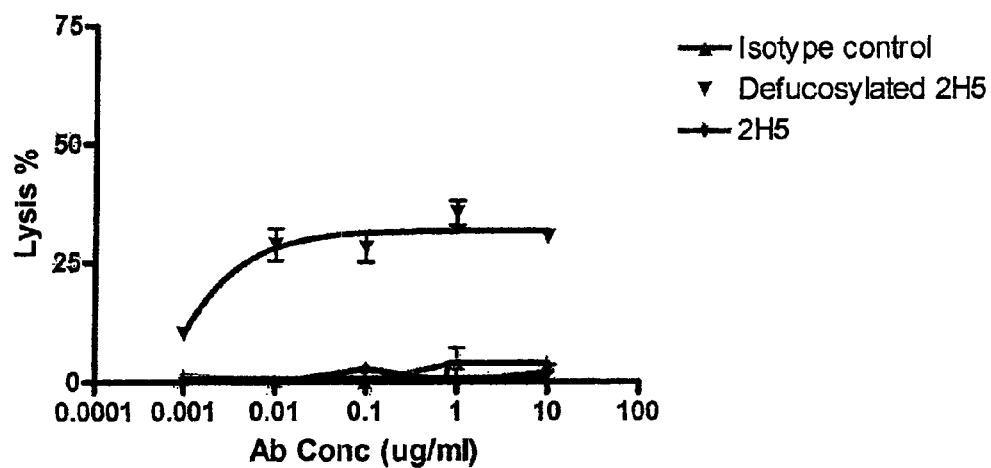
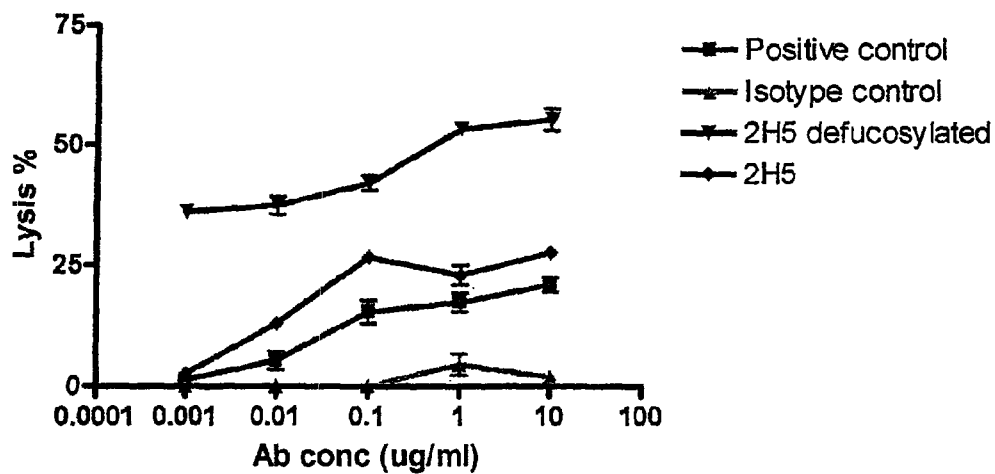
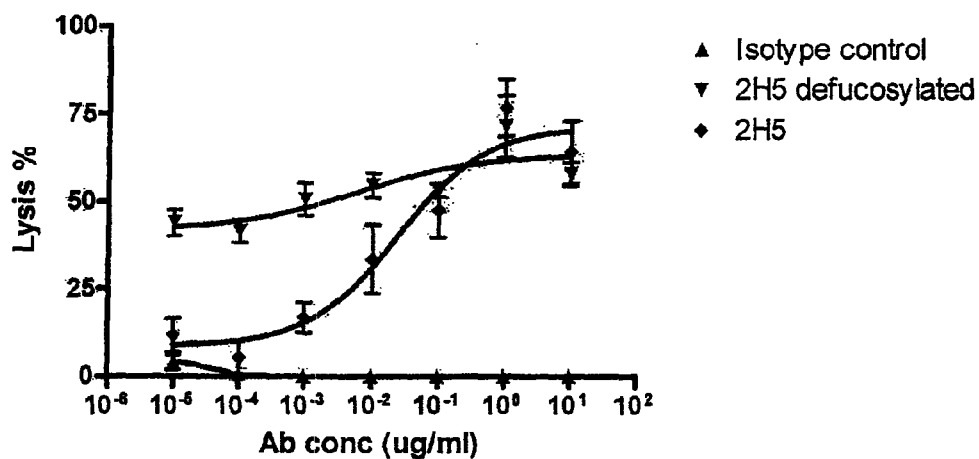


Fig. 27B

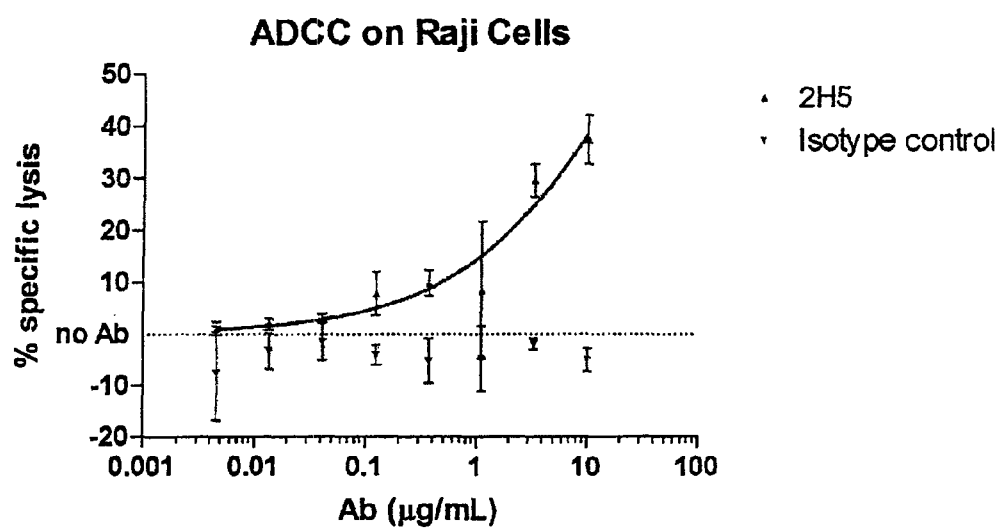
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ADCC on MEC-1 Cells with anti-CD16*Fig. 27C***ADCC on Su-DHL-6 Cells***Fig. 27D*

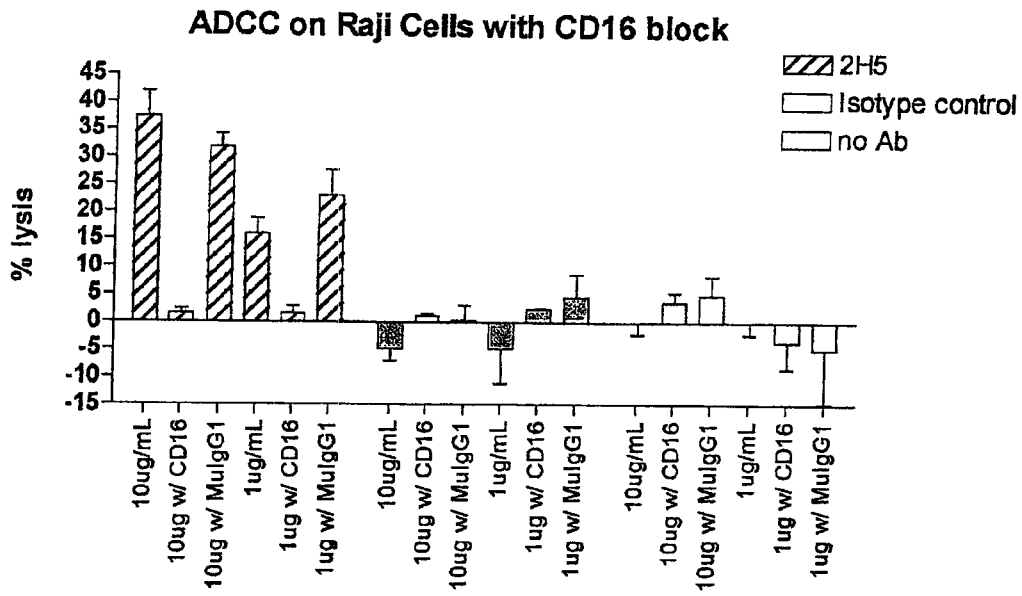
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ADCC on IM-9 Cells*Fig. 27E***ADCC on Hut78 Cells***Fig. 27F*

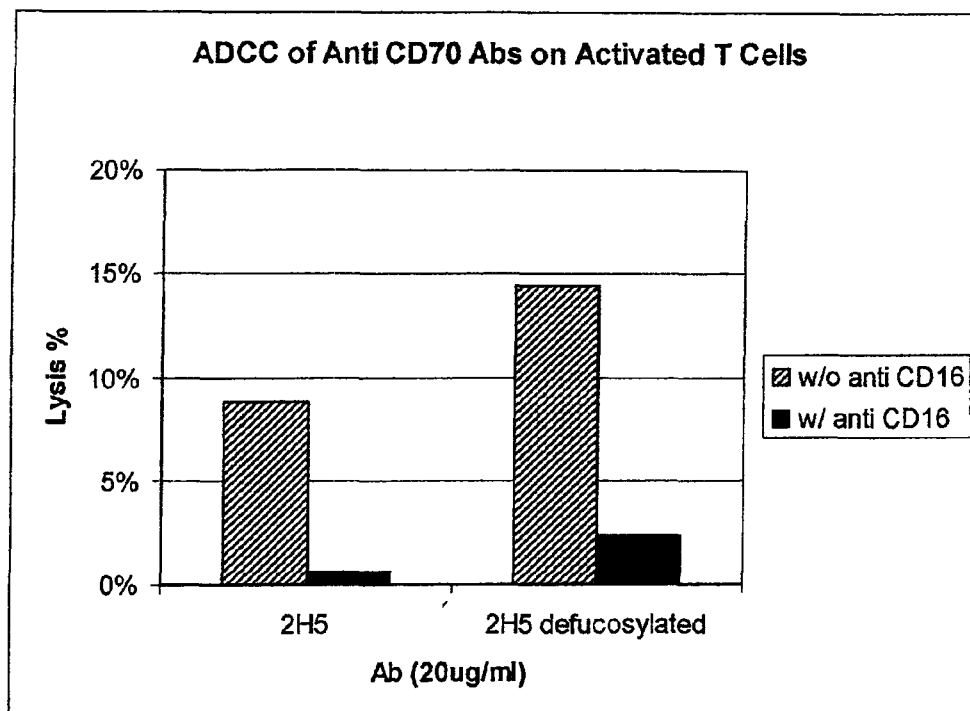
43/101

*Fig. 28*

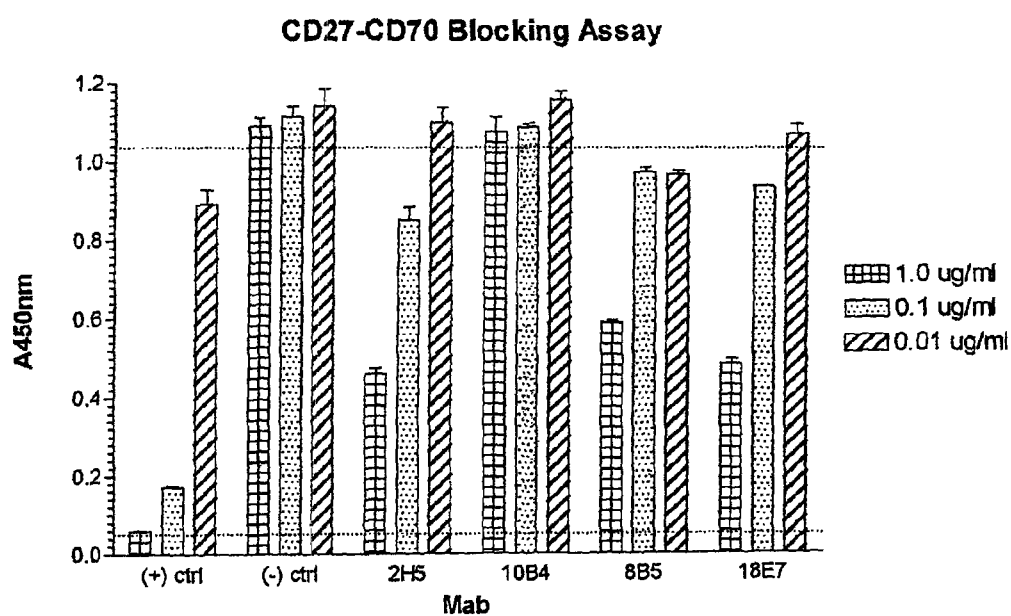
44/101

*Fig. 29*

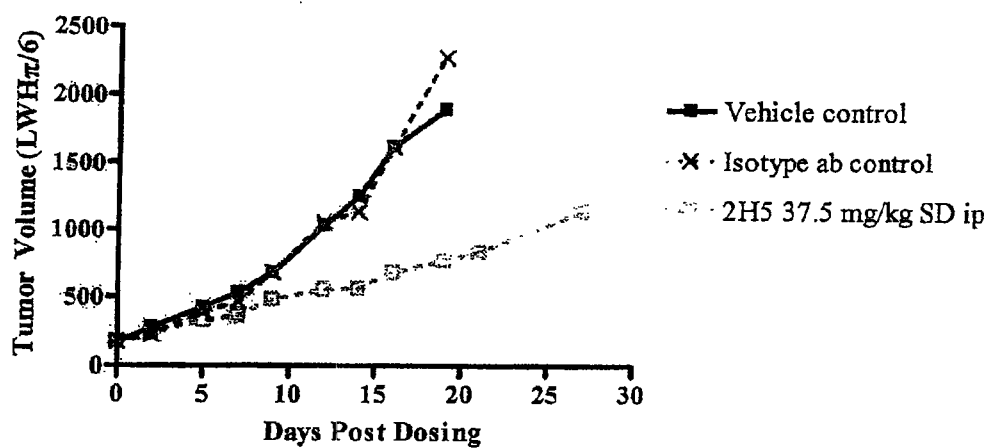
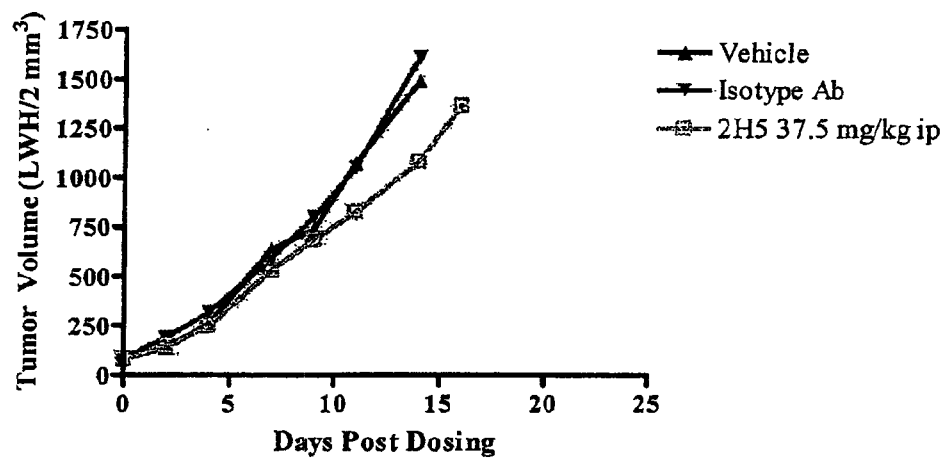
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*Fig. 30*

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*Fig. 31*

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Raji Model Efficacy Study*Fig. 32A***Single dose Efficacy of naked antibodies on ARH77 tumors***Fig. 32B*

