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Uda et al.

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(54) **ANTICANCER AGENT**

(71) Applicant: **Japan Science and Technology Agency**, Kawaguchi-shi, Saitama (JP)

(72) Inventors: **Taizo Uda**, Oita (JP); **Emi Hifumi**, Oita (JP)

(73) Assignee: **JAPAN SCIENCE AND TECHNOLOGY AGENCY**, Kawaguchi-Shi (JP)

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(30) **Foreign Application Priority Data**

Mar. 8, 2012 (JP) 2012-052334

(51) **Int. Cl.**

C07K 16/30	(2006.01)
C07K 16/18	(2006.01)
A61K 39/00	(2006.01)

(52) **U.S. Cl.**

CPC ***C07K 16/3023*** (2013.01); ***C07K 16/18*** (2013.01); *A61K 2039/505* (2013.01); *C07K 2317/21* (2013.01); *C07K 2317/515* (2013.01); *C07K 2317/60* (2013.01); *C07K 2317/73* (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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Primary Examiner — Peter J Reddig

(57) **ABSTRACT**

According to the present invention, an anticancer agent is provided that has as an active ingredient thereof a human antibody light chain that demonstrates cytotoxicity against cancer cells and particularly lung cancer cells. The anticancer agent of the present invention primarily comprises: a human antibody κ-type light chain in the form of a dimer in which the variable region is composed of a polypeptide represented by the amino acid sequence of SEQ ID NO: 1, 9 or 13 or an amino acid sequence in which one or a plurality of amino acids have been added, deleted or substituted in these amino acid sequences; or, a human antibody κ-type light chain in the form of a monomer in which the variable region is composed of a polypeptide represented by the amino acid sequence of SEQ ID NO: 19 or an amino acid sequence in which one or a plurality of amino acids have been added, deleted or substituted in the amino acid sequence.

5 Claims, 14 Drawing Sheets

FIG. 1

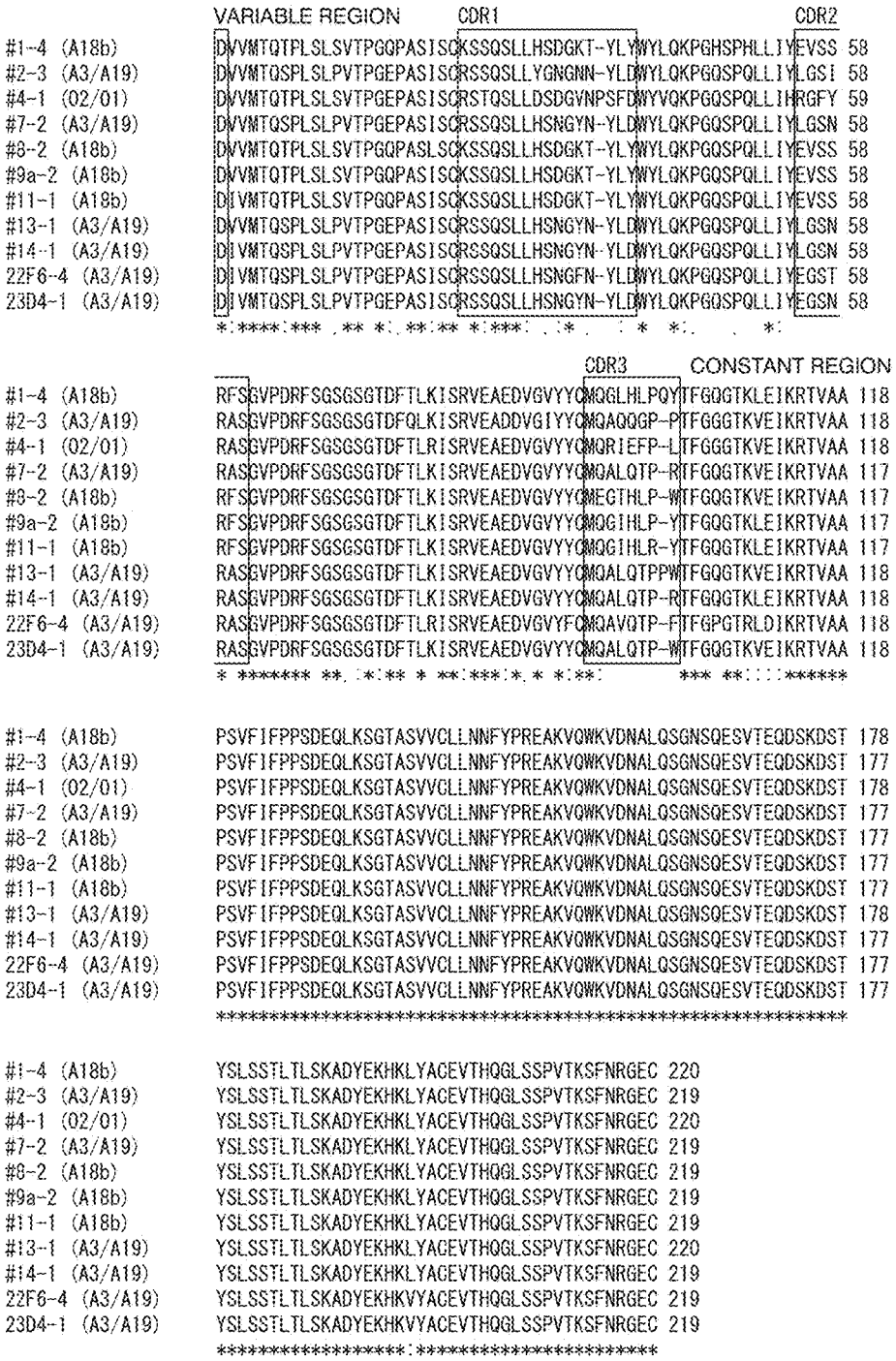

VARIABLE REGION
CDR1
CDR2
CDR3
CONSTANT REGION
#1-4 (A18b)
#2-3 (A3/A19)
#4-1 (02/01)
#7-2 (A3/A19)
#8-2 (A18b)
#9a-2 (A18b)
#11-1 (A18b)
#13-1 (A3/A19)
#14-1 (A3/A19)
22F6-4 (A3/A19)
23D4-1 (A3/A19)

FIG. 2A

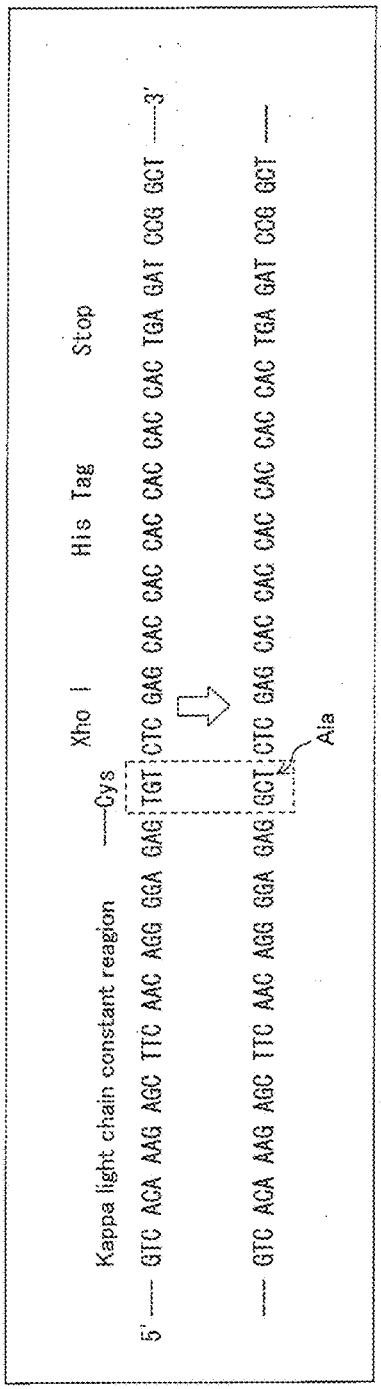

Kappa light chain constant reagion
Cys
Xho I
His Tag
Stop
5' — GTC ACA AAG AGC TTC AAC AGG GGA GAG TGT CTC GAG CAC CAC CAC CAC CAC TGA GAT CCG GCT — 3'
— GTC ACA AAG AGC TTC AAC AGG GGA GAG GCT CTC GAG CAC CAC CAC CAC CAC TGA GAT CCG GCT —
Ala