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ARH-77 Median Tumor Growth

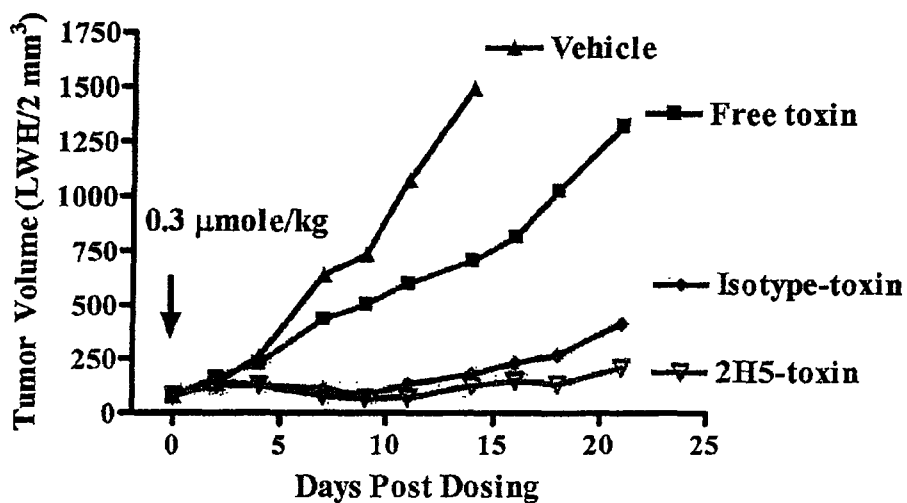


Fig. 33A

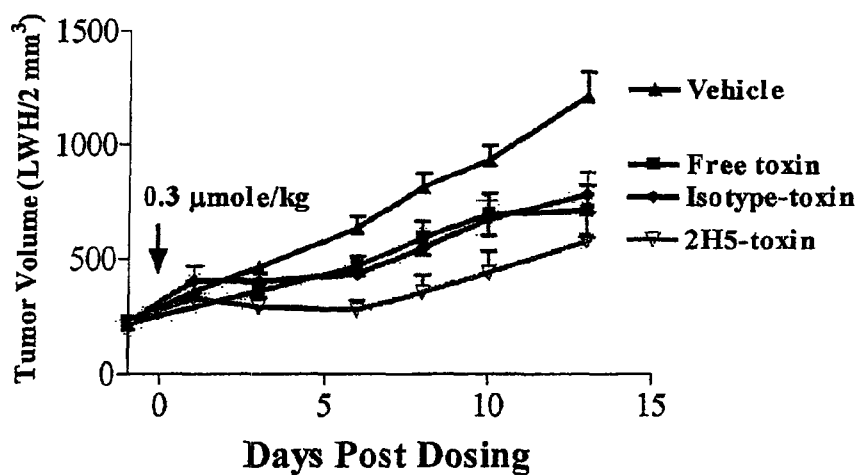
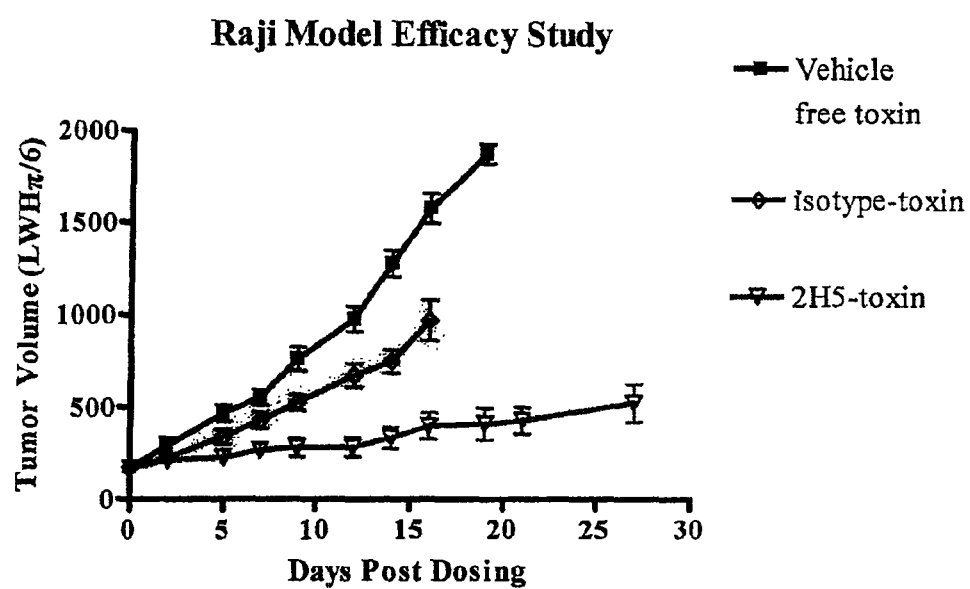
Efficacy of αCD70 -toxin conjugates on Granta 519 tumors

Fig. 33B

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*Fig. 33C*

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69A7 cross reacts with CD70+ rhesus lymphoma cell line (LCL)

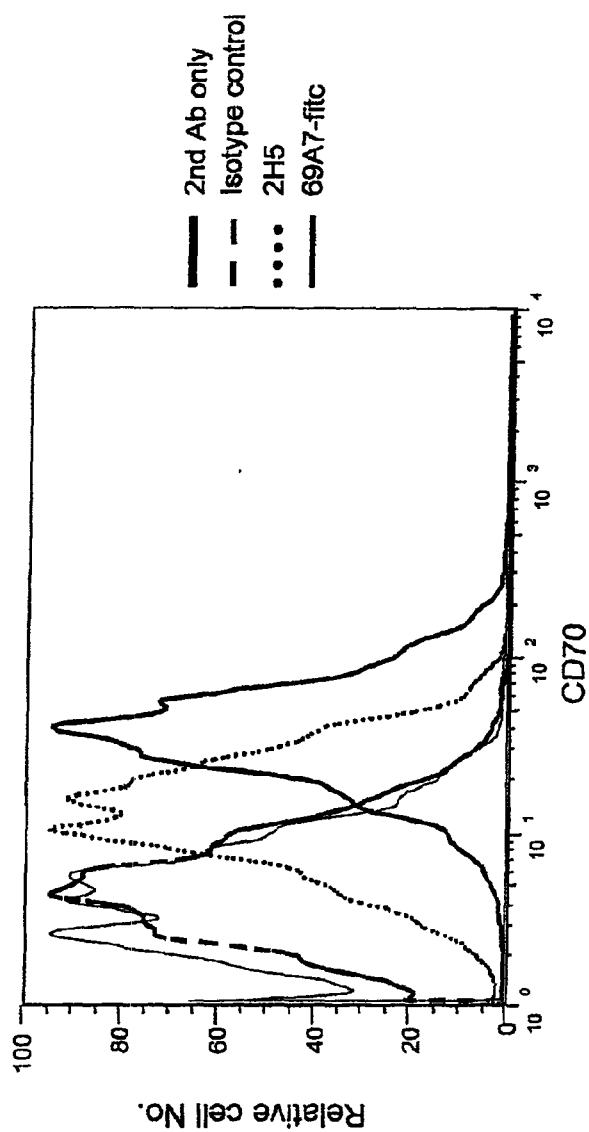
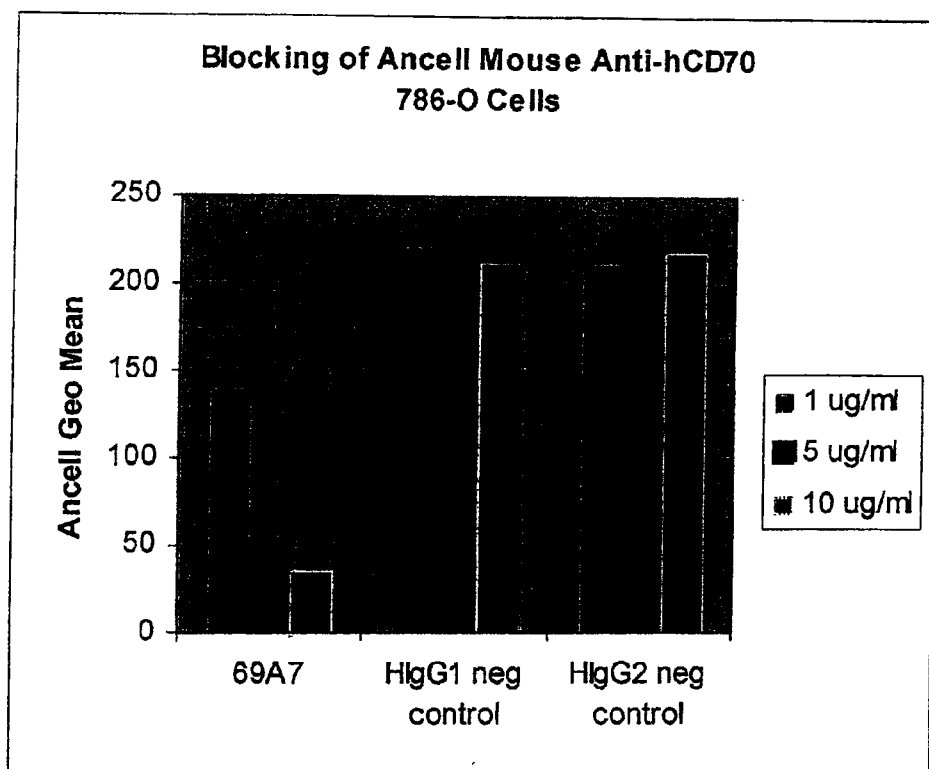
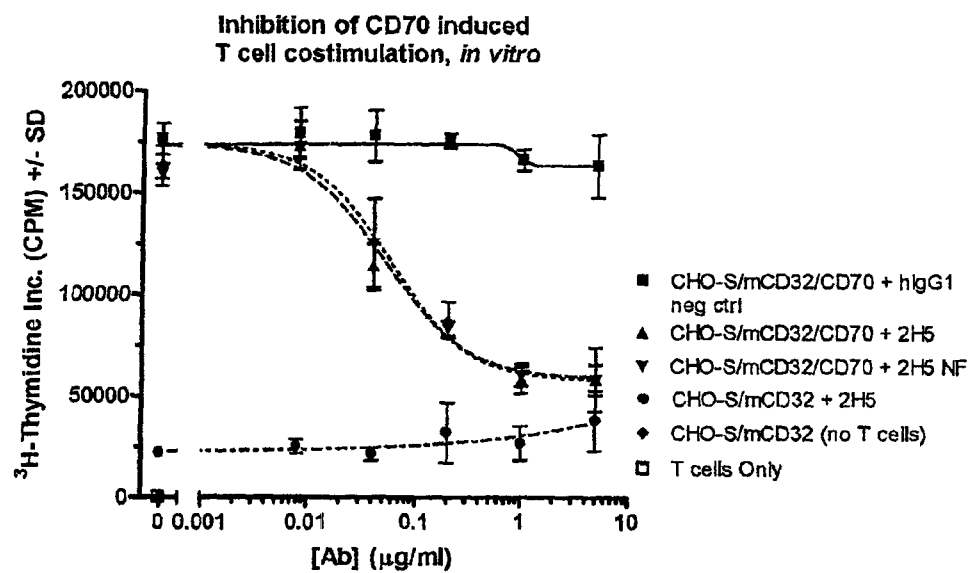


Fig. 34

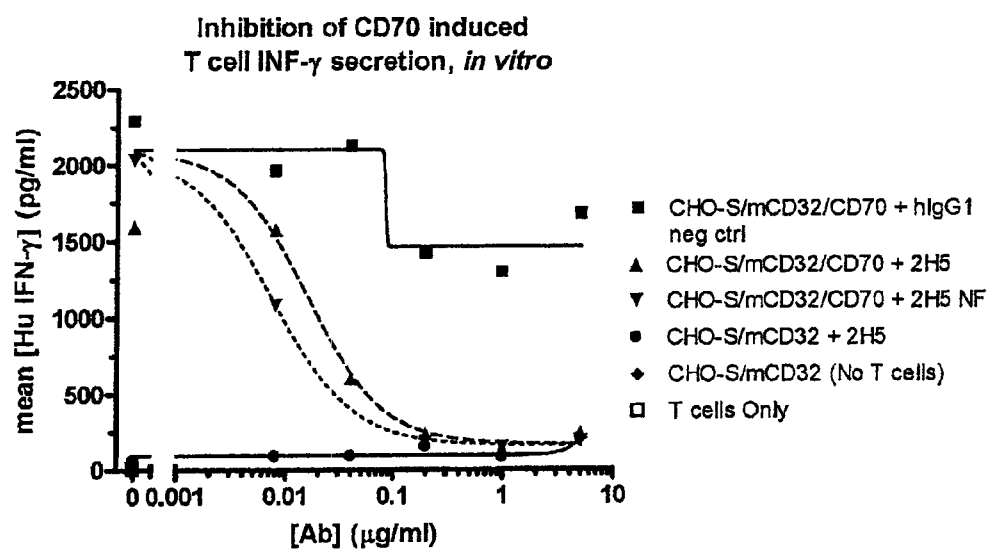
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*Fig. 35*

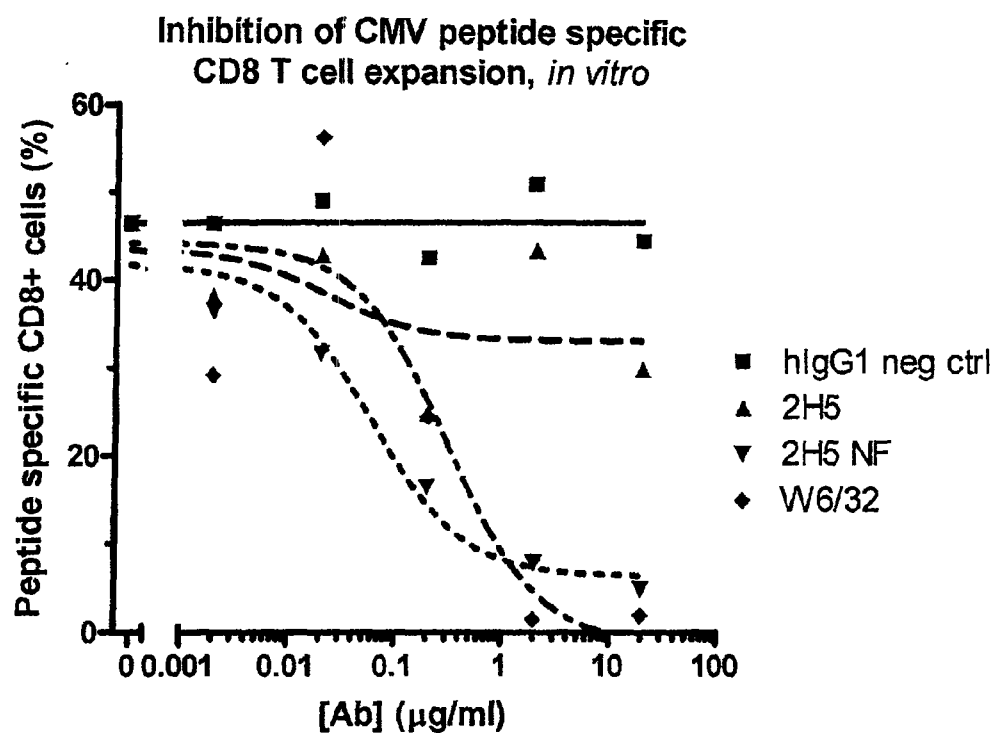
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*Fig. 36A*

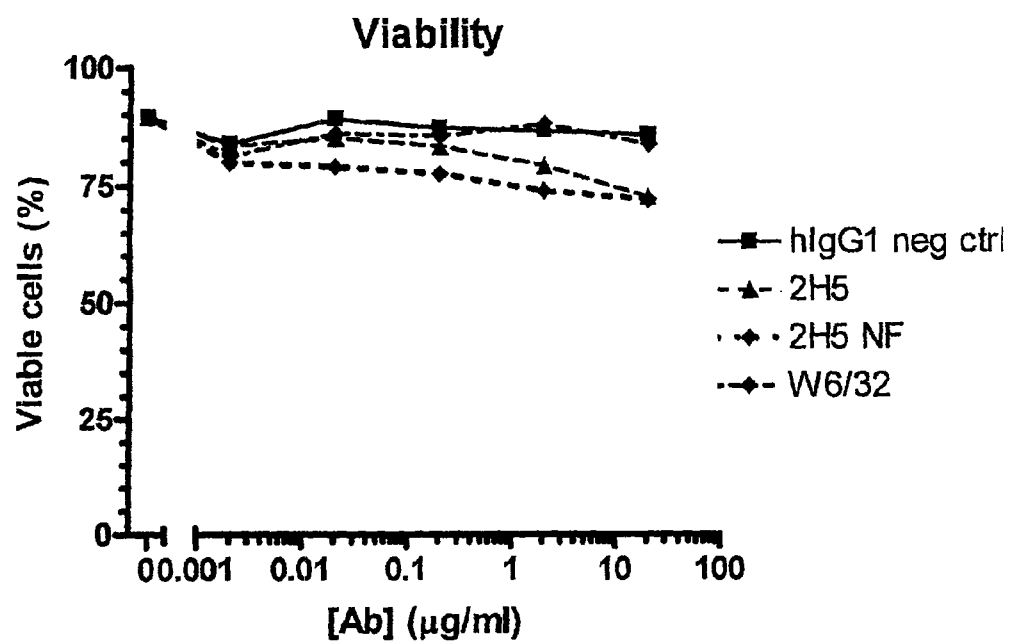
53/101

*Fig. 36B*

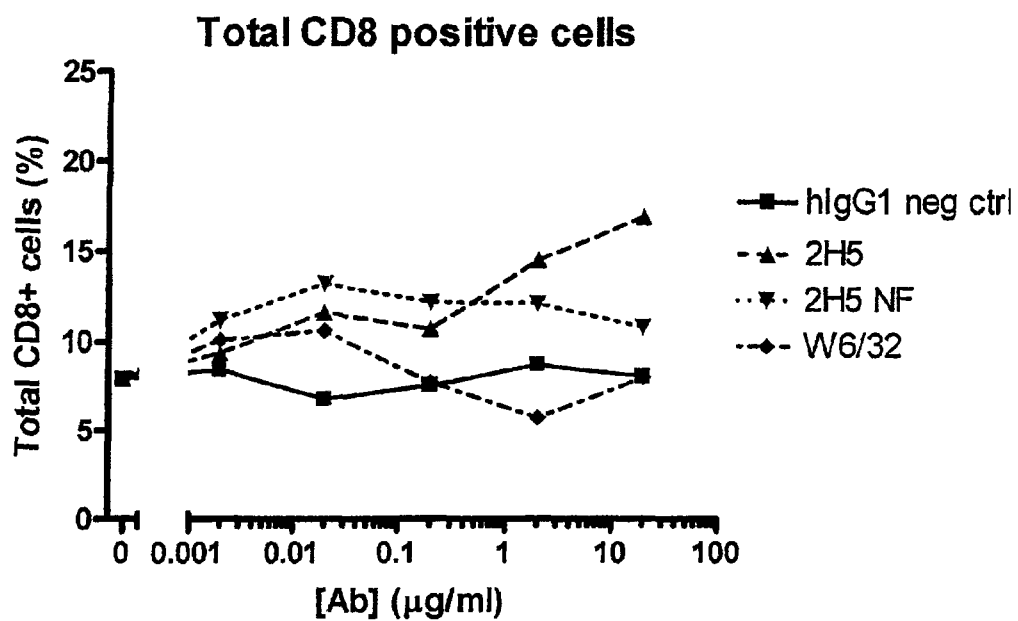
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*Fig. 37A*

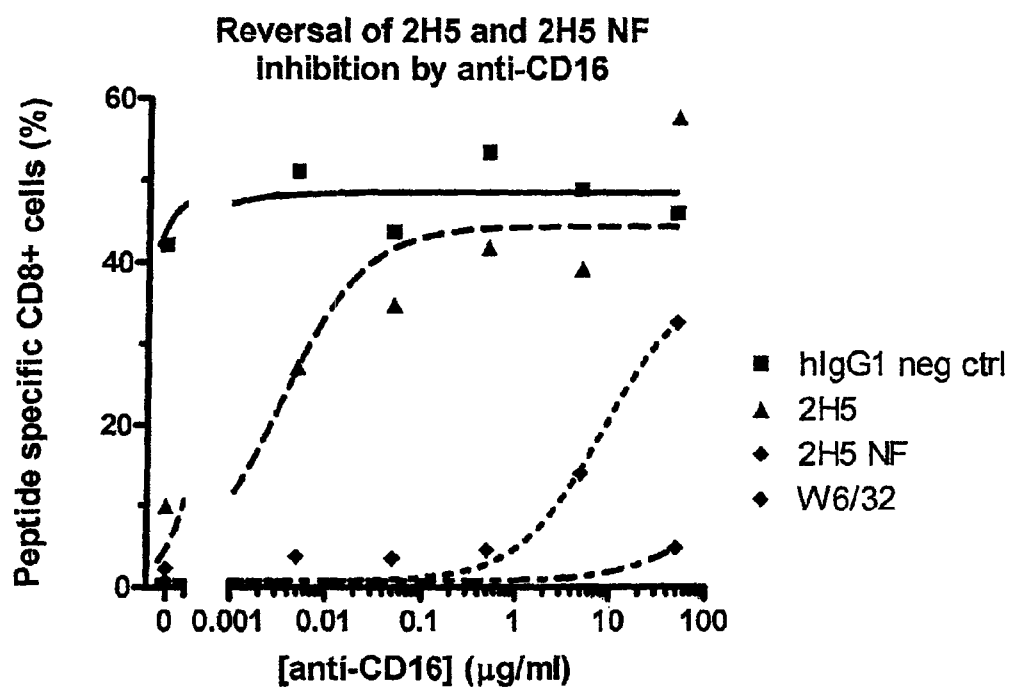
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*Fig. 37B*

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*Fig. 37C*

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*Fig. 38*

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1115-022 786-O Median Tumor Volume

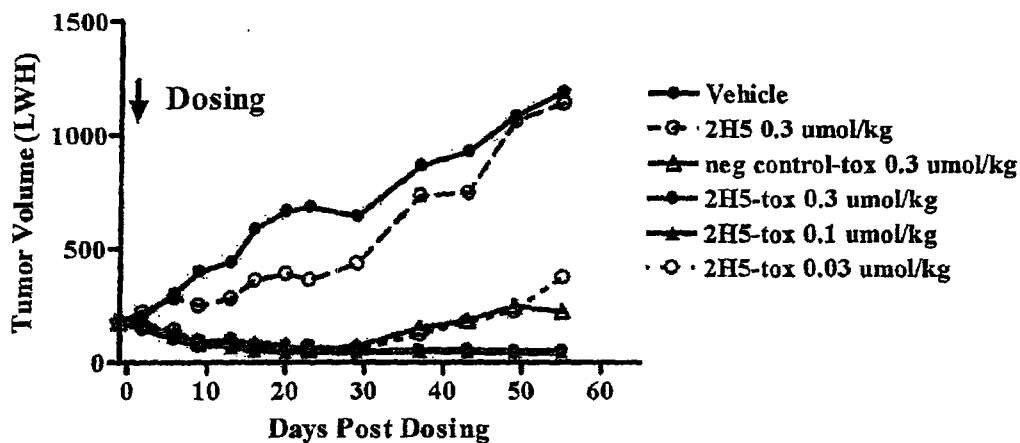


Fig. 39A

1115-025 Caki-1 Mean Tumor Volume

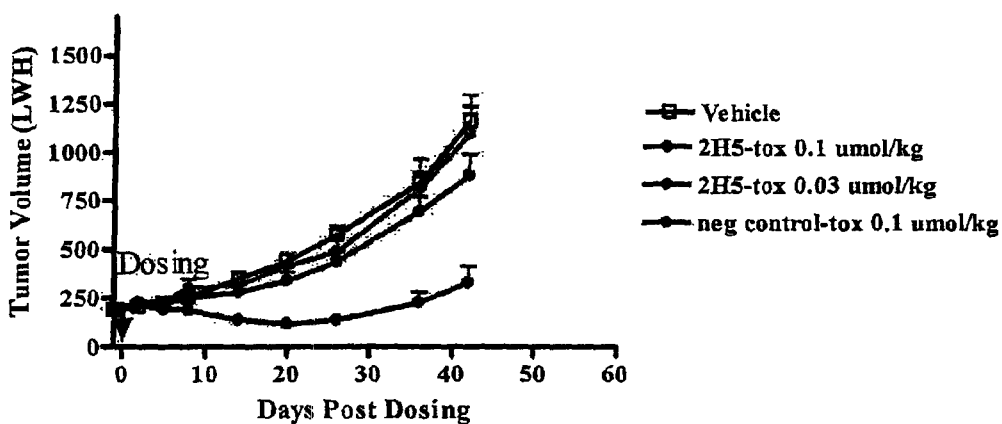
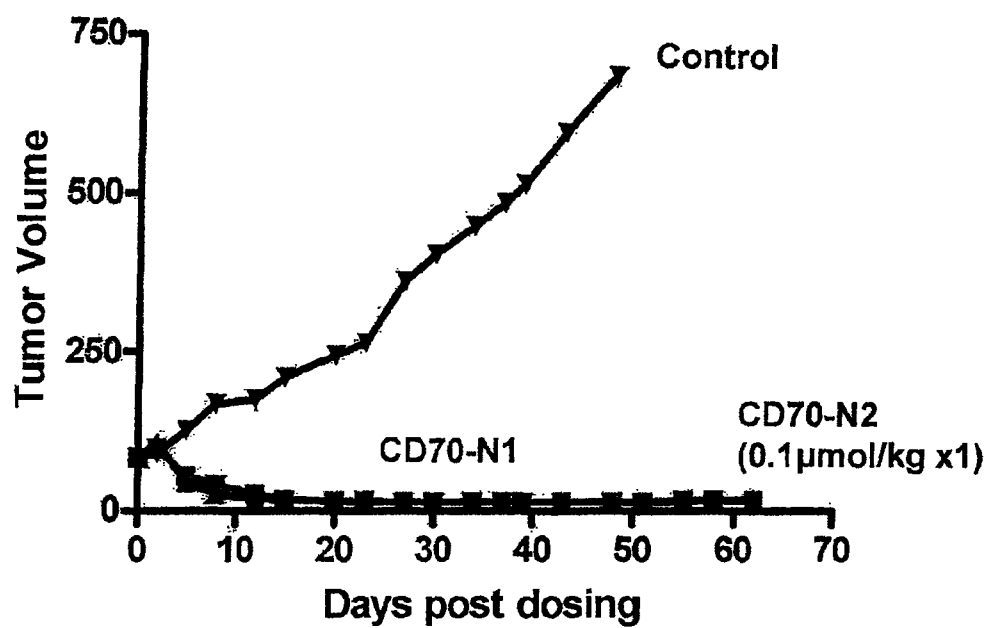
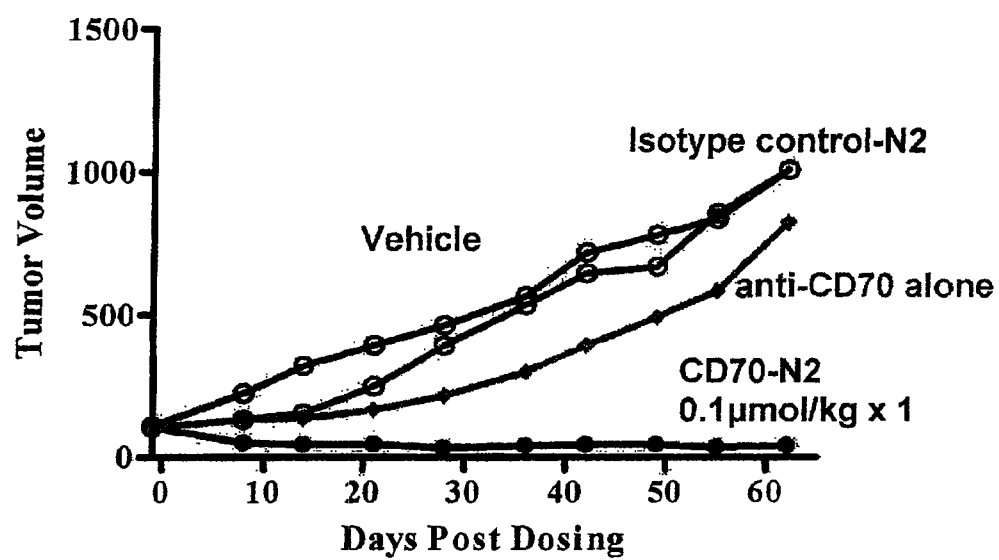


Fig. 39B

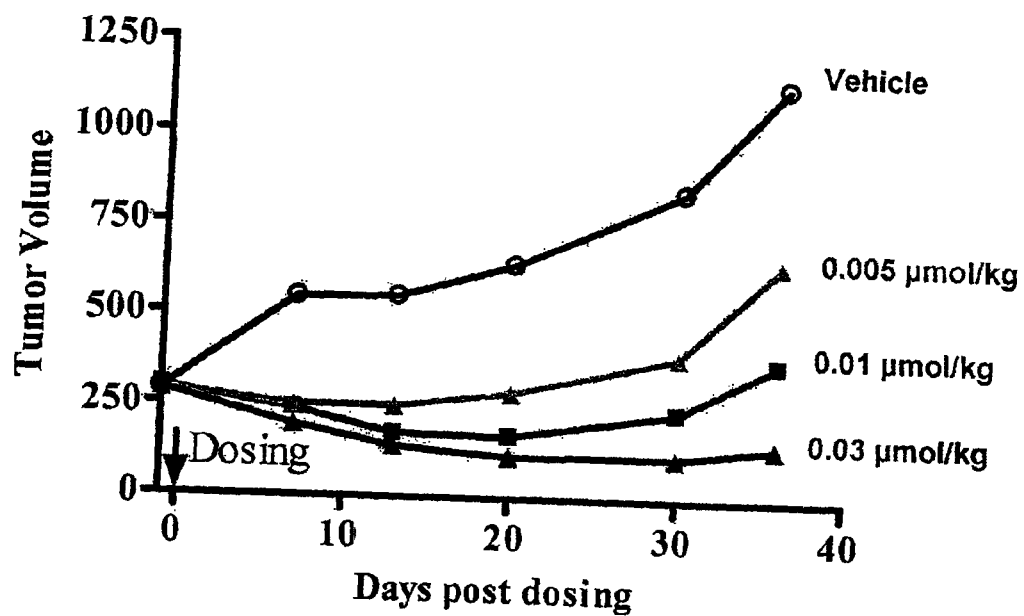
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*Fig. 40*

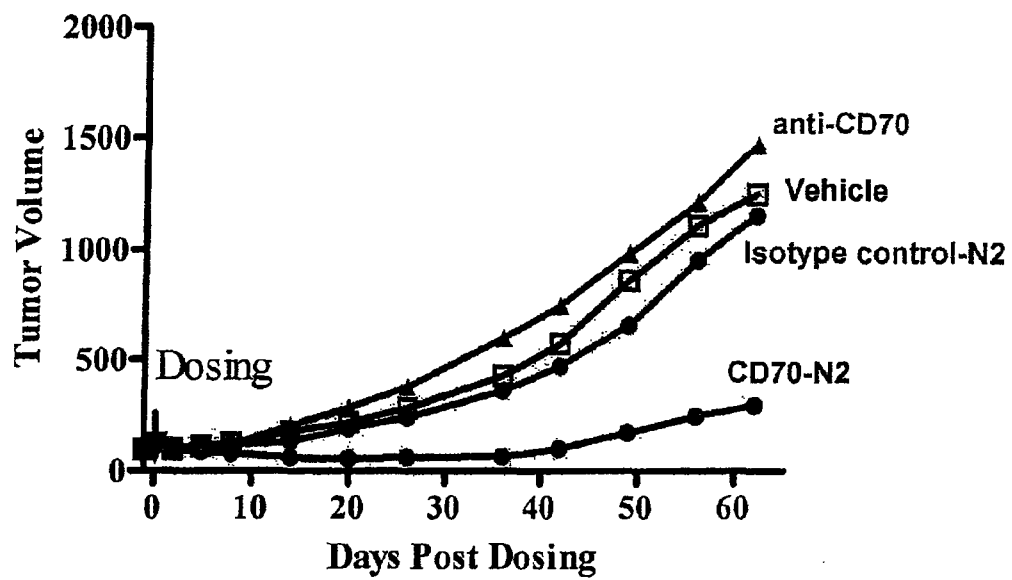
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*Fig. 41*

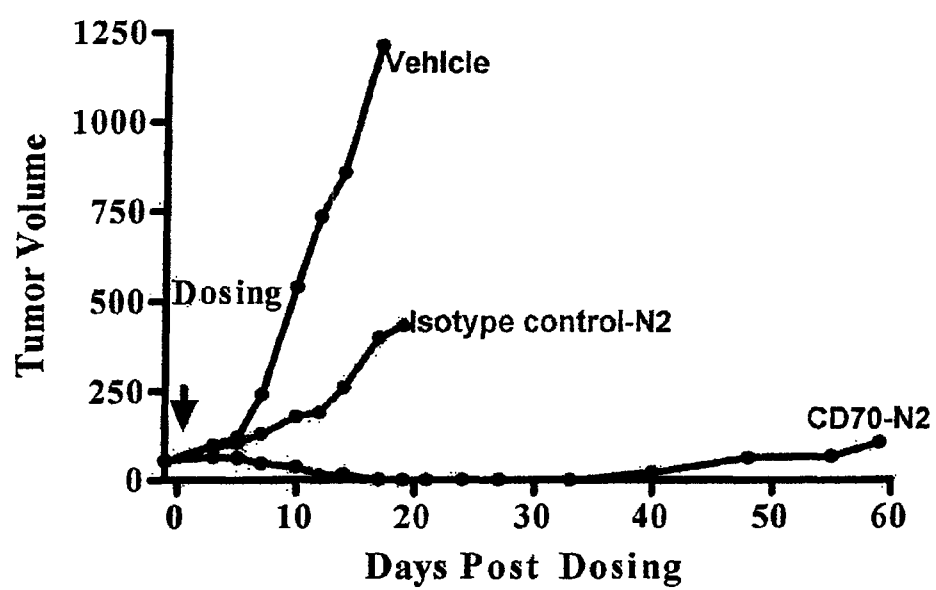
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*Fig. 42*