FIG. 2B

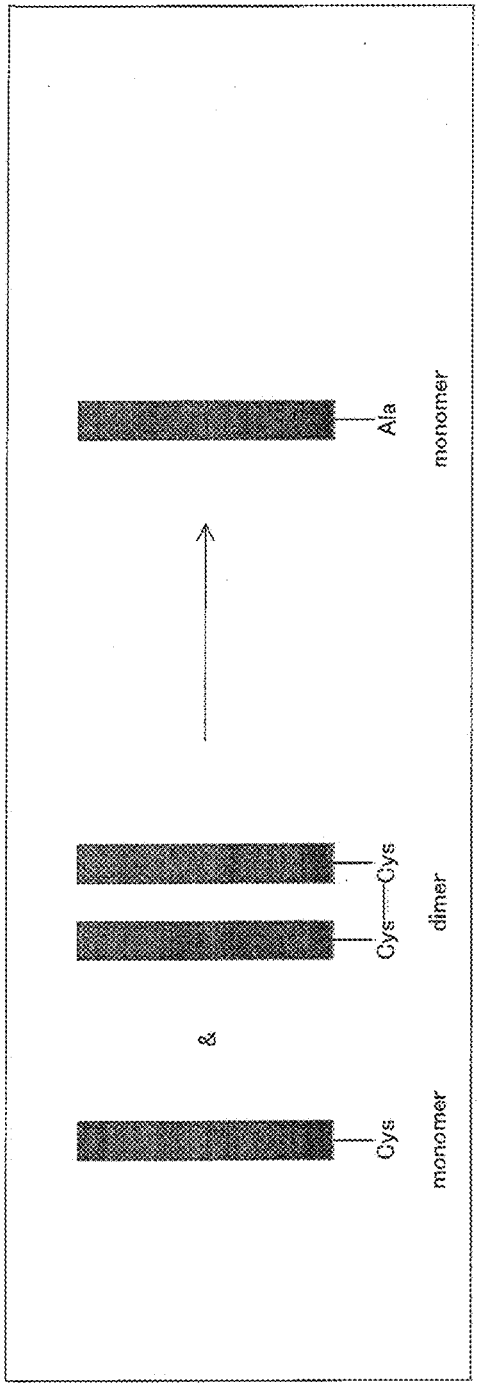

Cys
monomer
&
Cys
Cys
dimer
Ala
monomer

FIG. 3A

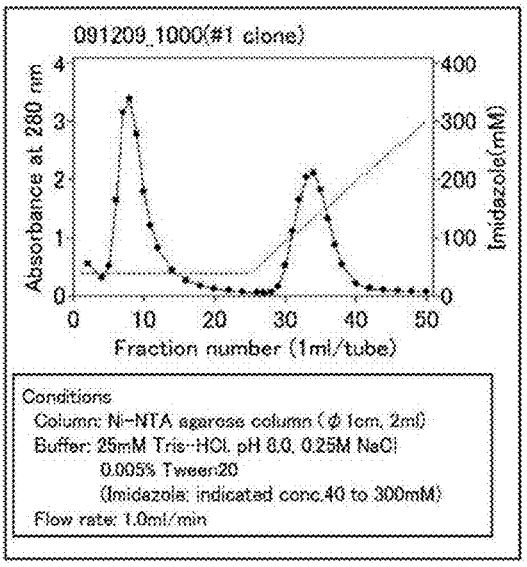


FIG. 3B

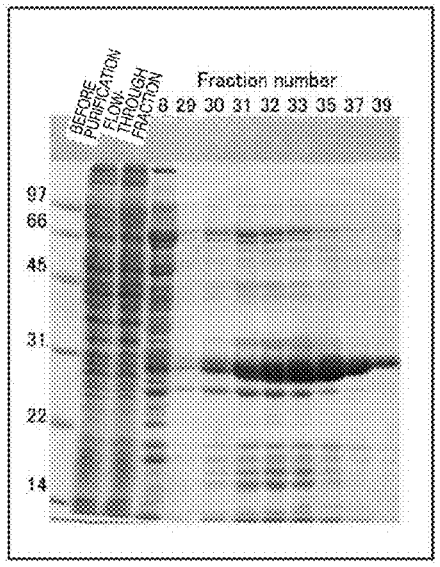
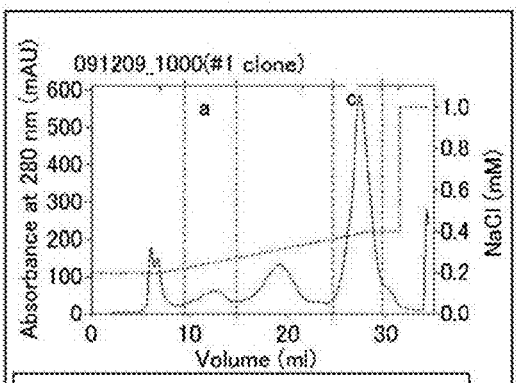


FIG. 3C



SAMPLE	CONCENTRATION (μm/ml)	VOLUME (ml)	PROTEIN (μg)
a	130	5.0	650
c	710	5.0	3600

FIG. 3D

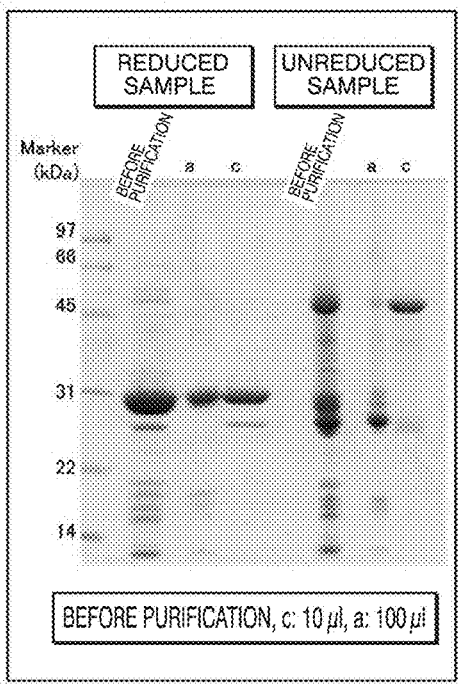


FIG. 4

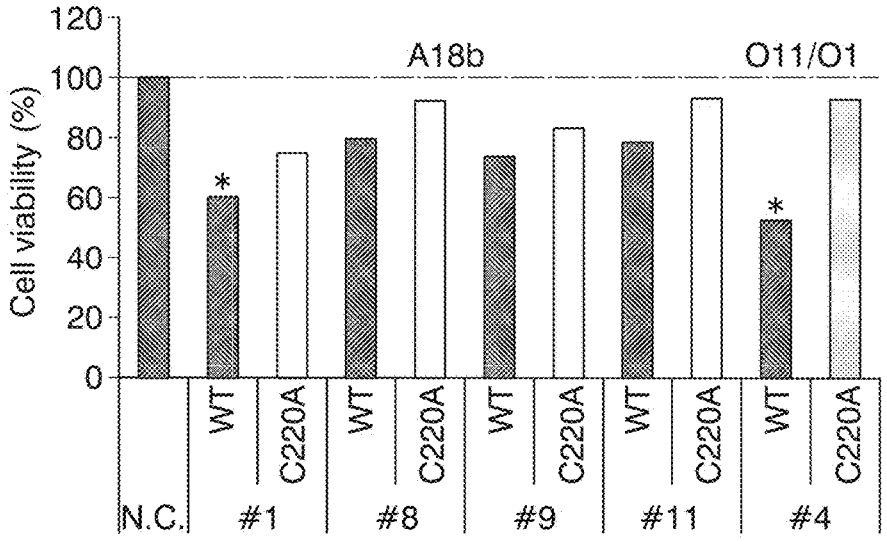

120
100
80
60
40
20
0
Cell viability (%)
A18b
O11/O1
*
*
WT
C220A
N.C.
#1
#8
#9
#11
#4

FIG. 5

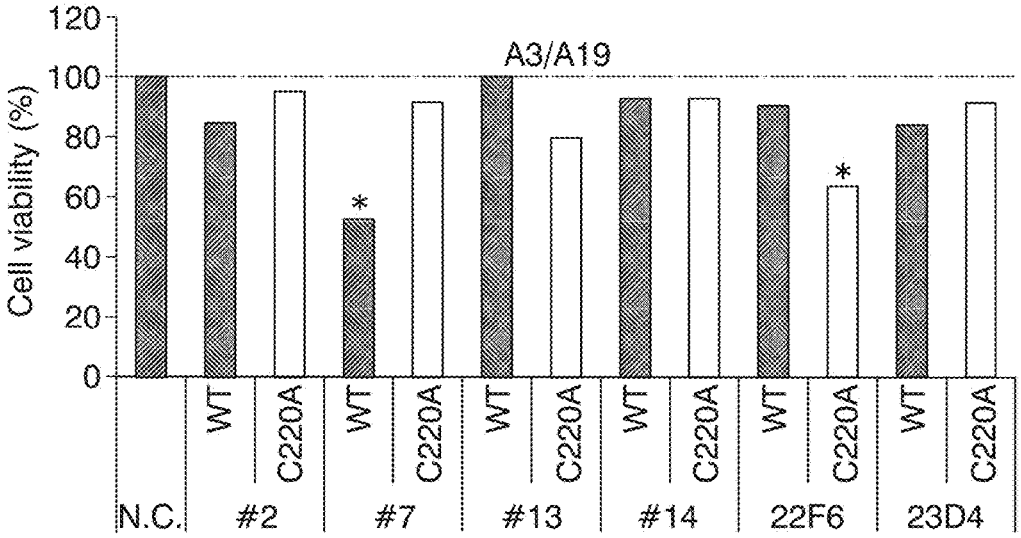

120
100
80
60
40
20
0
Cell viability (%)
A3/A19
*
*
WT
C220A
N.C.
#2
#7
#13
#14
22F6
23D4