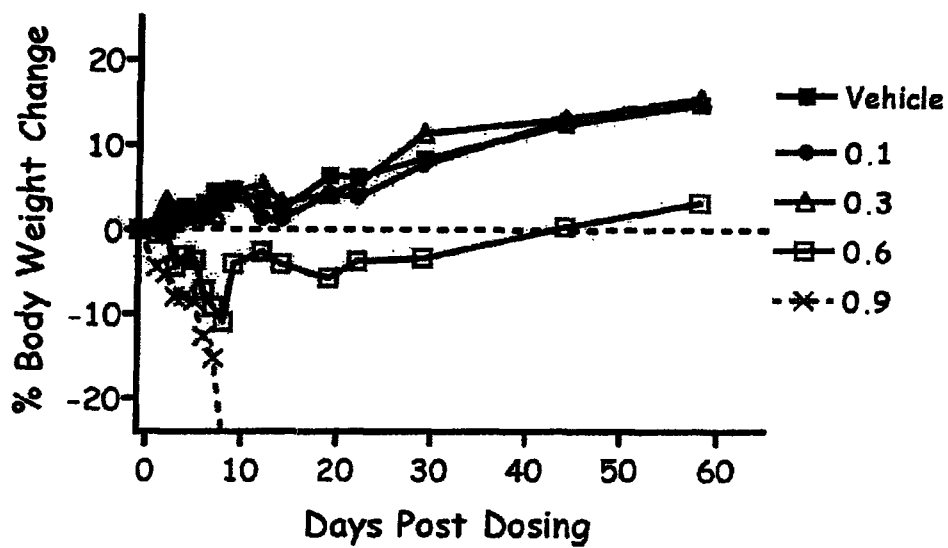
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*Fig. 43*

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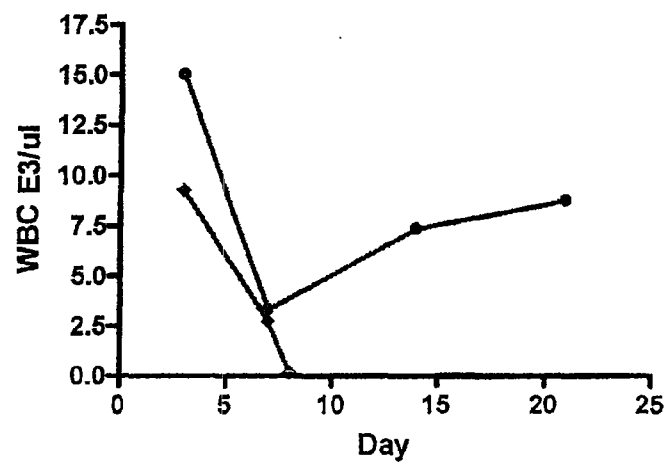
*Fig. 44*

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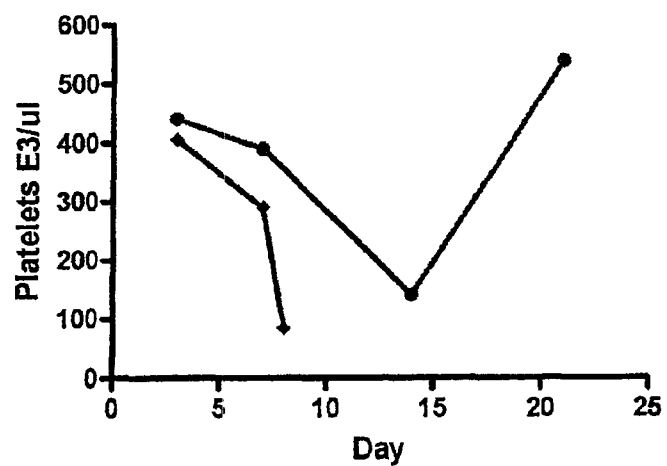
*Fig. 45*

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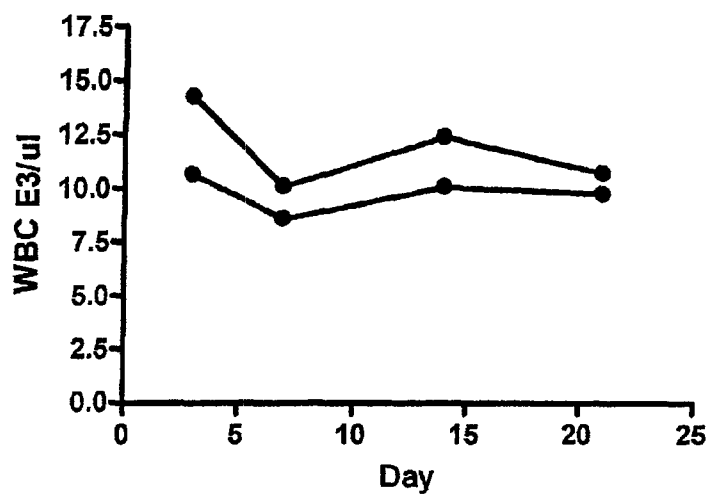
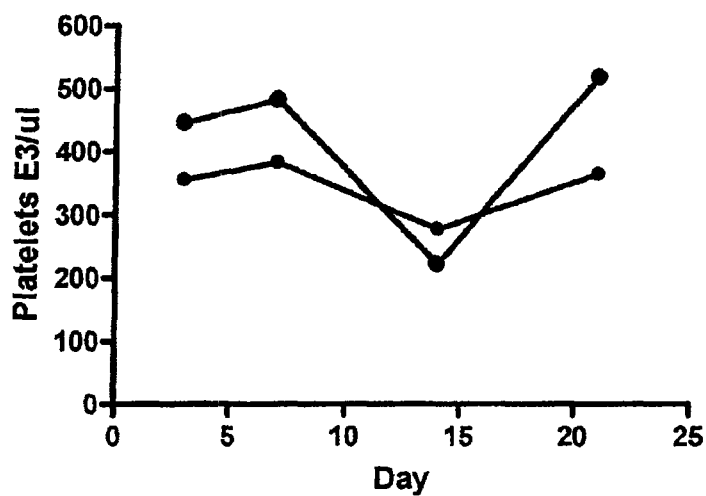
White Blood Cell Count - Free Drug

*Fig. 46A*

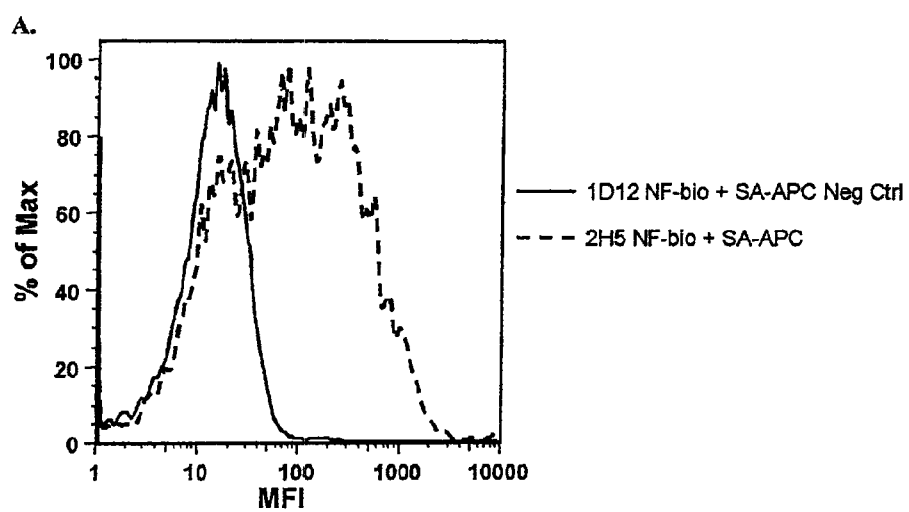
Platelets - Free Drug

*Fig. 46B*

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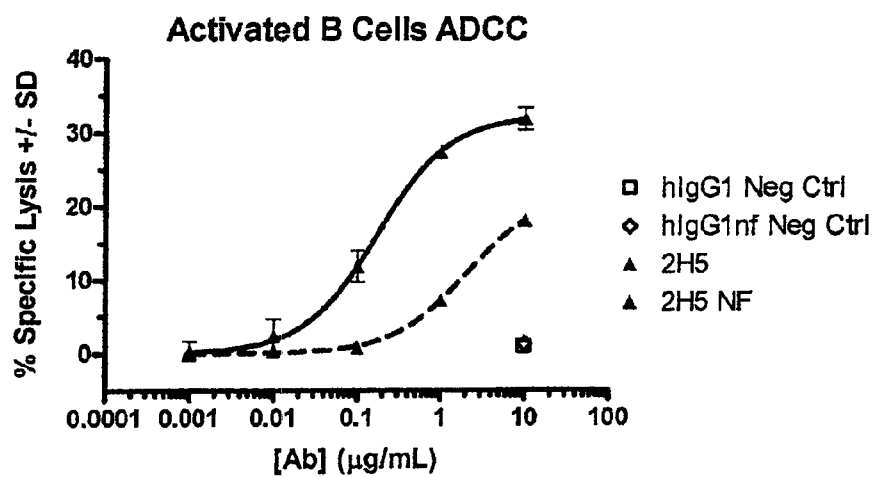
White Blood Cell Count - Conjugate*Fig. 46C***Platelets - Conjugate***Fig. 46D*

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*Fig. 47A*

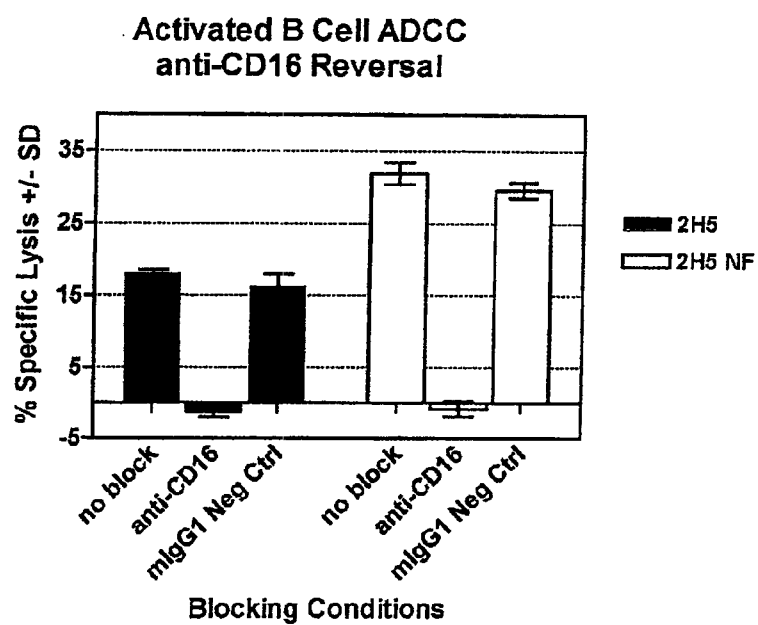
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B.

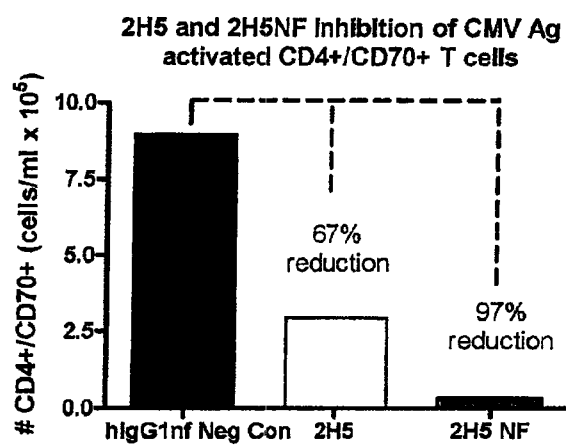
*Fig. 47B*

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C.

*Fig. 47C*

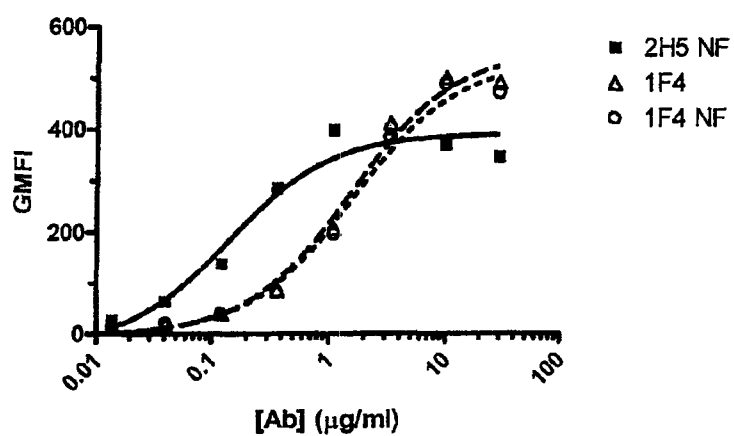
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*Fig. 48*

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Human anti-CD70 Ab binding to 786-0 cells

*Fig. 49*

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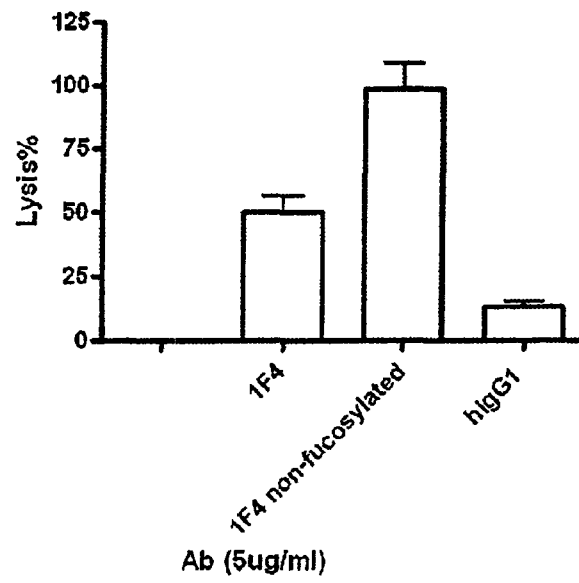
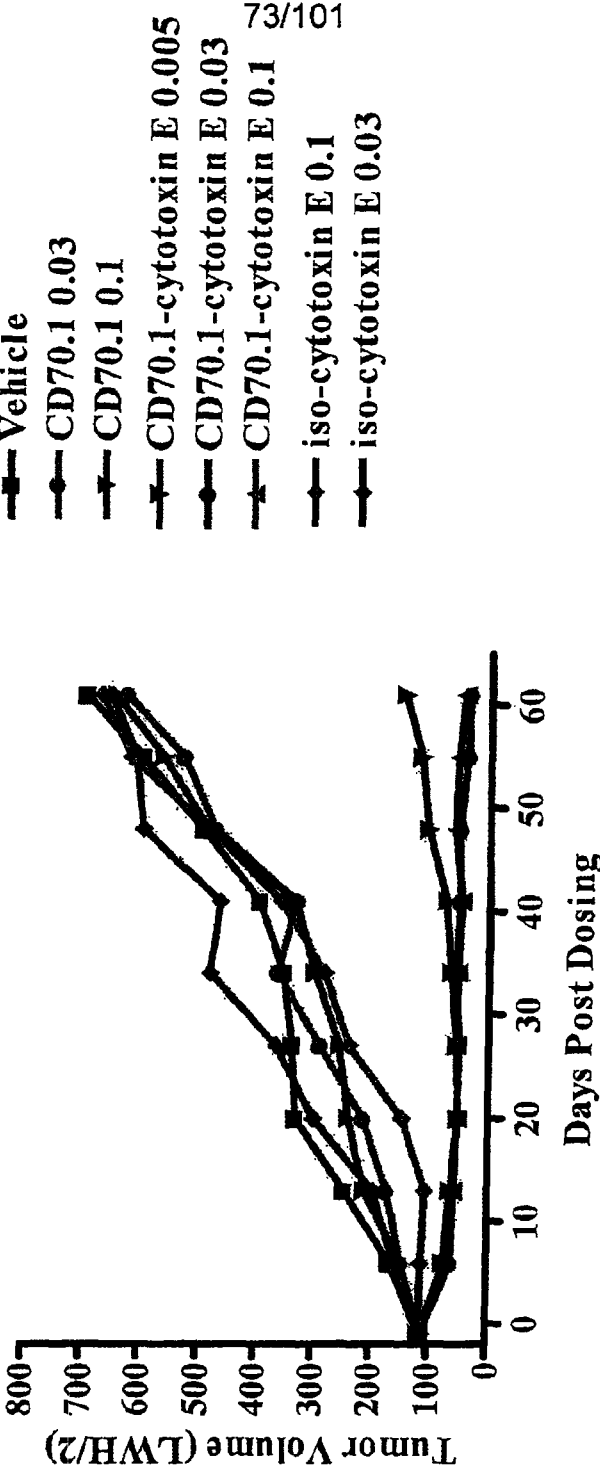
ADCC of Anti CD70 HuMAb 1F4 on ARH-77 Cells*Fig. 50*

Figure 51

1115-036 786-O Median Tumor Growth Curve



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Figure 52

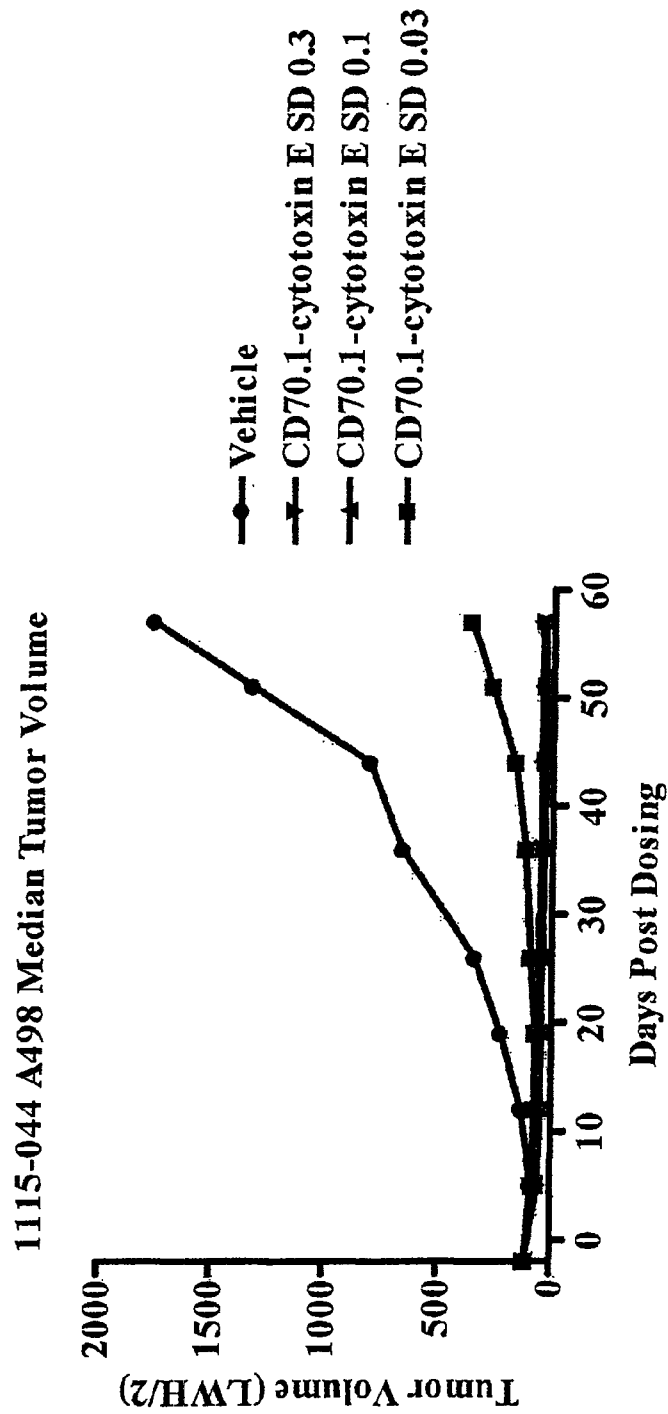


Figure 53

1115-043 Caki-1 Median Tumor Volume

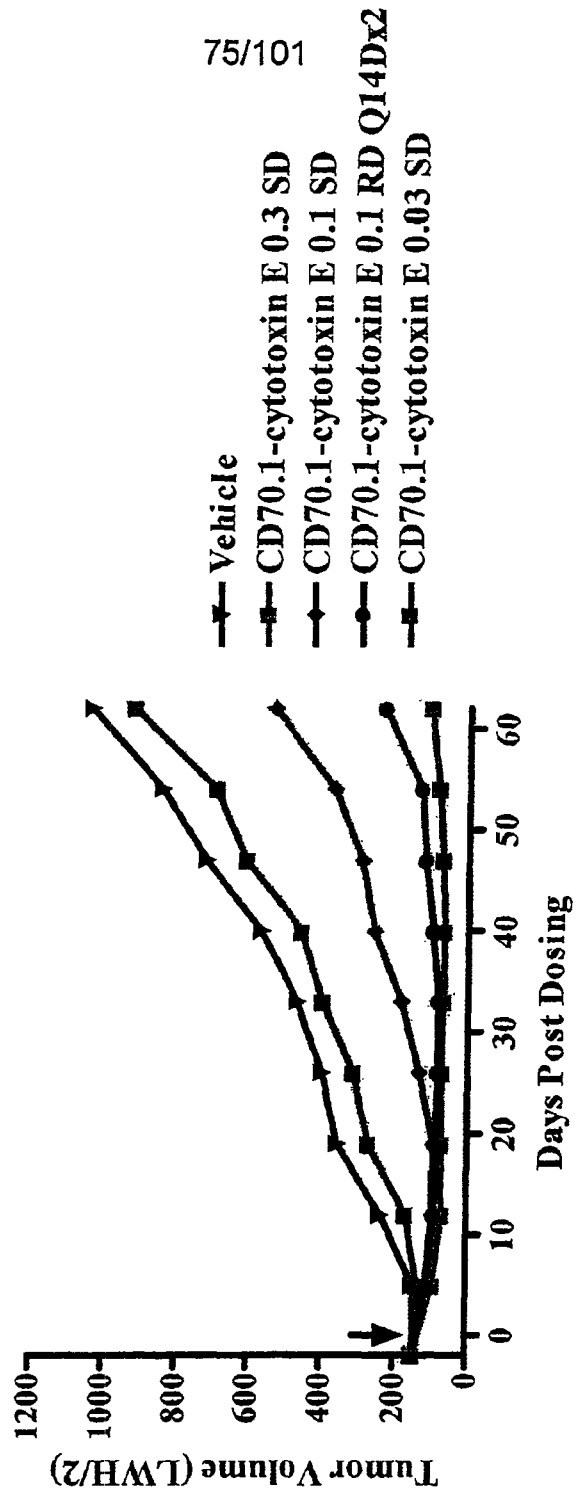
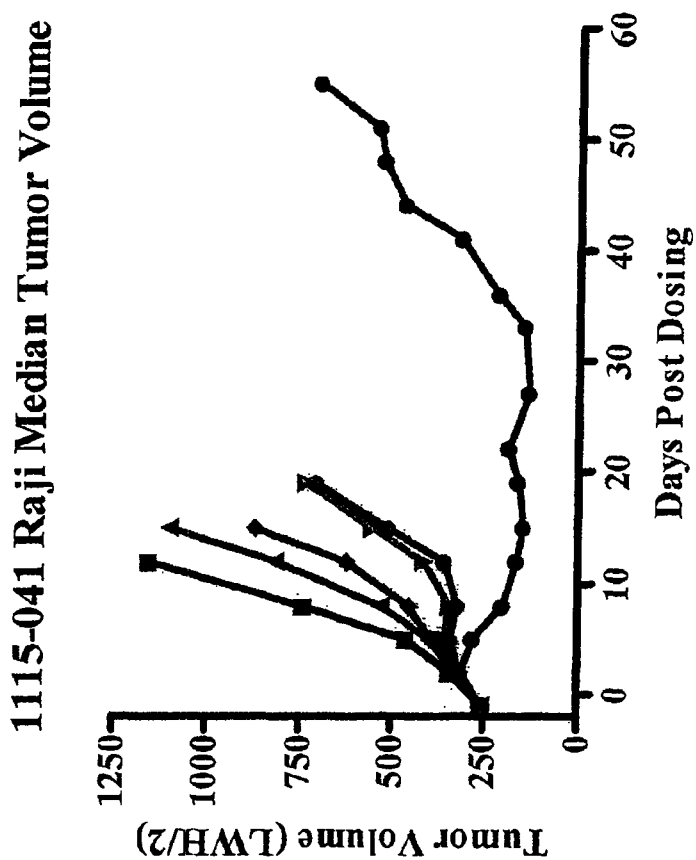


Figure 54

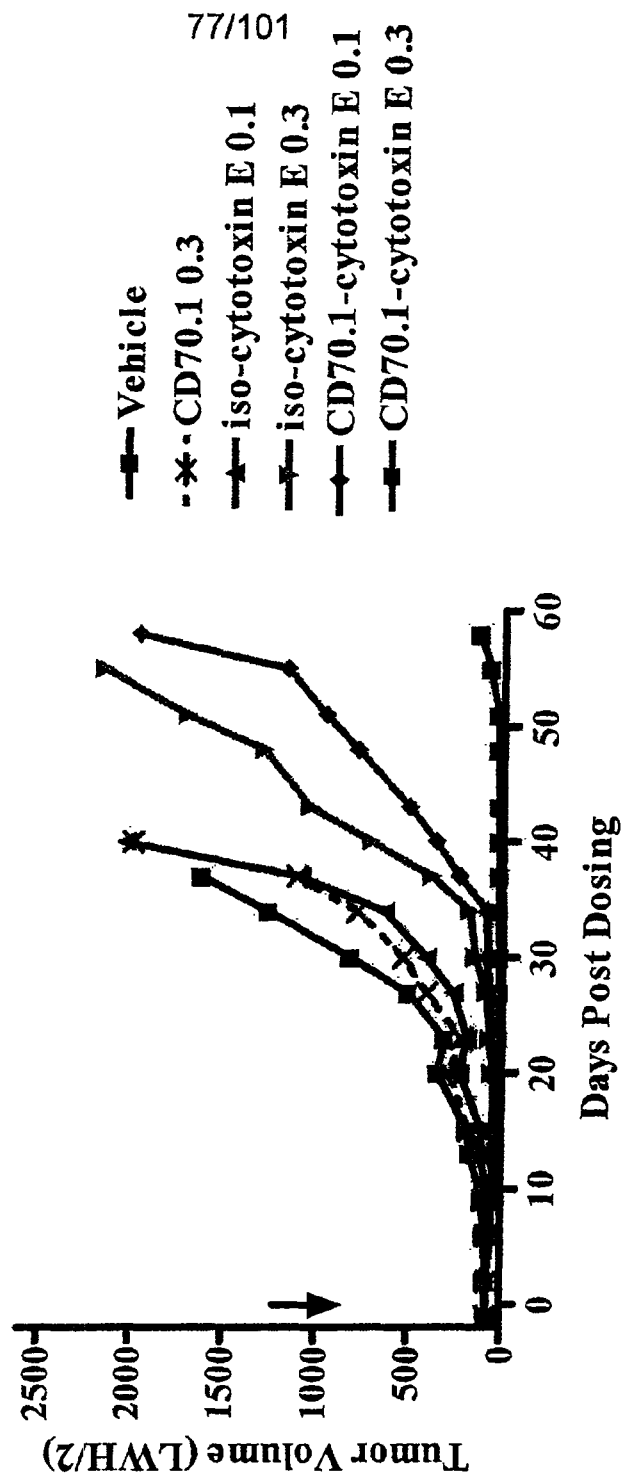


■ Vehicle
 ▼ iso-cytotoxin E 0.3 SD
 ● CD70.1-cytotoxin E 0.3 SD
 ▲ iso-cytotoxin E 0.1 SD
 ● CD70.1-cytotoxin E 0.1 SD
 ● CD70.1-cytotoxin E 0.03 SD