FIG. 6A

A549

```
                  ---------+---------+---------+---------+---------+
                           10        20        30        40        50
                  ---------+---------+---------+---------+---------+
#1H31YC220A.pro   DVVMTQTPLSLSVTPGQPASISCKSSQSLLYSDGKTYLYWYLQKPGHSPH          50
#7VL(I).pro       EIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNTRNYLDWYLQKPGQSPQ          50
#7RLI.pro         EIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNTRNYLDWYLQKPGQSPQ          50
C51.pro           EIVLTQSPATLSLSPGERATLSCRASQSV-----SSYLAWYQQKPGQAPR          45
C87.pro           EIVLTQSPATLSLSPGERATFSCRASQSL-----SSYVAWYQKKPGQAPR          45

                  ---------+---------+---------+---------+---------+
                           60        70        80        90        100
                  ---------+---------+---------+---------+---------+
#1H31YC220A.pro   LLIYEVSSRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGLHL-         99
#7VL(I).pro       LLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGLQT-         99
#7RLI.pro         LLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGLQT-         99
C51.pro           LLIYDASNRATGIPARFSGSGSGTDFTLTITSLEPEDFAVYYCQQR-SDW         94
C87.pro           LLIYDTSTRAAGIPARFSGGGSGTDFTLTISSLEPEDCAVYYCQRR-AT-         93

                  ---------+---------+---------+---------+---------+
                           110       120       130       140       150
                  ---------+---------+---------+---------+---------+
#1H31YC220A.pro   PQYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE        149
#7VL(I).pro       PI-TFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE        148
#7RLI.pro         PI-TFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE        148
C51.pro           PL-TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE        143
C87.pro           PY-TFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE        142

                  ---------+---------+---------+---------+---------+
                           160       170       180       190       200
                  ---------+---------+---------+---------+---------+
#1H31YC220A.pro   AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKLYA        199
#7VL(I).pro       AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKLYA        198
#7RLI.pro         AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKLYA        198
C51.pro           AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA        193
C87.pro           AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHRVYA        192

                  ---------+---------+-
                           210       220
                  ---------+---------+-
#1H31YC220A.pro   CEVTHQGLSSPVTKSFNRGEA                                    220
#7VL(I).pro       CEVTHQGLSSPVTKSFNRGEC                                    219
#7RLI.pro         CEVTHQGLSSPVTKSFNRGEC                                    219
C51.pro           CEVTHQGLSSPVTKSFNRGEC                                    214
C87.pro           CEVTHQGLSSPVTKSFNRGEC                                    213
```

FIG. 6B

```
MOLT-4
                    ---------+---------+---------+---------+---------+
                             10        20        30        40        50
                    ---------+---------+---------+---------+---------+
#1H31YC220A.pro     DVVMTQTPLSLSVTPGQPASISCKSSQSLLYSDG-KTYLYWYLQKPGHSP          49
#4.pro              DVVMTQTPLSLSVTPGEPASISCRSTQSLLDSDGVNPSFDWYVQKPGQSP          50
#7EI.pro            EIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNG-YNYLDWYLQKPGQSP          49
#7TR.pro            DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNT-RNYLDWYLQKPGQSP          49
#7RLI.pro           EIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNT-RNYLDWYLQKPGQSP          49
#7VL.pro            EIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNT-RNYLDWYLQKPGQSP          49
S13.pro             DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNG-YNYLDWYLQKPGQSP          49
S21.pro             DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNG-YNYLDWYLQKPGQSP          49
S38.pro             DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNG-YNYLDWYLQKPGQSP          49
CS1.pro             EIVLTQSPATLSLSPGERATLSCRASQS------VSSYLAWYQQKPGQAP          44

                    ---------+---------+---------+---------+---------+
                             60        70        80        90        100
                    ---------+---------+---------+---------+---------+
#1H31YC220A.pro     HLLIYEVSSRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGLHL          99
#4.pro              QLLIHRGFYRASGVPDRFSGSGSGTDFTLRISRVEAEDVGVYYCMQRIEF         100
#7EI.pro            QLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQT          99
#7TR.pro            QLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQT          99
#7RLI.pro           QLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGLQT          99
#7VL.pro            QLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGLQT          99
S13.pro             QLLIYLGSNRDSGVPDRFSGSGSGTDFTLKISSVEAEDVGVYYCMQALET          99
S21.pro             QLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQT          99
S38.pro             QLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQT          99
CS1.pro             RLLIYDASNRATGIPARFSGSGSGTDFTLTITSLEPEDFAVYYCQQRSDW          94

                    ---------+---------+---------+---------+---------+
                             110       120       130       140       150
                    ---------+---------+---------+---------+---------+
#1H31YC220A.pro     PQYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE         149
#4.pro              PL-TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE         149
#7EI.pro            PR-TFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE         148
#7TR.pro            PR-TFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE         148
#7RLI.pro           PI-TFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE         148
#7VL.pro            PR-TFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE         148
S13.pro             PP-TFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE         148
S21.pro             PR-TFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE         148
S38.pro             -Y-TFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE         147
CS1.pro             PL-TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE         143

                    ---------+---------+---------+---------+---------+
                             160       170       180       190       200
                    ---------+---------+---------+---------+---------+
#1H31YC220A.pro     AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKLYA         199
#4.pro              AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKLYA         199
#7EI.pro            AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKLYA         198
#7TR.pro            AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKLYA         198
#7RLI.pro           AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKLYA         198
#7VL.pro            AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKLYA         198
S13.pro             AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA         198
S21.pro             AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA         198
S38.pro             AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA         197
CS1.pro             AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA         193
```

FIG. 6C

```
                  ---------+---------+-
                           210       220
                  ---------+---------+-
#1H31YC220A.pro   CEVTHQGLSSPVTKSFNRGEA                          220
#4.pro            CEVTHQGLSSPVTKSFNRGEC                          220
#7EI.pro          CEVTHQGLSSPVTKSFNRGEC                          219
#7TR.pro          CEVTHQGLSSPVTKSFNRGEC                          219
#7RLI.pro         CEVTHQGLSSPVTKSFNRGEC                          219
#7VL.pro          CEVTHQGLSSPVTKSFNRGEC                          219
S13.pro           CEVTHQGLSSPVTKSFNRGEC                          219
S21.pro           CEVTHQGLSSPVTKSFNRGEC                          219
S38.pro           CEVTHQGLSSPVTKSFNRGEC                          218
C51.pro           CEVTHQGLSSPVTKSFNRGEC                          214
```

FIG. 6D

ES-Z

```
                  ---------+---------+---------+---------+---------+
                           10        20        30        40        50
                  ---------+---------+---------+---------+---------+
#1H31YC220A.pro   DVVMTQTPLSLSVTPGQPASISCKSSQSLLYSDG-KT-YLYWYLQKPGHS
#4.pro            DVVMTQTPLSLSVTPGEPASISCRSTQSLLDSDGVNP-SFDWYVQKPGQS
#7.pro            DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNG-YN-YLDWYLQKPGQS
#7RLI.pro         EIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNT-RN-YLDWYLQKPGQS
#10.pro           DVVMTQTPLSLSVTPGQPASISCKSSQSLLHSDG-KT-YFYWYLQRPGRS
#11.pro           DIVMTQTPLSLSVTPGQPASISCKSSQSLLHSDG-KT-YLYWYLQKPGQS
Z2F6.pro          DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNG-FN-YLDWYLQKPGQS
Z2F6C220A.pro     DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNG-FN-YLDWYLQKPGQS
C51.pro           EIVLTQSPATLSLSPGERATLSCRASQS------VSS-YLAWYQQKPGQA
C67.pro           EIVLTQSPGTLSLSPGERATLSCRASQS------VSSSNLAWYQQKPGQA
C82.pro           EIVLTQSPATLSLSPGERATLSCRASQS------VGP-FLAWYQQKPGQA
C88.pro           EIVLTQSPATLSLSPGERATLSCRASES------VSG-YLAWYQQKPGQA

                  ---------+---------+---------+---------+---------+
                           60        70        80        90        100
                  ---------+---------+---------+---------+---------+
#1H31YC220A.pro   PHLLIYEVSSRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQ--G
#4.pro            PQLLIHRGFYRASGVPDRFSGSGSGTDFTLRISRVEAEDVGVYYCMQ--R
#7.pro            PQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQ--A
#7RLI.pro         PQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQ--G
#10.pro           PQLLIQEVSRRFSGVPDRFSGSGSGSDFTLKISRVEAEDVGVYYCMQ--G
#11.pro           PQLLIYEVSSRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQ--G
Z2F6.pro          PQLLIYLGSTRASGVPDRFSGSGSGTDFTLRISRVEAEDVGVYFCMQ--A
Z2F6C220A.pro     PQLLIYLGSTRASGVPDRFSGSGSGTDFTLRISRVEAEDVGVYFCMQ--A
C51.pro           PRLLIYDASNRATGIPARFSGSGSGTDFTLTITSLEPEDFAVYYCQQ--R
C67.pro           PRLLIYGASSRATGIPDRFSGSGSGTDYTLTISRLEPEDFALYYCQQYGS
C82.pro           PRLLIYDTSTRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQ--R
C88.pro           PRLLIYEASNRATGIPARFSGSGSGPDFTLTISSLEPEDFAFYYCQQ--R
```

FIG. 6E

```
                 ---------+---------+---------+---------+---------+
                          110       120       130       140       150
                 ---------+---------+---------+---------+---------+
#1H31YC220A.pro  LHLP---QYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN
#4.pro           IEFP----LTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN
#7.pro           LQTP----RTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN
#7RLI.pro        LQTP----ITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN
#10.pro          TYVP----HTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN
#11.pro          IHLP----YTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN
22F6.pro         VQTP----FTFGPGTRLDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN
22F6C220A.pro    VQTP----FTFGPGTRLDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN
C51.pro          SDWP----LTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN
C67.pro          SLW------TFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN
C82.pro          YTWP--G-NSFGGGAKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN
C88.pro          SNWPPR--STFGQGTRLEMKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN

                 ---------+---------+---------+---------+---------+
                          160       170       180       190       200
                 ---------+---------+---------+---------+---------+
#1H31YC220A.pro  NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE
#4.pro           NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE
#7.pro           NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE
#7RLI.pro        NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE
#10.pro          NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE
#11.pro          NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE
22F6.pro         NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE
22F6C220A.pro    NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE
C51.pro          NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE
C67.pro          NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE
C82.pro          NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE
C88.pro          NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE
```

FIG. 6F

```
                  ---------+---------+-------
                           210       220
                  ---------+---------+-------
#1H31YC220A.pro   KHKLYACEVTHQGLSSPVTKSFNRGEA
#4.pro            KHKLYACEVTHQGLSSPVTKSFNRGEC
#7.pro            KHKLYACEVTHQGLSSPVTKSFNRGEC
#7RLI.pro         KHKLYACEVTHQGLSSPVTKSFNRGEC
#10.pro           KHKLYACEVTHQGLSSPVTKSFNRGEC
#11.pro           KHKLYACEVTHQGLSSPVTKSFNRGEC
22F6.pro          KHKVYACEVTHQGLSSPVTKSFNRGEC
22F6C220A.pro     KHKVYACEVTHQGLSSPVTKSFNRGEA
C51.pro           KHKVYACEVTHQGLSSPVTKSFNRGEC
C67.pro           KHKVYACEVTHQGLSSPVTKSFNRGEC
C82.pro           KHKVYACEVTHQGLSSPVTKSFNRGEC
C88.pro           KHKVYACEVTHQGLSSPVTKSFNRGEC
```

FIG. 6G

BxPC-3

```
                10        20        30        40        50
#4.pro      DVVMTQTPLSLSVTPGEPASISCRSTQSLLDSDGVNPSFDWYVQKPGQSP          50
#7G.pro     DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYN-YLDWYLQKPGQSP          49
#7EI.pro    EIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYN-YLDWYLQKPGQSP          49
#7RLI.pro   EIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNTRN-YLDWYLQKPGQSP          49
#7VL.pro    EIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNTRN-YLDWYLQKPGQSP          49
#13.pro     DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYN-YLDWYLQKPGQSP          49
#14.pro     DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYN-YLDWYLQKPGQSP          49
22F6.pro    DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGFN-YLDWYLQKPGQSP          49

                60        70        80        90        100
#4.pro      QLLIHRGFYRASGVPDRFSGSGSGTDFTLRISRVEAEDVGVYYCMQRIEF         100
#7G.pro     QLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGLQT          99
#7EI.pro    QLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQT          99
#7RLI.pro   QLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGLQT          99
#7VL.pro    QLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGLQT          99
#13.pro     QLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQT          99
#14.pro     QLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQT          99
22F6.pro    QLLIYLGSTRASGVPDRFSGSGSGTDFTLRISRVEAEDVGVYFCMQAVQT          99

                110       120       130       140       150
#4.pro      PL-TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE         149
#7G.pro     PR-TFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE         148
#7EI.pro    PR-TFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE         148
#7RLI.pro   PI-TFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE         148
#7VL.pro    PR-TFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE         148
#13.pro     PPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE         149
#14.pro     PR-TFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE         148
22F6.pro    PF-TFGPGTRLDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE         148

                160       170       180       190       200
#4.pro      AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKLYA         199
#7G.pro     AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKLYA         198
#7EI.pro    AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKLYA         198
#7RLI.pro   AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKLYA         198
#7VL.pro    AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKLYA         198
#13.pro     AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKLYA         199
#14.pro     AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKLYA         198
22F6.pro    AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA         198
```

FIG. 6H

```
          ---------+---------+-
                   210       220
          ---------+---------+-
#4.pro    CEVTHQGLSSPVTKSFNRGEC                                    220
#7G.pro   CEVTHQGLSSPVTKSFNRGEC                                    219
#7EI.pro  CEVTHQGLSSPVTKSFNRGEC                                    219
#7RLI.pro CEVTHQGLSSPVTKSFNRGEC                                    219
#7VL.pro  CEVTHQGLSSPVTKSFNRGEC                                    219
#13.pro   CEVTHQGLSSPVTKSFNRGEC                                    220
#14.pro   CEVTHQGLSSPVTKSFNRGEC                                    219
22F6.pro  CEVTHQGLSSPVTKSFNRGEC                                    219
```

FIG. 6I

```
B-16

          ---------+---------+---------+---------+---------+
                   10        20        30        40        50
          ---------+---------+---------+---------+---------+
#7.pro DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQ

          ---------+---------+---------+---------+---------+
                   60        70        80        90        100
          ---------+---------+---------+---------+---------+
#7.pro LLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTP

          ---------+---------+---------+---------+---------+
                   110       120       130       140       150
          ---------+---------+---------+---------+---------+
#7.pro RTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK

          ---------+---------+---------+---------+---------+
                   160       170       180       190       200
          ---------+---------+---------+---------+---------+
#7.pro VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKLYACE

          ---------+---------
                   210
          ---------+---------
#7.pro VTHQGLSSPVTKSFNRGEC
```

FIG. 7A

In vivo assay(via oral)

ADMINISTRATION METHOD	DOSE (mg/kg)	DOSING VOLUME (mg/ml)	ADMINISTERED SAMPLE CONCENTRATION (mg/ml)	No. OF ANIMALS	OBSERVATION PERIOD (DAYS)
SINGLE-DOSE ORAL ADMINISTRATION	33.2	20	1.66	3	7
SINGLE-DOSE ORAL ADMINISTRATION	0	20	0	3	7

FIG. 7B

FIG. 7C

DOSE (mg/kg)	MACROSCOPIC FINDINGS – FREE OF ABNORMALITIES				
	APPEARANCE	CRANIAL CAVITY	THORACIC CAVITY	ABDOMINAL CAVITY	LYMPH NODE
33.2	3/3	3/3	3/3	3/3	3/3
0	3/3	3/3	3/3	3/3	3/3

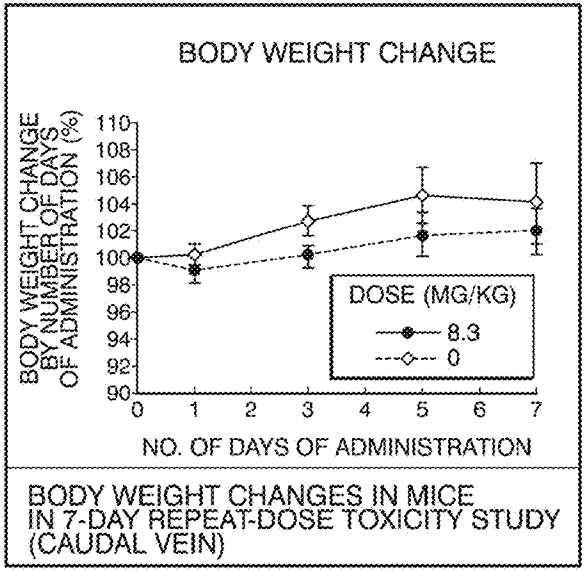
FIG. 8A

SAFETY STUDY OF HUMAN "SUPER ANTIBODY ENZYME" (TOXICITY STUDY)

1. SINGLE-DOSE ORAL DOSE STUDY (OBSERVATION PERIOD: 7 DAYS)
2. SINGLE-DOSE INTRAPERITONEAL ACUTE TOXICITY STUDY (OBSERVATION PERIOD: 7 DAYS)
3. SINGLE-DOSE INTRAVENOUS ACUTE TOXICITY STUDY (OBSERVATION PERIOD: 7 DAYS)
4. 7-DAY REPEAT-DOSE TOXICITY STUDY
5. SINGLE-DOSE INTRAVENOUS TOXICITY STUDY (OBSERVATION PERIOD: 28 DAYS)

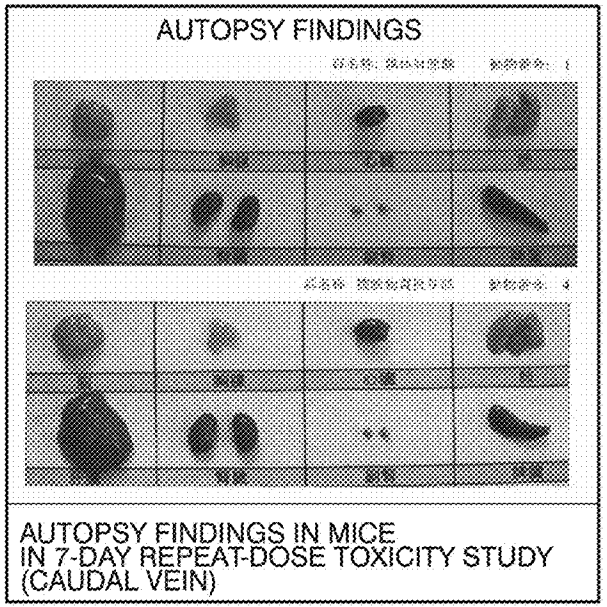
NO ABNORMALITIES IN ANY OF THE STUDY ANIMALS