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Figure 55

1335-005 Daudi Median Tumor Volume



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Figure 56

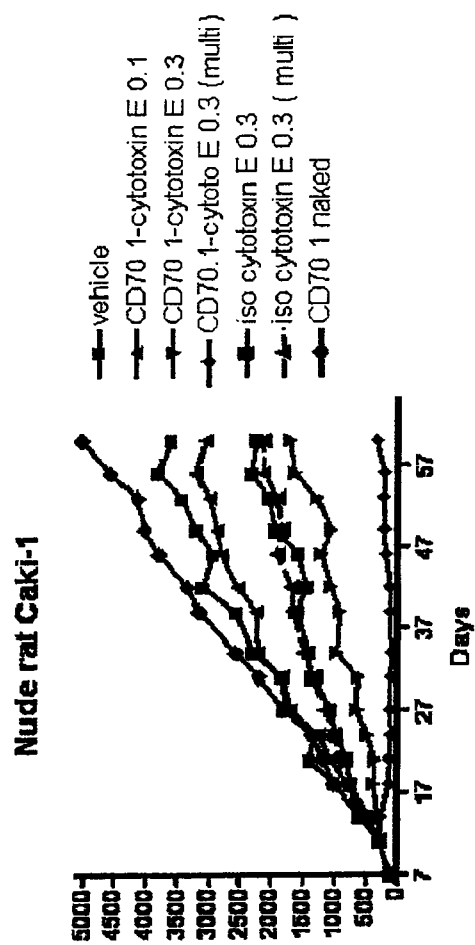


Figure 57

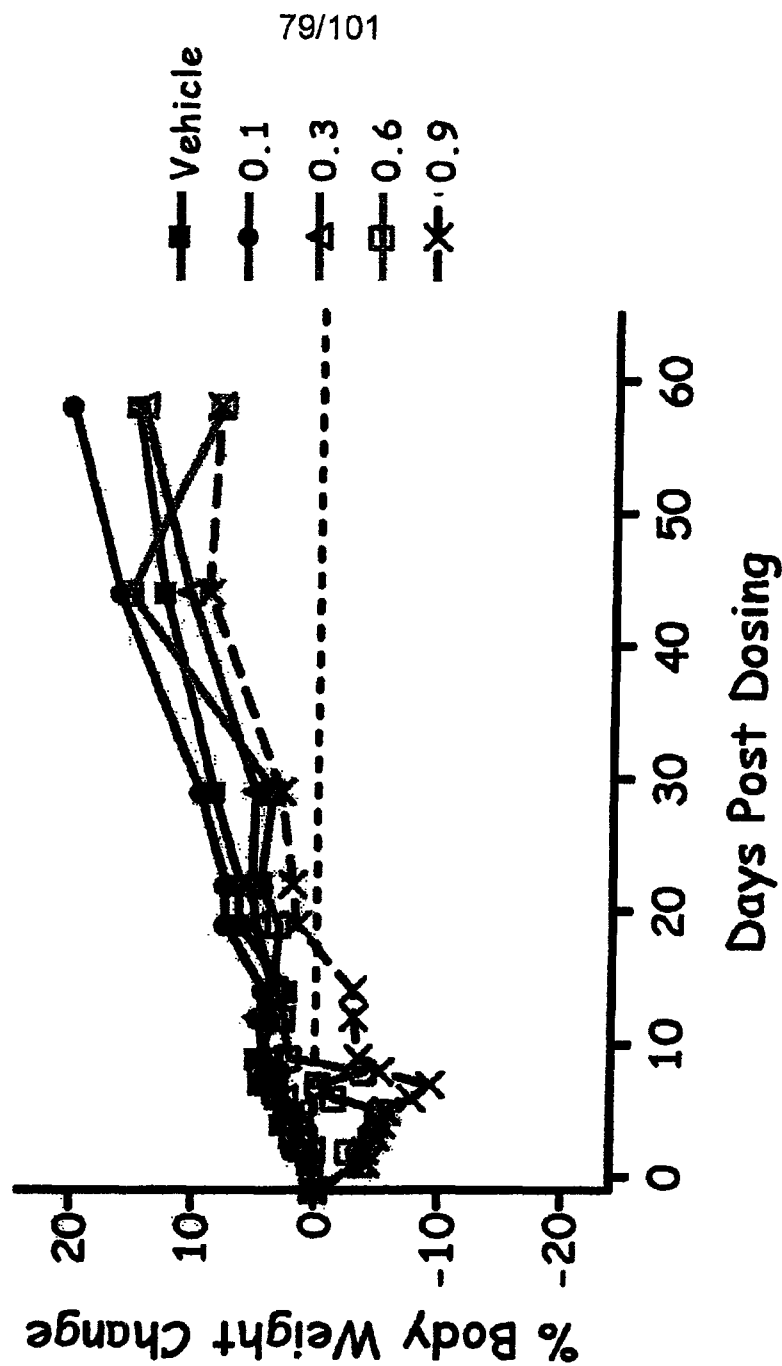


Figure 58

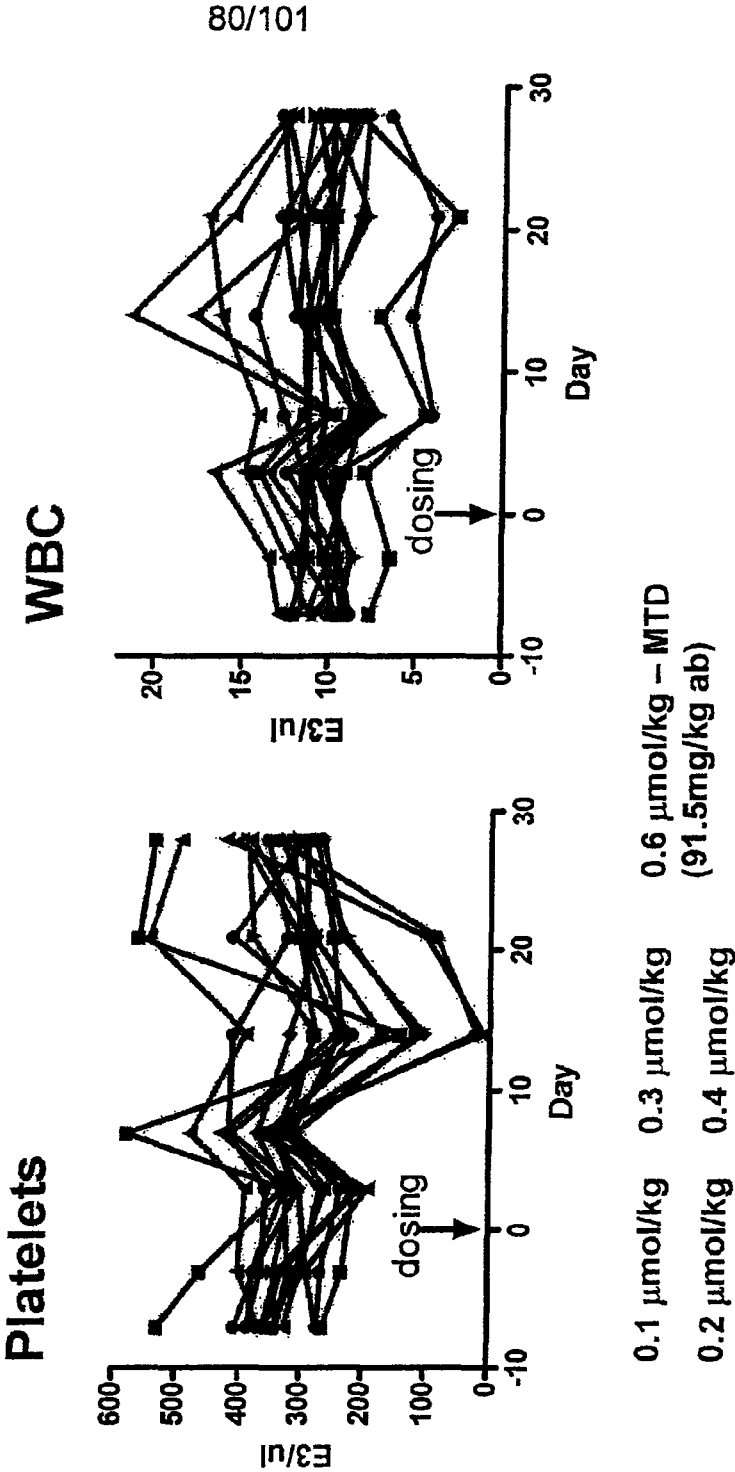


Figure 59

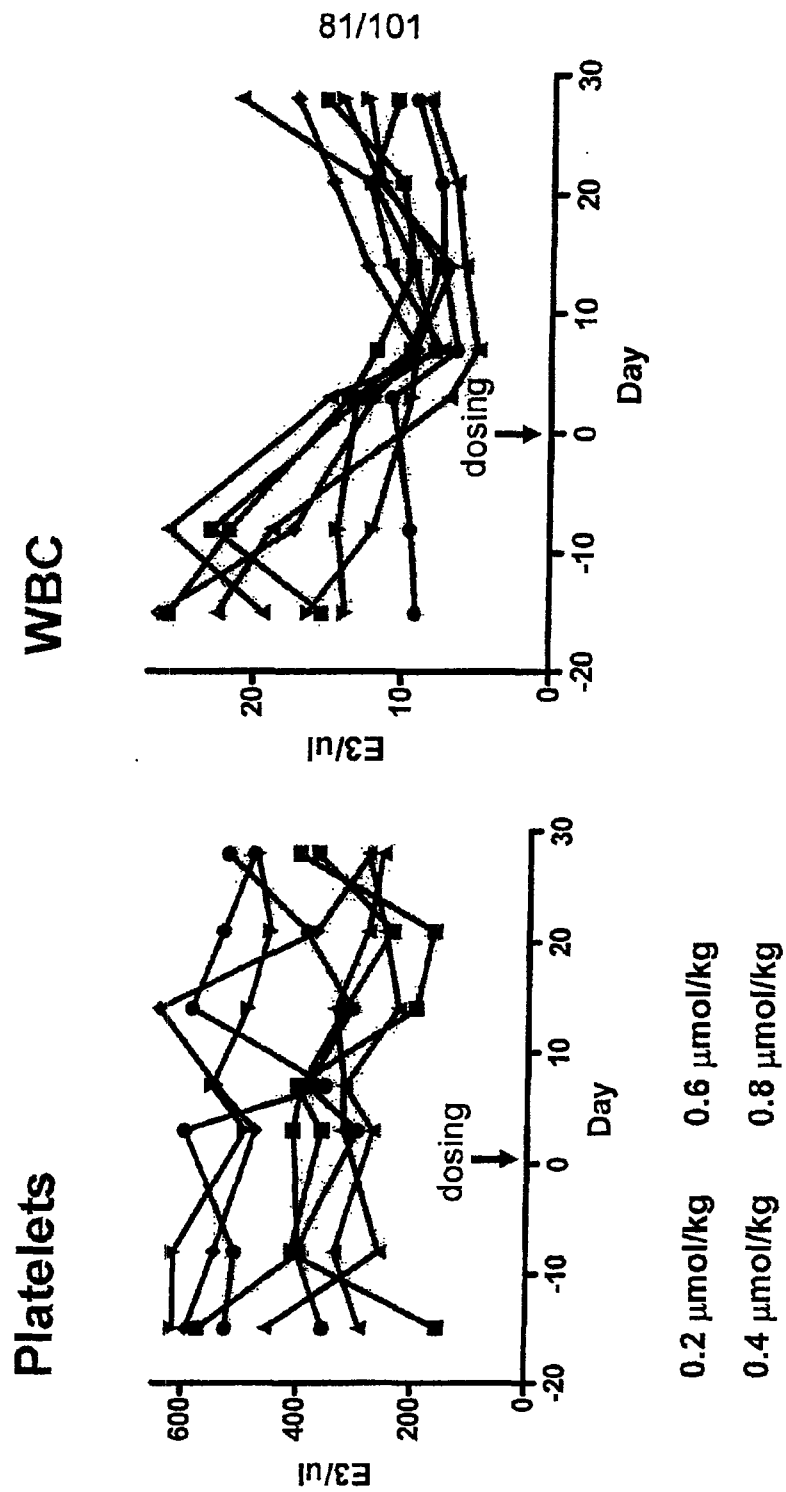


Figure 60

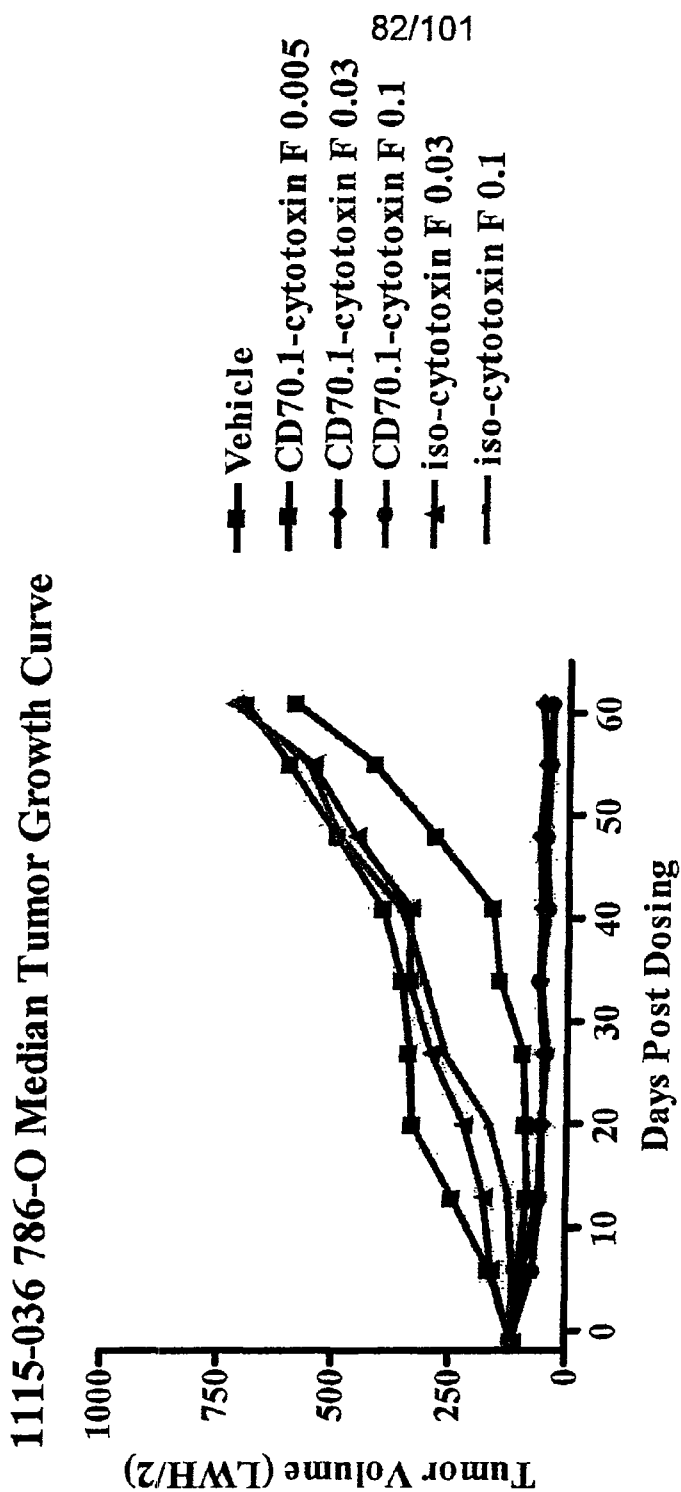


Figure 61