FIG. 8B



BODY WEIGHT CHANGES IN MICE IN 7-DAY REPEAT-DOSE TOXICITY STUDY (CAUDAL VEIN)

FIG. 8C



AUTOPSY FINDINGS IN MICE IN 7-DAY REPEAT-DOSE TOXICITY STUDY (CAUDAL VEIN)

ANTICANCER AGENT

CROSS REFERENCE TO RELATED APPLICATIONS

This patent application is a divisional of co-pending U.S. application Ser. No. 14/383,118 having a § 371(c) (1), (2) date of Sep. 5, 2014, which is a U.S. national stage entry under 35 U.S.C. § 371 of International Patent Application No. PCT/JP2013/055927 filed on Mar. 5, 2013, which claims the benefit of foreign priority to Japanese Patent Application No. JP 2012-052334 filed on Mar. 8, 2012, the disclosures of all of which are hereby incorporated by reference in their entireties. The U.S. application Ser. No. 14/383,118 was published on Mar. 5, 2015, as US 2015/0064203 A1, and is now abandoned. The International Application was published in Japanese on Sep. 12, 2013, as International Publication No. WO 2013/133253 A1 under PCT Article 21(2).

INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC OR AS A TEXT FILE VIA THE OFFICE ELECTRONIC FILING SYSTEM (EFS-WEB)

The sequence listings disclosed in the ASCII text file submitted herewith, named "seqlist.txt" and created on Jan. 25, 2018, the size of which is 74,598 bytes, are hereby incorporated by reference.

TECHNICAL FIELD

The present invention relates to an anticancer agent containing a human antibody κ-type light chain that demonstrates cytotoxicity against cancer cells and particularly lung cancer cells.

The present application claims priority on the basis of Japanese Patent Application No. 2012-52334, filed in Japan on Mar. 8, 2012, the contents of which are incorporated herein by reference.

BACKGROUND ART

Antibodies are composed of heavy chains (H chains) and light chains (L chains). The heavy chains and light chains are composed of a variable region (VR) and a constant region (CR), and the variable region has a complementarity determining region (CDR). Moreover, antibody light chains are classified into κ chains and λ chains.

In recent years, attention has been focused on antibodies having an enzyme-like activity, namely, antibody enzymes. Since antibody enzymes have both the ability of antibodies to accurately recognize molecules and the activity of enzymes, they are expected to be applied in numerous fields, including medicine, the chemical industry and the food industry. In particular, since antibody enzymes exhibit high specificity for a target molecule and are able to impair target molecules due to their enzyme activity, they are expected to serve as superior anticancer agents that demonstrate few adverse side effects.

The inventors of the present invention have heretofore conducted various innovative research on antibody enzymes (see, for example, Patent Document 1). Antibody enzymes having complete human sequences have conventionally been unable to be obtained with the exception of the Bence-Jones Protein (BJP) obtained from multiple myeloma patients. Since there are few multiple myeloma patients and only a small amount of BJP that has enzyme activity, it was difficult to acquire a human antibody enzyme. However, since human antibody enzymes are predicted to demonstrate few adverse side effects when administered to a human body, pharmaceutical companies both at home and overseas are awaiting the development of a useful human antibody enzyme.

PRIOR ART DOCUMENTS

Patent Documents

Patent Document 1: Japanese Unexamined Patent Application, First Publication No. 2006-197930

DISCLOSURE OF THE INVENTION

Problems to be Solved by the Invention

An object of the present invention is to provide an anticancer agent that has for an active ingredient thereof a human antibody light chain that demonstrates cytotoxicity against cancer cells and particularly against lung cancer cells.

Means for Solving the Problems

The inventors of the present invention acquired a novel human antibody light chain from peripheral blood obtained from volunteers hyperimmunized over a plurality of times using a rabies vaccine virus, and as a result of studying those volunteers, surprisingly found that several of the resulting human antibody κ-type light chains demonstrated a high degree of cytotoxicity against cancer cells and particularly lung cancer cells, thereby leading to completion of the present invention.

Namely, the anticancer agent according to the present invention is characterized in that it contains:

(1) a human antibody κ-type light chain in the form of a dimer in which the variable region is composed of a polypeptide represented by the amino acid sequence of SEQ ID NO: 1, an amino acid sequence in which one or a plurality of the amino acids in that amino acid sequence have been substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence;

(2) a human antibody κ-type light chain in the form of a dimer in which the variable region is composed of a polypeptide represented by the amino acid sequence of SEQ ID NO: 7, an amino acid sequence in which one or a plurality of the amino acids in that amino acid sequence have been substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence;

(3) a human antibody κ-type light chain in the form of a dimer in which the variable region is composed of a polypeptide represented by the amino acid sequence of SEQ ID NO: 9, an amino acid sequence in which one or a plurality of the amino acids in that amino acid sequence have been substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence;

(4) a human antibody κ-type light chain in the form of a dimer in which the variable region is composed of a polypeptide represented by the amino acid sequence of SEQ ID NO: 13, an amino acid sequence in which one or a plurality of the amino acids in that amino acid sequence have been

substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence;

(5) a human antibody κ-type light chain in the form of a monomer in which the variable region is composed of a polypeptide represented by the amino acid sequence of SEQ ID NO: 19, an amino acid sequence in which one or a plurality of the amino acids in that amino acid sequence have been substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence;

(6) a human antibody κ-type light chain in the form of a monomer in which the variable region is composed of a polypeptide represented by an amino acid sequence consisting of the 1st to 113th amino acids of SEQ ID NO: 38, an amino acid sequence in which one or a plurality of the amino acids in that amino acid sequence have been substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence;

(7) a human antibody κ-type light chain in the form of a dimer in which the variable region is composed of a polypeptide represented by an amino acid sequence consisting of the 1st to 112th amino acids of SEQ ID NO: 40, an amino acid sequence in which one or a plurality of the amino acids in that amino acid sequence have been substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence; or

(8) a human antibody κ-type light chain in the form of a dimer in which the variable region is composed of a polypeptide represented by an amino acid sequence consisting of the 1st to 107th amino acids of SEQ ID NO: 41, an amino acid sequence in which one or a plurality of the amino acids in that amino acid sequence have been substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence.

Effects of the Invention

According to the present invention, an anticancer agent can be provided that is highly cytotoxic against cancer cells and particularly lung cancer cells. Since the anticancer agent of the present invention has an antibody enzyme for the active ingredient thereof, it is highly specific for cancer cells. Moreover, since the amino acid sequence of the antibody enzyme is completely human, it is free of problems such as allergies with respect to humans. Consequently, the anticancer agent of the present invention is extremely useful as a highly active, innovative and novel pharmaceutical and as a test piece for the development thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a diagram indicating amino acid sequences of wild type human antibody κ-type light chains. The amino acid sequences appearing in FIG. **1** correspond to the sequence ID numbers assigned in the sequence listing as follows.

#1-4(A18b) is SEQ ID NO: 1.
#2-3(A3/A19) is SEQ ID NO: 11.
#4-1(O2/O1) is SEQ ID NO: 9.
#7-2(A3/A19) is SEQ ID NO: 13.
#8-2(A18b) is SEQ ID NO: 3.
#9a-2(A18b) is SEQ ID NO: 5.
#11-1(A18b) is SEQ ID NO: 7.
#13-1(A3/A19) is SEQ ID NO: 15.
#14-1(A3/A19) is SEQ ID NO: 17.
22F6-4(A3/A19) is SEQ ID NO: 19.
23D4-1(A3/A19) is SEQ ID NO: 21.

FIG. **2**A schematically indicates a cDNA design for obtaining a monomer human antibody light chain. The nucleotide sequences appearing in FIG. **2**A correspond to the sequence ID numbers assigned in the sequence listing as follows.

The upper nucleotide sequence is SEQ ID NO: 55.
The lower nucleotide sequence is SEQ ID NO: 56.

FIG. **2**B schematically indicates the compositions of a human antibody light chain prior to introduction of a mutation and a human antibody light chain following introduction of a mutation.

FIG. **3**A is a diagram indicating the results of newly carrying out primary purification of a polypeptide of clone #1, and more particularly, is a diagram indicating the results of Ni-NTA column chromatography.

FIG. **3**B is a diagram indicating the results of newly carrying out primary purification of a polypeptide of clone #1, and more particularly, is a stained image of SDS-PAGE analysis.

FIG. **3**C is a diagram indicating the results of newly carrying out secondary purification of the polypeptide of clone #1, and more particularly, is a diagram indicating the results of cation exchange chromatography.

FIG. **3**D is a diagram indicating the results of newly carrying out secondary purification of the polypeptide of clone #1, and more particularly, is a stained image of SDS-PAGE analysis.

FIG. **4** is a graph indicating the results of investigating the cytotoxicity of various clones against cancer cells.

FIG. **5** is a graph indicating the results of investigating the cytotoxicity of various clones against cancer cells.

FIG. **6**A is a diagram indicating the amino acid sequences of wild type human antibody κ-type light chains. The amino acid sequences appearing in FIG. **6**A correspond to the sequence ID numbers assigned in the sequence listing as follows.

#1H31YC220A.pro is SEQ ID NO: 38.
#7VL(I).pro is SEQ ID NO: 39.
#7RLI.pro is SEQ ID NO: 40.
C51.pro is SEQ ID NO: 41.
C87.pro is SEQ ID NO: 42.

FIG. **6**B is a diagram indicating the amino acid sequences of wild type human antibody κ-type light chains.

FIG. **6**C is a diagram indicating the amino acid sequences of wild type human antibody κ-type light chains continuing from FIG. **6**B.

The amino acid sequences appearing in FIG. **6**B and FIG. **6**C correspond to the sequence ID numbers assigned in the sequence listing as follows.

#1H31YC220A.pro is SEQ ID NO: 38.
#4.pro is SEQ ID NO: 10.
#7EI.pro is SEQ ID NO: 43.
#7TR.pro is SEQ ID NO: 44.
#7RLI.pro is SEQ ID NO: 40.
#7VL.pro is SEQ ID NO: 45.
S13.pro is SEQ ID NO: 46.
S21.pro is SEQ ID NO: 47.
S38.pro is SEQ ID NO: 48.
C51.pro is SEQ ID NO: 41.

FIG. **6**D is a diagram indicating the amino acid sequences of wild type human antibody κ-type light chains.

FIG. **6**E is a diagram indicating the amino acid sequences of wild type human antibody κ-type light chains continuing from FIG. **6**D.

FIG. **6**F is a diagram indicating the amino acid sequences of wild type human antibody κ-type light chains continuing from FIG. **6**E.

The amino acid sequences appearing in FIG. **6**D, FIG. **6**E, and FIG. **6**F correspond to the sequence ID numbers assigned in the sequence listing as follows.

#1H31YC220A.pro is SEQ ID NO: 38.
#4.pro is SEQ ID NO: 10.
#7.pro is SEQ ID NO: 14.
#7RLI.pro is SEQ ID NO: 40.
#10.pro is SEQ ID NO: 49.
#11.pro is SEQ ID NO: 8.
22F6.pro is SEQ ID NO: 20.
22F6C220A.pro is SEQ ID NO: 54.
C51.pro is SEQ ID NO: 41.
C67.pro is SEQ ID NO: 50.
C82.pro is SEQ ID NO: 51.
C88.pro is SEQ ID NO: 52.

FIG. **6**G is a diagram indicating the amino acid sequences of wild type human antibody κ-type light chains.

FIG. **6**H is a diagram indicating the amino acid sequences of wild type human antibody κ-type light chains continuing from FIG. **6**G.

The amino acid sequences appearing in FIG. **6**G and FIG. **6**H correspond to the sequence ID numbers assigned in the sequence listing as follows.

#4.pro is SEQ ID NO: 10.
#7G.pro is SEQ ID NO: 53.
#7EI.pro is SEQ ID NO: 43.
#7RLI.pro is SEQ ID NO: 40.
#7VL.pro is SEQ ID NO: 45.
#13.pro is SEQ ID NO: 16.
#14.pro is SEQ ID NO: 18.
22F6.pro is SEQ ID NO: 20.

FIG. **6**I is a diagram indicating the amino acid sequence of a wild type human antibody κ-type light chain. The amino acid sequence ("#7.pro") appearing in FIG. **6**I corresponds to SEQ ID NO: 14 assigned in the sequence listing.

FIG. **7**A is a diagram indicating the results of an in vivo assay, and more particularly, indicating the condition of a single-dose oral administration study in animals.

FIG. **7**B is a diagram indicating the results of an in vivo assay, and more particularly, indicating the body weight change in animals in the single-dose oral administration study.

FIG. **7**C is a diagram indicating the results of an in vivo assay, and more particularly, indicating the macroscopic findings in animals in the single-dose oral administration study.

FIG. **8**A is a diagram indicating the results of safety studies (toxicity studies), and more particularly, indicating the toxicity studies conducted in order to confirm the safety to human.

FIG. **8**B is a diagram indicating the results of safety studies (toxicity studies), and more particularly, indicating the body weight change in mice in the 7-day repeat-dose toxicity study (caudal vein).

FIG. **8**C is a diagram indicating the results of safety studies (toxicity studies), and more particularly, indicating the autopsy findings in mice in the 7-day repeat-dose toxicity study (caudal vein).

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention provides an anticancer agent containing a human antibody κ-type light chain that demonstrates cytotoxicity against cancer cells. In the description of the present application, a "human antibody κ-type light chain" refers to a κ-type light chain of human-derived immunoglobulin.

In the description of the present application, an "anticancer agent" refers to a pharmaceutical agent having an activity that eradicates cancer cells or suppresses or inhibits the proliferation thereof.

In addition, in the description of the present application, "cytotoxicity" refers to a property that induces cell death or causes functional impairment in cells.

More specifically, the active ingredient of the anticancer agent according to the present invention in the form of a human antibody κ-type light chain (to also be referred to as the "human antibody κ-type light chain according to the present invention") is any of those described in (1) to (8) below.

(1) A human antibody κ-type light chain in the form of a dimer in which the variable region is composed of a polypeptide represented by the amino acid sequence of SEQ ID NO: 1, an amino acid sequence in which one or a plurality of the amino acids in that amino acid sequence have been substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence.

(2) A human antibody κ-type light chain in the form of a dimer in which the variable region is composed of a polypeptide represented by the amino acid sequence of SEQ ID NO: 7, an amino acid sequence in which one or a plurality of the amino acids in that amino acid sequence have been substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence.

(3) A human antibody κ-type light chain in the form of a dimer in which the variable region is composed of a polypeptide represented by the amino acid sequence of SEQ ID NO: 9, an amino acid sequence in which one or a plurality of the amino acids in that amino acid sequence have been substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence.

(4) A human antibody κ-type light chain in the form of a dimer in which the variable region is composed of a polypeptide represented by the amino acid sequence of SEQ ID NO: 13, an amino acid sequence in which one or a plurality of the amino acids in that amino acid sequence have been substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence.

(5) A human antibody κ-type light chain in the form of a monomer in which the variable region is composed of a polypeptide represented by the amino acid sequence of SEQ ID NO: 19, an amino acid sequence in which one or a plurality of the amino acids in that amino acid sequence have been substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence.

(6) A human antibody κ-type light chain in the form of a monomer in which the variable region is composed of a polypeptide represented by an amino acid sequence consisting of the 1st to 113th amino acids of SEQ ID NO: 38, an amino acid sequence in which one or a plurality of the amino acids in that amino acid sequence have been substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence.

(7) A human antibody κ-type light chain in the form of a dimer in which the variable region is composed of a poly-

peptide represented by an amino acid sequence consisting of the 1st to 112th amino acids of SEQ ID NO: 40, an amino acid sequence in which one or a plurality of the amino acids in that amino acid sequence have been substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence.

(8) A human antibody κ-type light chain in the form of a dimer in which the variable region is composed of a polypeptide represented by an amino acid sequence consisting of the 1st to 107th amino acids of SEQ ID NO: 41, an amino acid sequence in which one or a plurality of the amino acids in that amino acid sequence have been substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence.

The human antibody κ-type light chain in the form of a dimer in which the variable region is composed of a polypeptide represented by the amino acid sequence of SEQ ID NO: 1 may also be referred to as human antibody κ-type light chain (#1). The human antibody κ-type light chain (#1) can have a known human antibody constant region added to the aforementioned variable region, and in one embodiment, the entire length of the amino acid sequence is as shown in SEQ ID NO: 2. CDR1 in the human antibody κ-type light chain (#1) consists of the 24th to 39th amino acids in the amino acid sequences of SEQ ID NO: 1 and SEQ ID NO: 2, CDR2 consists of the 55th to 61st amino acids in the amino acid sequences of SEQ ID NO: 1 and SEQ ID NO: 2, and CDR3 consists of the 94th to 102nd amino acids in the amino acid sequences of SEQ ID NO: 1 and SEQ ID NO: 2.

A cysteine residue for forming a disulfide bond is present in a wild type antibody κ-type light chain that results in the formation of a dimer. The human antibody κ-type light chain (#1) also has a cysteine residue for forming a disulfide bond with another light chain in the same manner as the wild type. For example, in the case the human antibody κ-type light chain (#1) is composed of a polypeptide represented by the amino acid sequence of SEQ ID NO: 2, then the cysteine residue is the cysteine residue at position 220 in the amino acid sequence of SEQ ID NO: 2.

As will be subsequently indicated in the examples, the human antibody κ-type light chain (#1) demonstrates cytotoxicity against cancer cells and particularly lung cancer cells. Consequently, it is preferable for use as an active ingredient of an anticancer agent. Since the ability to accurately recognize a target molecule is important for the human antibody κ-type light chain (#1) to demonstrate anticancer activity, the active center of the anticancer activity of the human antibody κ-type light chain (#1) is in the variable region.