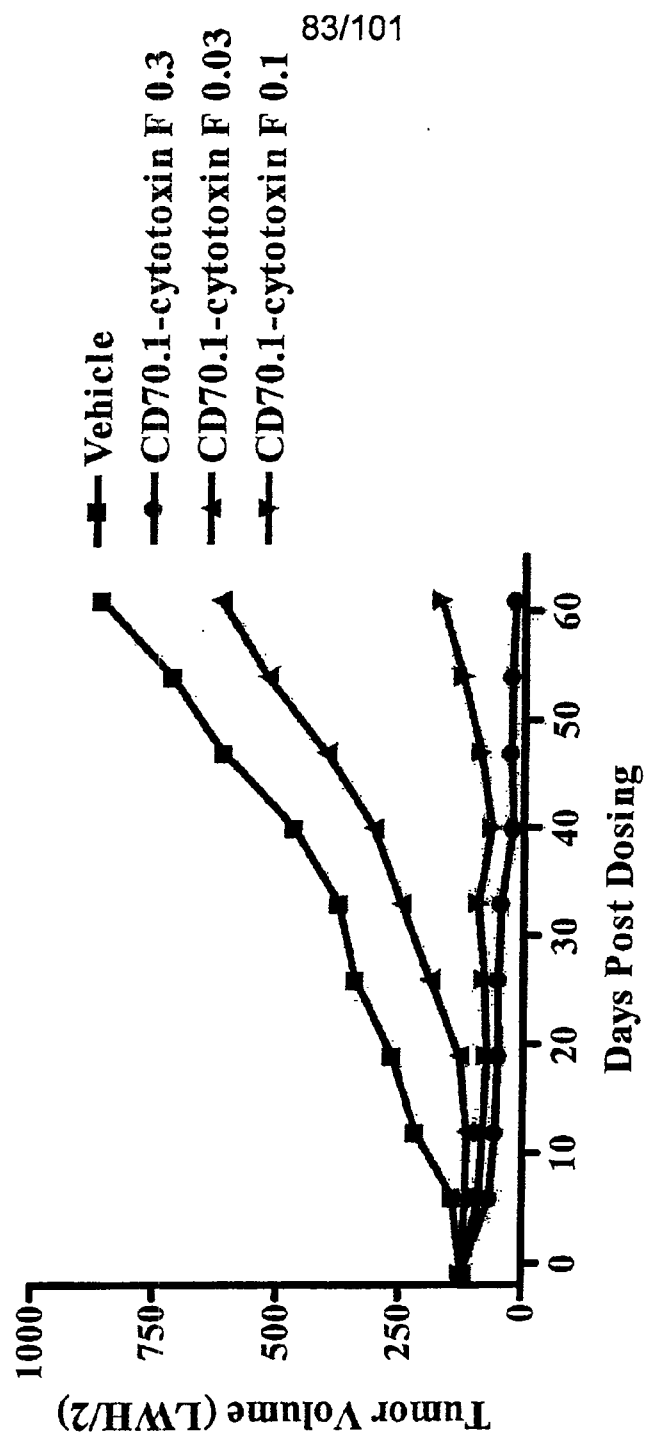


Figure 62

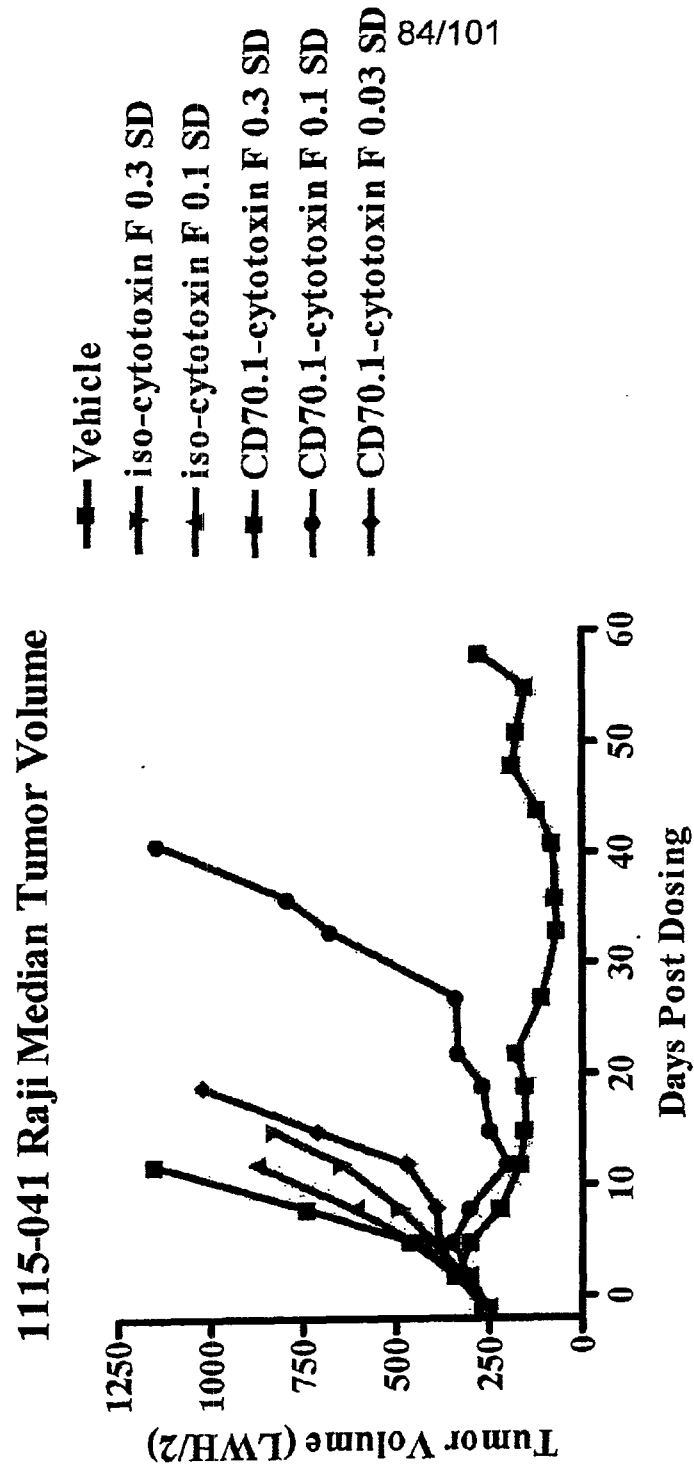


Figure 63

1115-036 786-O Median Tumor Growth Curve

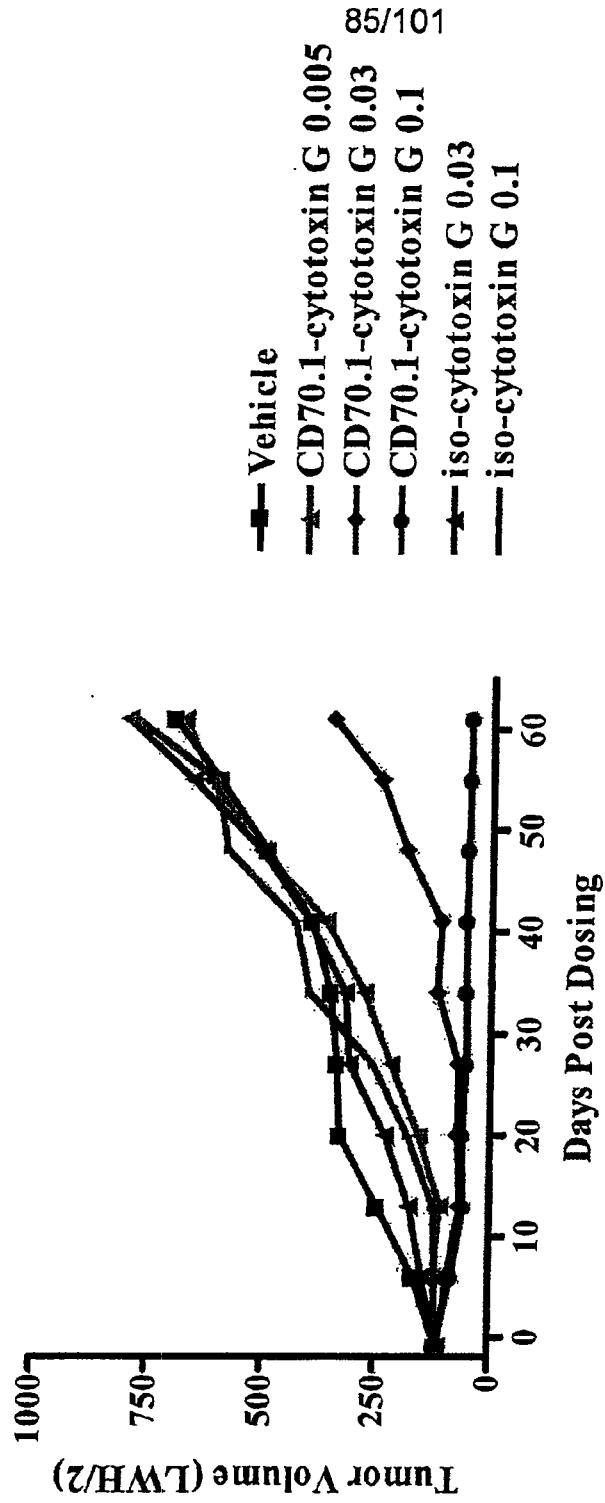


Figure 64

Caki-1 Median Tumor Volume

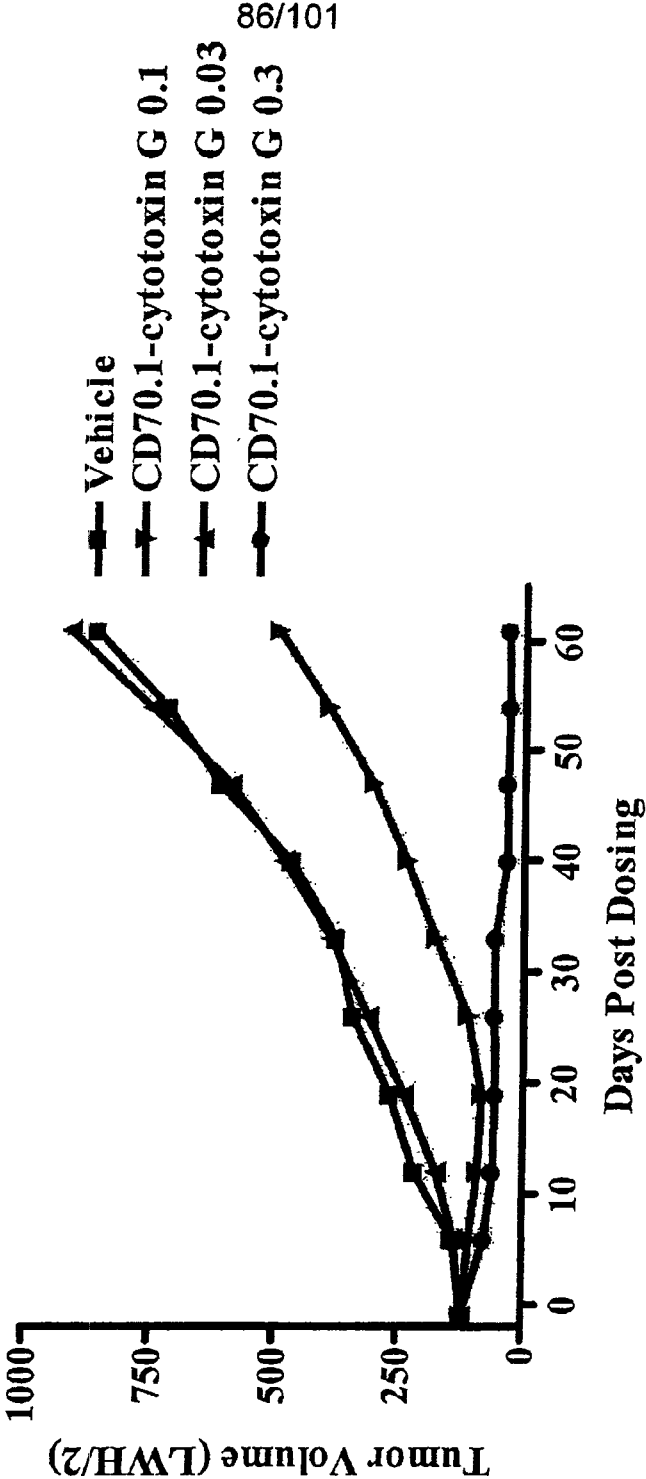


Figure 65

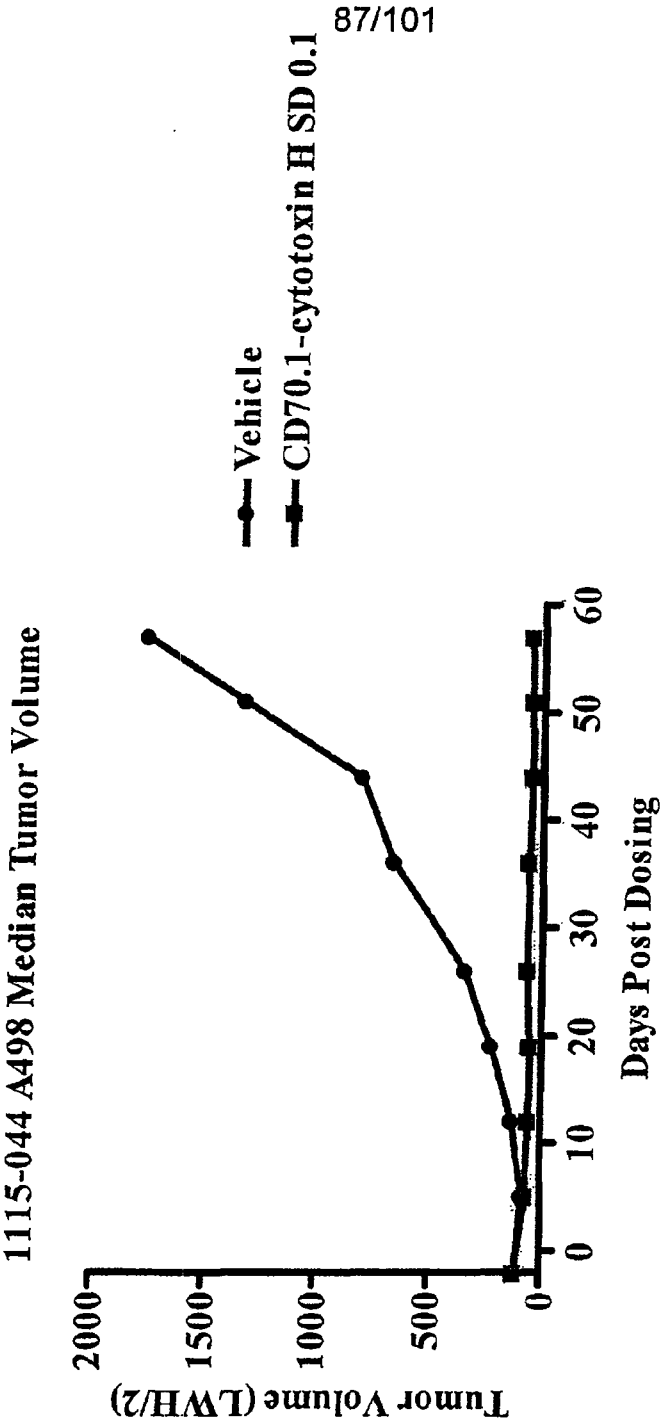


Figure 66

1115-047 Caki-1 Median Tumor Volume

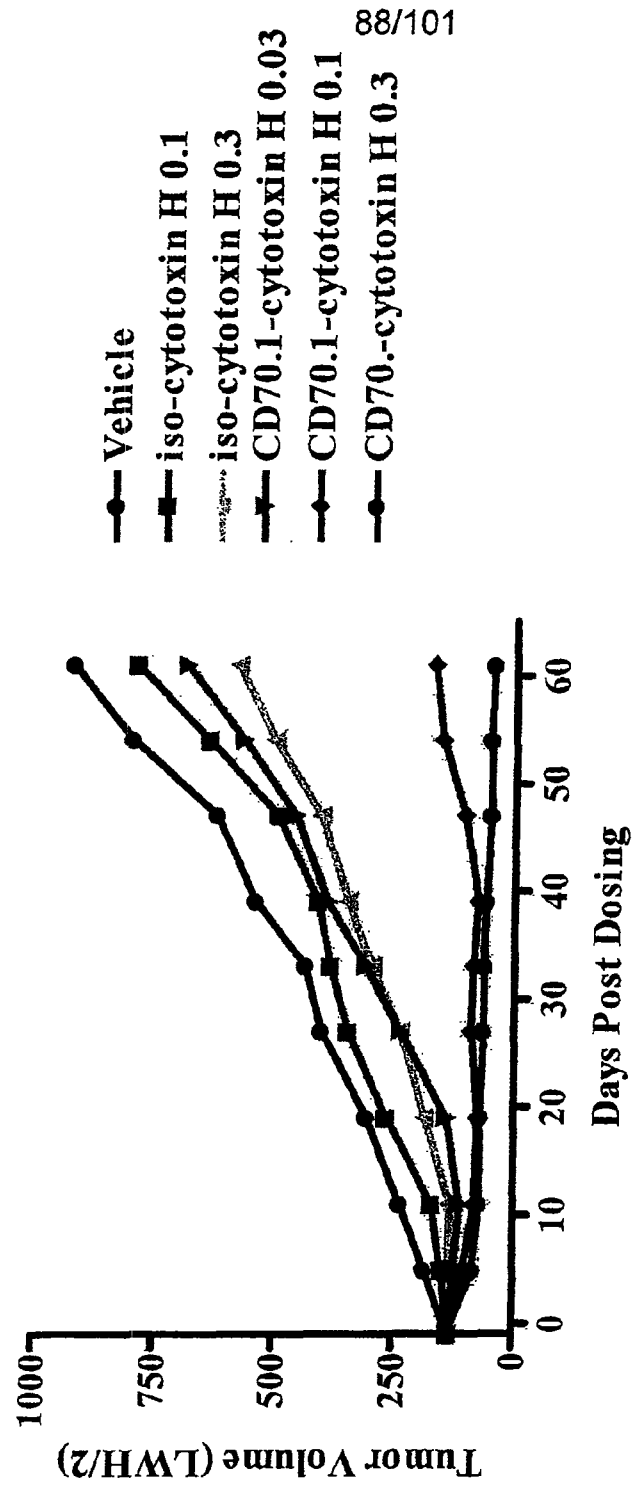
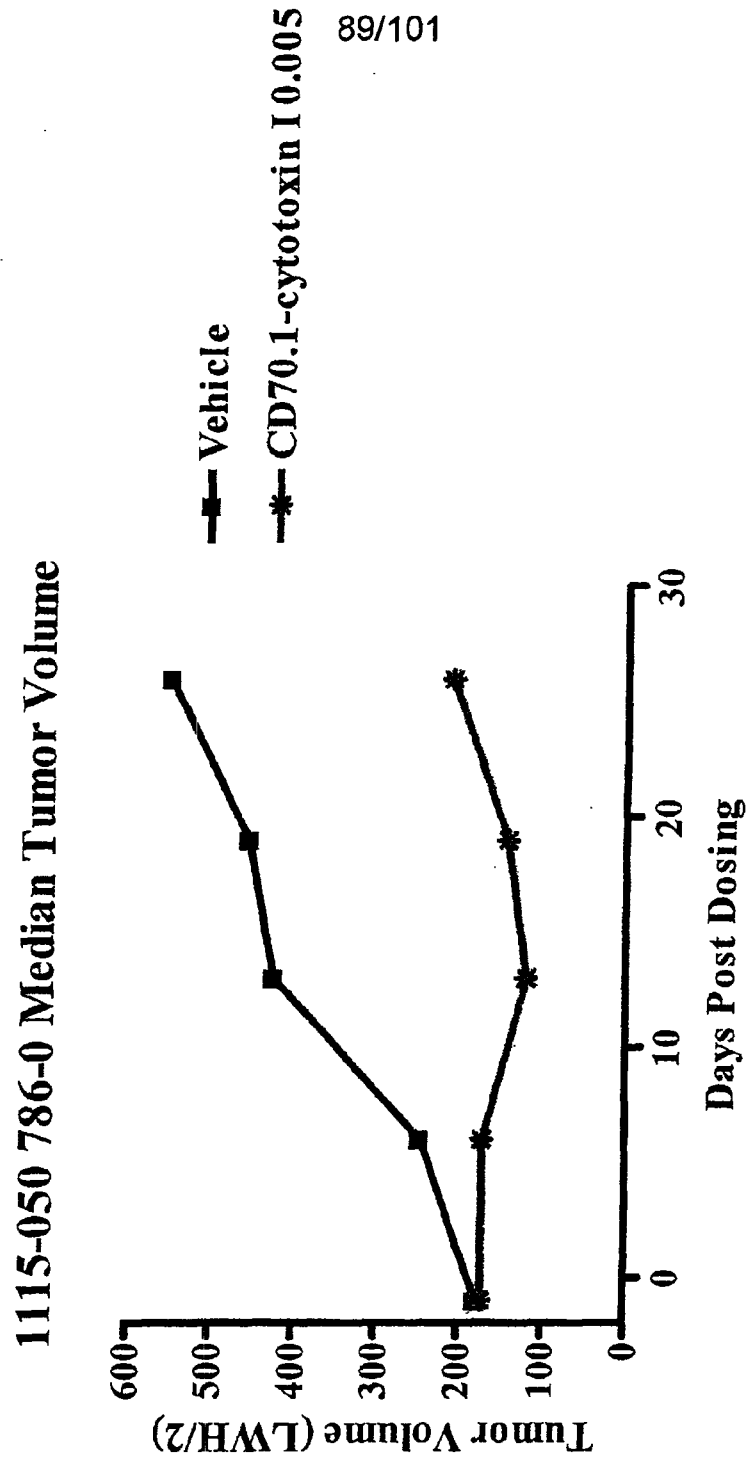