Being able to easily modify several amino acids among amino acid residues composing a polypeptide without having a significant effect on the structure or function of the polypeptide is commonly known in the art. Moreover, in addition to artificial modification, mutants are also commonly known to exist in naturally-occurring proteins that do not cause a significant change in the structure or function of that protein. Furthermore, in the description of the present application, the substitution, addition or deletion of one or a plurality of amino acids in a specific amino acid sequence X is referred to as mutation.

The human antibody κ-type light chain according to the present invention may form a dimer in which the variable region is composed of a polypeptide represented by an amino acid sequence in which one or a plurality of amino acids in the amino acid sequence of SEQ ID NO: 1 have been substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence. This polypeptide may also be referred to as a mutant of the human antibody κ-type light chain (#1). A mutant of the human antibody κ-type light chain (#1) may also be composed of a polypeptide represented by an amino acid sequence in which one or a plurality of amino acids other than the cysteine at position 220 in the amino acid sequence of SEQ ID NO: 2 have been substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence.

A mutant of the human antibody κ-type light chain (#1) used as the human antibody κ-type light chain according to the present invention is a dimer having an anticancer action in the same manner as the human antibody κ-type light chain (#1). Consequently, CDR1, CDR2 and CDR3 of a mutant of the human antibody κ-type light chain (#1) are identical to the amino acid sequence of SEQ ID NO:1 or SEQ ID NO: 2 (are preserved therein), and the cysteine corresponding to cysteine at position 220 in the amino acid sequence of SEQ ID NO: 2 is also preserved. In other words, a mutant of the human antibody κ-type light chain (#1) is preferably such that amino acids in regions other than CDR1, CDR2 and CDR3 are mutated and amino acids in other regions of the variable region are mutated.

A human antibody κ-type light chain in the form of a dimer in which the variable region is composed of a polypeptide represented by the amino acid sequence of SEQ ID NO: 9 may also be referred to as human antibody κ-type light chain (#4). The human antibody κ-type light chain (#4) can have a known human antibody constant region added to the aforementioned variable region, and in one embodiment, the entire length of the amino acid sequence is as shown in SEQ ID NO: 10. CDR1 in the human antibody κ-type light chain (#4) consists of the 24th to 40th amino acids in the amino acid sequences of SEQ ID NO: 9 and SEQ ID NO: 10, CDR2 consists of the 56th to 62nd amino acids in the amino acid sequences of SEQ ID NO: 9 and SEQ ID NO: 10, and CDR3 consists of the 95th to 102nd amino acids in the amino acid sequences of SEQ ID NO: 9 and SEQ ID NO: 10. In addition, a cysteine residue for forming a disulfide bond with another light chain is the cysteine residue at position 220 in the amino acid sequence of SEQ ID NO: 10.

As will be subsequently indicated in the examples, the human antibody κ-type light chain (#4) demonstrates cytotoxicity against cancer cells and particularly lung cancer cells. Consequently, it is preferable for use as an active ingredient of an anticancer agent.

The human antibody κ-type light chain according to the present invention may form a dimer in which the variable region is composed of a polypeptide represented by an amino acid sequence in which one or a plurality of amino acids in the amino acid sequence of SEQ ID NO: 9 have been substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence. This polypeptide may also be referred to as a mutant of the human antibody κ-type light chain (#4). A mutant of the human antibody κ-type light chain (#4) may also be composed of a polypeptide represented by an amino acid sequence in which one or a plurality of amino acids other than the cysteine at position 220 in the amino acid sequence of SEQ ID NO: 10 have been substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence.

A mutant of the human antibody κ-type light chain (#4) used as the human antibody κ-type light chain according to the present invention is a dimer having an anticancer action in the same manner as the human antibody κ-type light chain (#4). Consequently, CDR1, CDR2 and CDR3 of a mutant of

the human antibody κ-type light chain (#4) are identical to the amino acid sequence of SEQ ID NO:9 or SEQ ID NO: 10 (are preserved therein), and the cysteine corresponding to cysteine at position 220 in the amino acid sequence of SEQ ID NO: 10 is also preserved. In other words, a mutant of the human antibody κ-type light chain (#4) is preferably such that amino acids in regions other than CDR1, CDR2 and CDR3 are mutated and amino acids in other regions of the variable region are mutated.

A human antibody κ-type light chain in the form of a dimer in which the variable region is composed of a polypeptide represented by the amino acid sequence of SEQ ID NO: 13 may also be referred to as human antibody κ-type light chain (#7). The human antibody κ-type light chain (#7) can have a known human antibody constant region added to the aforementioned variable region, and in one embodiment, the entire length of the amino acid sequence is as shown in SEQ ID NO: 14. CDR1 in the human antibody κ-type light chain (#7) consists of the 24th to 39th amino acids in the amino acid sequences of SEQ ID NO: 13 and SEQ ID NO: 14, CDR2 consists of the 55th to 61st amino acids in the amino acid sequences of SEQ ID NO: 13 and SEQ ID NO: 14, and CDR3 consists of the 94th to 101st amino acids in the amino acid sequences of SEQ ID NO: 13 and SEQ ID NO: 14. In addition, a cysteine residue for forming a disulfide bond with another light chain is the cysteine residue at position 219 in the amino acid sequence of SEQ ID NO: 14.

As will be subsequently indicated in the examples, the human antibody κ-type light chain (#7) demonstrates cytotoxicity against cancer cells and particularly lung cancer cells. Consequently, it is preferable for use as an active ingredient of an anticancer agent.

The human antibody κ-type light chain according to the present invention may form a dimer in which the variable region is composed of a polypeptide represented by an amino acid sequence in which one or a plurality of amino acids in the amino acid sequence of SEQ ID NO: 13 have been substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence. This polypeptide may also be referred to as a mutant of the human antibody κ-type light chain (#7). A mutant of the human antibody κ-type light chain (#7) may also be composed of a polypeptide represented by an amino acid sequence in which one or a plurality of amino acids other than the cysteine at position 219 in the amino acid sequence of SEQ ID NO: 14 have been substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence.

A mutant of the human antibody κ-type light chain (#7) used as the human antibody κ-type light chain according to the present invention is a dimer having an anticancer action in the same manner as the human antibody κ-type light chain (#7). Consequently, CDR1, CDR2 and CDR3 of a mutant of the human antibody κ-type light chain (#7) are identical to the amino acid sequence of SEQ ID NO:13 or SEQ ID NO: 14 (are preserved therein), and the cysteine corresponding to cysteine at position 219 in the amino acid sequence of SEQ ID NO: 14 is also preserved. In other words, a mutant of the human antibody κ-type light chain (#7) is preferably such that amino acids in regions other than CDR1, CDR2 and CDR3 are mutated and amino acids in other regions of the variable region are mutated.

A human antibody κ-type light chain in the form of a monomer in which the variable region is composed of a polypeptide represented by the amino acid sequence of SEQ ID NO: 19 may also be referred to as human antibody κ-type light chain (22F6_monomer). The human antibody κ-type light chain (22F6_monomer) can have a known human antibody constant region added to the aforementioned variable region, and in one embodiment, the entire length of the amino acid sequence is represented by an amino acid sequence in which the 219th cysteine in the amino acid sequence of SEQ ID NO: 20 has been deleted or substituted with another amino acid (such as alanine). CDR1 in the human antibody κ-type light chain (22F6_monomer) consists of the 24th to 39th amino acids in the amino acid sequences of SEQ ID NO: 19 and SEQ ID NO: 20, CDR2 consists of the 55th to 61st amino acids in the amino acid sequences of SEQ ID NO: 19 and SEQ ID NO: 20, and CDR3 consists of the 94th to 101st amino acids in the amino acid sequences of SEQ ID NO: 19 and SEQ ID NO: 20.

As will be subsequently indicated in the examples, the human antibody κ-type light chain (22F6_monomer) demonstrates cytotoxicity against cancer cells and particularly lung cancer cells. Consequently, it is preferable for use as an active ingredient of an anticancer agent.

The human antibody κ-type light chain according to the present invention may be a monomer in which the variable region is composed of a polypeptide represented by an amino acid sequence in which one or a plurality of amino acids in the amino acid sequence of SEQ ID NO: 20 have been substituted, added or deleted, or an amino acid sequence having homology of 95% or more with that amino acid sequence. This polypeptide may also be referred to as a mutant of the human antibody κ-type light chain (22F6_monomer). A mutant of the human antibody κ-type light chain (22F6_monomer) may also be composed of a polypeptide represented by an amino acid sequence in which the 219th cysteine has been deleted or substituted with another amino acid and one or a plurality of amino acids other than the amino acid at position 219 have been substituted, added or deleted in the amino acid sequence of SEQ ID NO: 20, or an amino acid sequence having homology of 95% or more with that amino acid sequence.

A mutant of the human antibody κ-type light chain (22F6_monomer) used as the human antibody κ-type light chain according to the present invention is a monomer having an anticancer action in the same manner as the human antibody κ-type light chain (22F6_monomer). Consequently, CDR1, CDR2 and CDR3 of a mutant of the human antibody κ-type light chain (22F6_monomer) are identical to the amino acid sequence of SEQ ID NO: 19 or SEQ ID NO: 20 (are preserved therein), and the cysteine corresponding to cysteine at position 219 in the amino acid sequence of SEQ ID NO: 20 is deleted or substituted with another amino acid. In other words, a mutant of the human antibody κ-type light chain (22F6_monomer) is preferably such that amino acids in regions other than CDR1, CDR2 and CDR3 are mutated and amino acids in other regions of the variable region are mutated.