Figure 67



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Figure 68

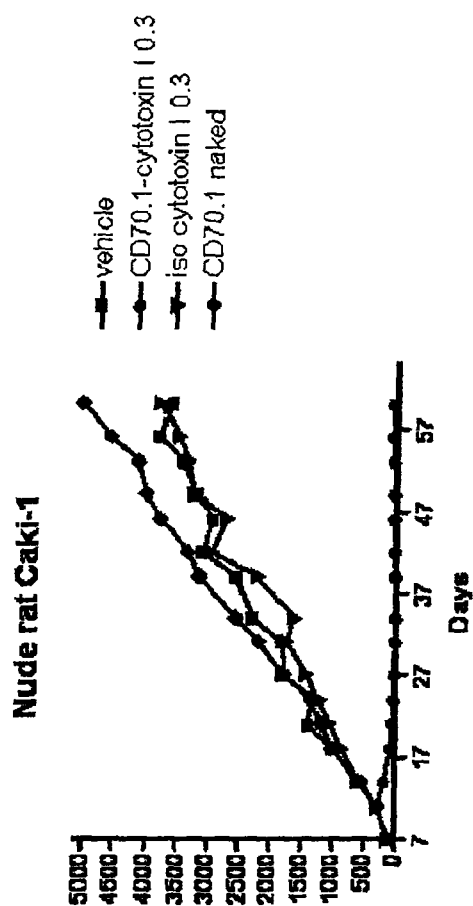
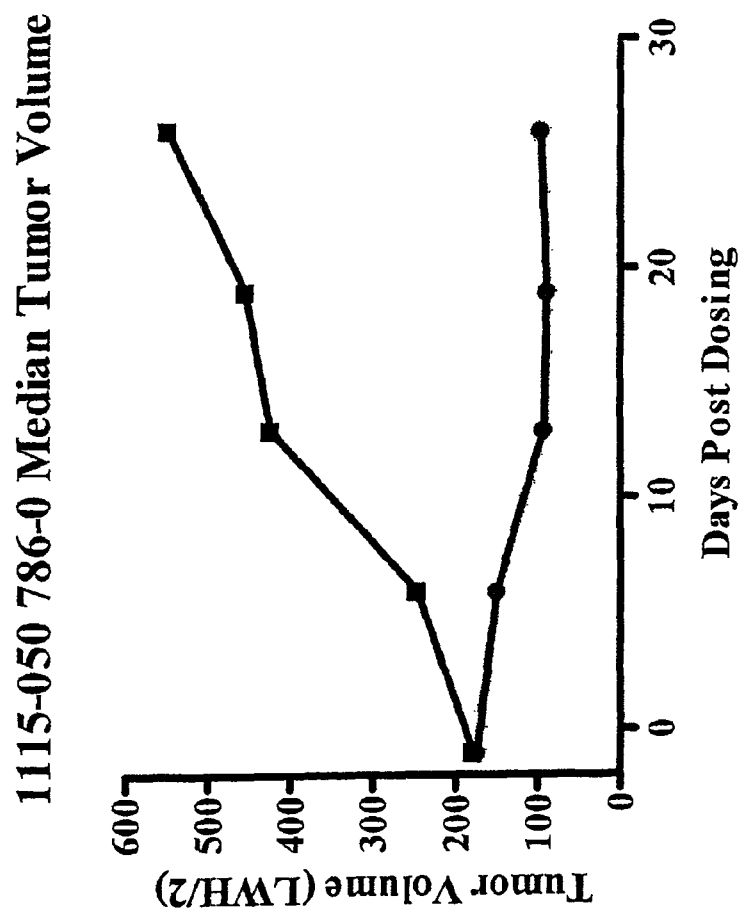
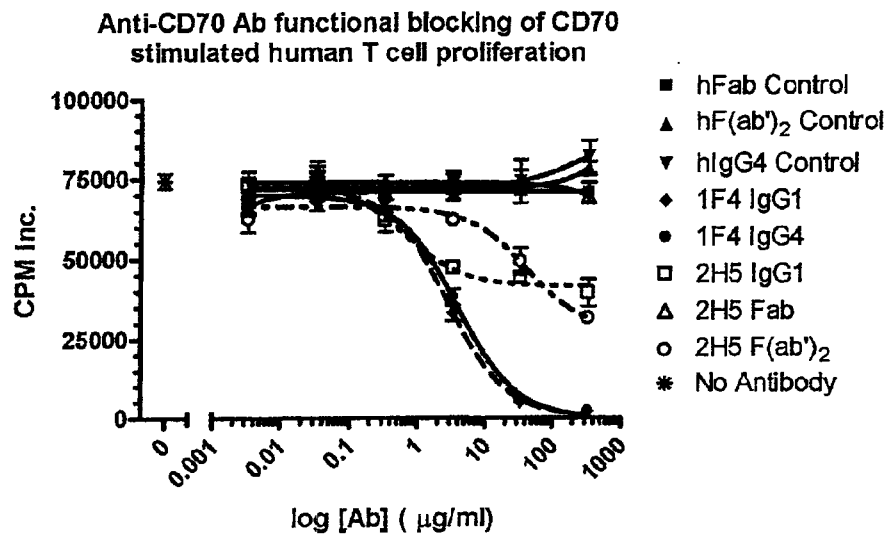


Figure 69



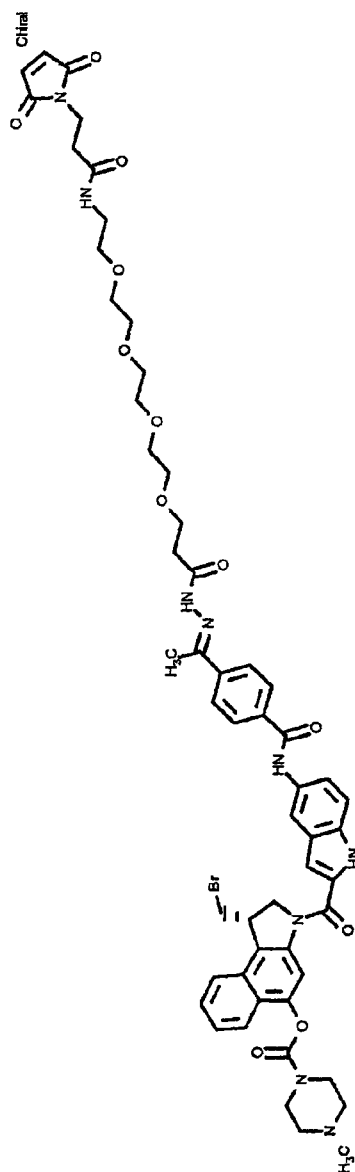
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*Fig. 70*

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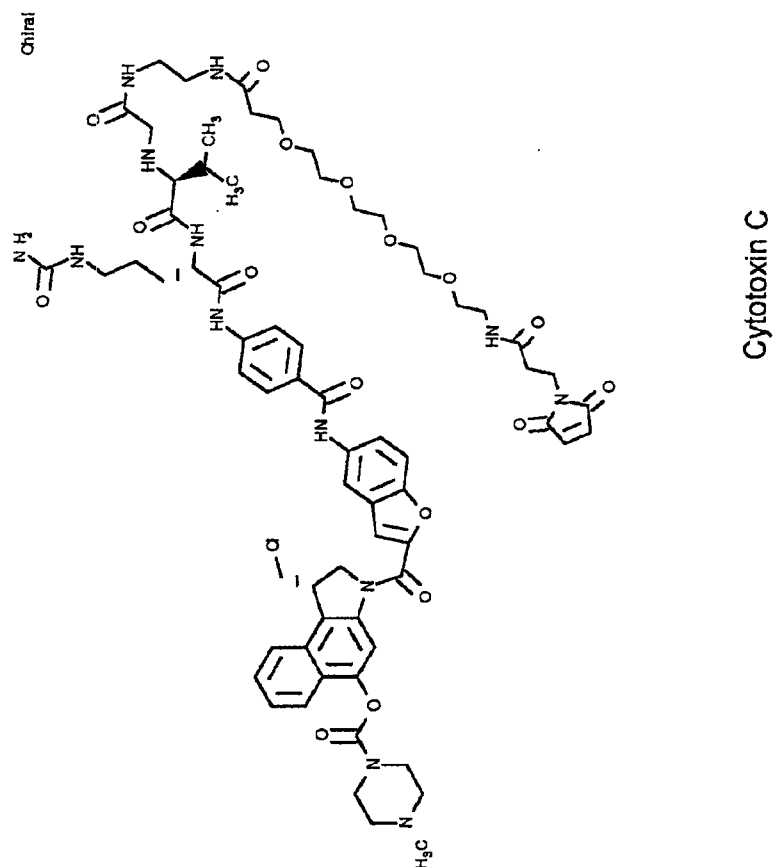
Figure 71



Cytotoxin B

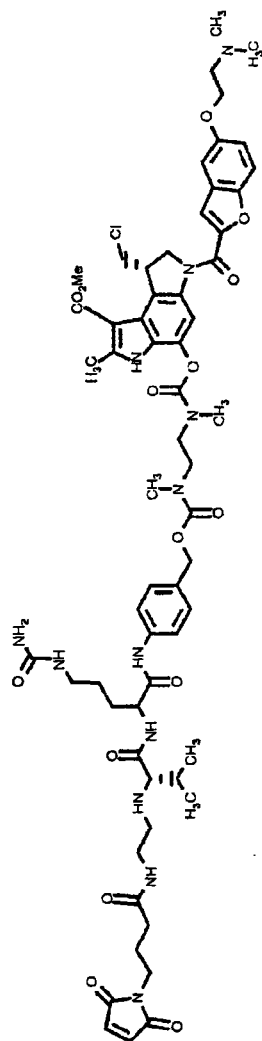
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Figure 72



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Figure 73



Cytotoxin D

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Cytotoxin E

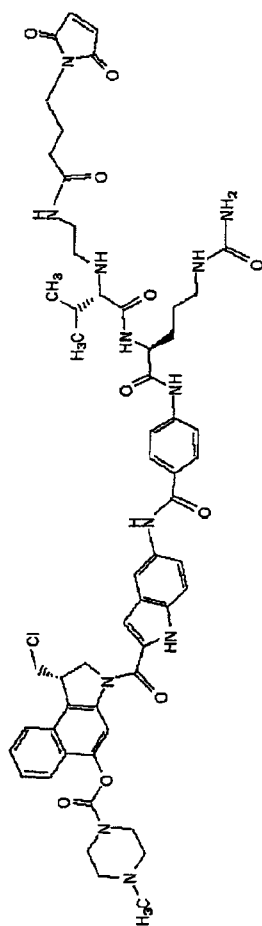


Figure 74

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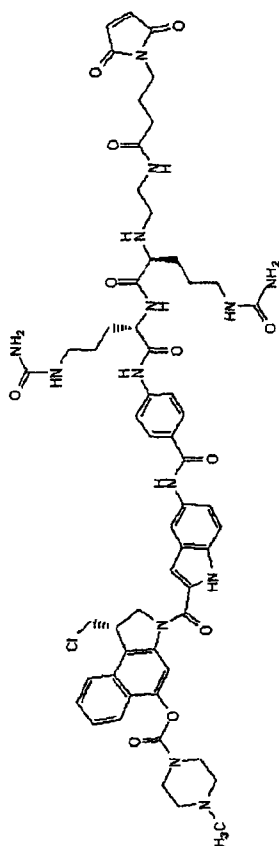
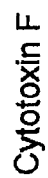


Figure 75

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Cytotoxin G

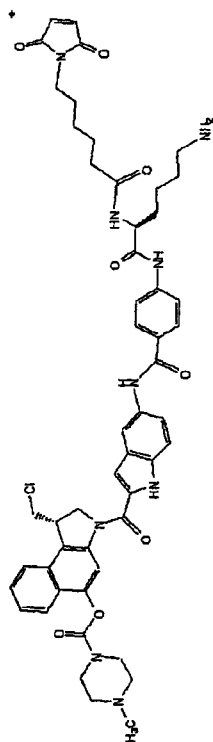


Figure 76

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Cytotoxin H

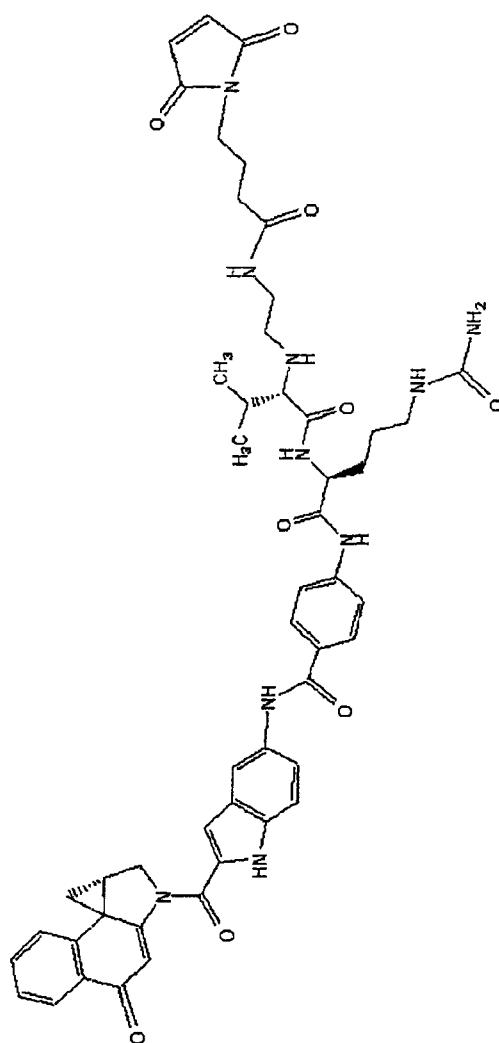


Figure 77

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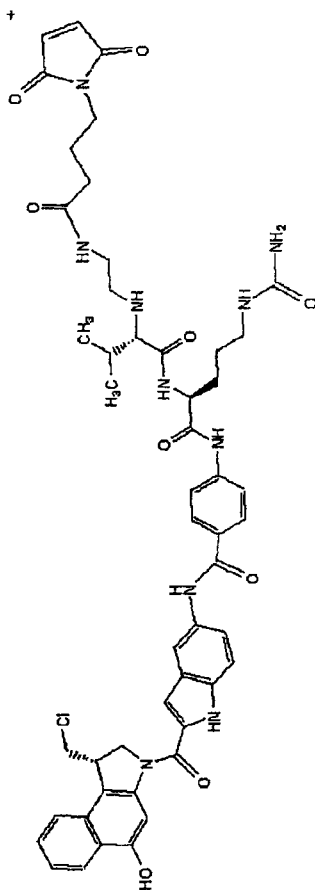


Figure 78

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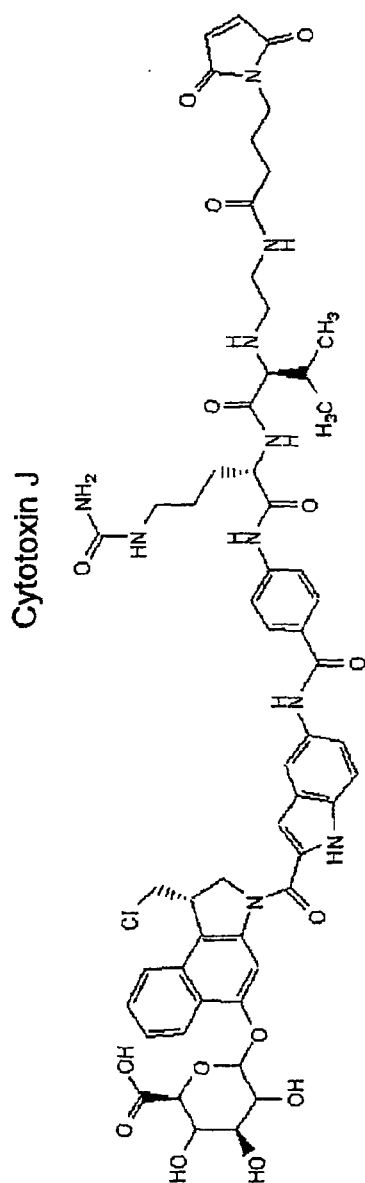


Figure 79