In addition, the human antibody κ-type light chain according to the present invention may also contain an additional polypeptide. Typical examples of additional polypeptides include epitope-tagged polypeptides such as those tagged with His tag, Myc or Flag.

A person with ordinary skill in the art is able to easily mutate one or a plurality of amino acids among amino acid residues that compose a polypeptide or add an epitope-tagged polypeptide using a known technology. For example, an arbitrary base of a polynucleotide that encodes a polypeptide can be mutated in accordance with a known point mutagenesis method. In addition, a primer corresponding to

an arbitrary site of a polynucleotide that encodes a polypeptide can be designed to create a deletion mutant or an addition mutant.

The human antibody κ-type light chain according to the present invention includes a naturally-occurring purification product, a product obtained by a chemical synthesis procedure, and a product produced by recombination technology from a prokaryotic host or eukaryotic host (including bacterial cells, yeast cells, higher plant cells, insect cells and mammalian cells). The human antibody κ-type light chain may or may not be glycosylated depending on the host used in the recombinant production procedure. Moreover, the human antibody κ-type light chain according to the present invention can contain a modified initiating methionine group in several cases as a result of a host intervention process.

Although the human antibody κ-type light chain according to the present invention may be a polypeptide in which amino acids are linked by peptide bonds, it is not limited thereto, and the polypeptide may also be a composite polypeptide containing a structure other than that of a polypeptide. As used in the present description, although examples of a "structure other than that of a polypeptide" include sugar chains and isoprenoid groups, there are no particular limitations thereon.

The human antibody κ-type light chain according to the present invention can be produced using an expression system known in the art, such as a recombination expression system or a cell-free expression system, by using a vector containing a polynucleotide encoding the human antibody κ-type light chain (polypeptide).

In the case of using a recombination expression system, a method can be employed having the steps of, for example, incorporating a polynucleotide encoding the human antibody κ-type light chain according to the present invention into a recombination expression vector followed by introducing into a host enabling expression thereof according to a known method, translating within the host (transformant) and purifying the resulting polypeptide. The recombination expression vector may or may not be a plasmid, and is only required to enable the target polynucleotide to be introduced into the host.

In the case of introducing an exogenous polynucleotide into a host in this manner, a promoter that functions in the host so as to express exogenous polynucleotides is preferably incorporated into the expression vector. Although the method used to purify the recombinantly produced polypeptide varies according to the properties of the host and polypeptide used, a target polypeptide can be purified comparatively easily using a tag and the like.

In the case of using a cell-free expression system (cell-free protein synthesis system), a polynucleotide encoding the human antibody κ-type light chain according to the present invention is preferably added to a solution containing components such as ribosomes or t-RNA required for protein translation and synthesis followed by incubating at a suitable temperature and purifying the synthesized polypeptide.

Examples of cell-free protein synthesis systems include systems using wheat germ extract, systems using rabbit reticulocyte extract, systems using *E. coli* S30 extract and systems using cell component extracts obtained from plant devacuolated protoplasts. In general, although eukaryotic cell systems, namely, systems using wheat germ extract or systems using rabbit reticulocyte extract, are selected for translation of eukaryotic genes, the aforementioned synthesis system is selected in consideration of such factors as the origin of the gene to be translated (prokaryotic or eukaryotic) or the purpose for which the protein is to be used following synthesis. Various commercially available kits can be used for these synthesis systems.

Furthermore, since various viral gene products frequently express activity by going through a complex biochemical reaction involving the cytomembrane, such as the endoplasmic reticulum or Golgi bodies, following translation, it is necessary to add cytomembrane components (such as microsomal membrane) in order to reproduce the various biochemical reactions in vitro. Cell component extracts obtained from plant devacuolated protoplasts are preferable since they can be used as a cell-free protein synthesis liquid that retains cytomembrane components, thereby eliminating the need to add microsomal membrane.

As used in the present description, "cytomembrane components" are intended to refer to cell organelles composed of lipid membrane present in the cytomembrane (namely, all types of intracellular granules such as endoplasmic reticulum, Golgi bodies, mitochondria, chloroplast and vacuoles). In particular, since endoplasmic reticulum and Golgi bodies fulfill an important role in post-translation modification of proteins, they are essential cell components for maturation of membrane proteins and secretory proteins.

Human antibody κ-type light chain synthesized with a host expression system or a cell-free protein synthesis system is preferably purified. Although a step for purifying human antibody κ-type light chain is preferably a step in which a cell extract is prepared from cells or tissue using a known method (such as a method in which the cells or tissue is homogenized, followed by centrifuging and recovering the soluble fraction), followed by purifying the human antibody κ-type light chain from this cell extract using a known method (such as ammonium sulfate precipitation or ethanol precipitation, acid extraction, anionic or cationic chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxyapatite chromatography or lectin chromatography), it is not limited thereto. High-performance liquid chromatography (HPLC) is most preferably used for purification.

In addition, the human antibody κ-type light chain according to the present invention can also be purified from cells or tissues that express the human antibody κ-type light chain in nature. For example, cells or tissues that express the human antibody κ-type light chain according to the present invention in nature can be identified using an antibody or an oligonucleotide. Purification of a human antibody κ-type light chain from cells or tissue can also be carried out in the same manner as in the case of purifying a human antibody κ-type light chain synthesized using a host expression system and the like.

In addition, the human antibody κ-type light chain according to the present invention can also be chemically synthesized. There are no particular limitations on the chemical synthesis method, and may be carried out by any method used when chemically synthesizing polypeptides.

The anticancer agent according to the present invention has the human antibody κ-type light chain according to the present invention as an active ingredient thereof. Although the mechanism of action by which the human antibody κ-type light chain according to the present invention demonstrates cytotoxicity against cancer cells has not been completely determined, it is presumed that, as a result of the human antibody κ-type light chain according to the present invention specifically recognizing and binding to a specific molecule or structure on the surface of cancer cells simultaneous to decomposing a portion of the components of

cancer cells by utilizing its own enzyme activity, the function of the cancer cells is impaired, proliferation thereof is inhibited or cell death is induced.

The anticancer agent according to the present invention can be injected or administered directly for use in humans or animals. The anticancer agent according to the present invention can also be formulated for parenteral administration, mucosal administration, intramuscular administration, intravenous administration, subcutaneous administration, intraocular administration or transcutaneous administration. Typically, protein contained in a composition can be administered at a dose of 0.01 mg/kg to 30 mg/kg of body weight, preferably at 0.1 mg/kg to 10 mg/kg of body weight, and even more preferably at 0.1 mg/kg to 1 mg/kg of body weight.

The anticancer agent according to the present invention can also contain a pharmaceutically acceptable carrier, diluent or vehicle (including combinations thereof) in addition to the human antibody κ-type light chain according to the present invention. Pharmaceutically acceptable carriers or vehicles for therapeutic use are commonly known in the field of pharmacy, and are described in, for example, Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro, ed., 1985). Pharmaceutically usable carriers, vehicles or diluents can be suitably selected by a person with ordinary skill in the art in accordance with the intended administration route and standard pharmaceutical practices. In addition, the anticancer agent according to the present invention can further contain an arbitrary suitable binder, lubricant, suspension agent, coating agent or solubilizing agent.

Conditions required for composition and/or formulation can vary depending on the use of different delivery systems. As an example thereof, the anticancer agent according to the present invention can be formulated so as to be delivered using a minipump, by a mucosal route in the form of, for example, a nasal spray or aerosol for inhalation, or for parenteral delivery (here, the anticancer agent according to the present invention is formulated in an injectable form for delivery via, for example, an intravenous route, an intramuscular route or a subcutaneous route). Alternatively, the formula can be designed so as to be delivered by both routes. For example, the anticancer agent according to the present invention demonstrates a high level of cytotoxicity against lung cancer cells in particular. Consequently, the anticancer agent according to the present invention is preferably in the form of a nasal spray or aerosol for inhalation that enables it to be efficiently delivered to pneumocytes from the nose or bronchi.

In addition, in the case of using the anticancer agent according to the present invention in an application in which it is administered into the body, various technologies can be used for improving the stability (half-life in blood) of the active ingredient in the form of the human antibody κ-type light chain in the body. For example, the half-life in the blood of antibodies such as IgG is known to be prolonged if neonatal Fc receptor (FcRn) is bound to the Fc region (see, for example, Roopenian, D. C., et al., Nat. Rev. Immunol., Vol. 7, 715-725 (2007)), and the C-terminal of the human antibody κ-type light chain according to the present invention can be modified so as to have binding activity with FcRn. In addition, the human antibody κ-type light chain according to the present invention can be in the form of a dimer, and polyethylene glycol (PEG) can be added as well.

The anticancer agent according to the present invention can be incorporated in a kit, for example, together with instructions and the like on the form in which it is to be administered. The kit can also contain various other pharmaceuticals that can be used with the anticancer agent according to the present invention.

In addition, since the anticancer agent according to the present invention has for the active ingredient thereof an antibody κ-type light chain that is highly effective in recognizing a target molecule, it does not demonstrate cytotoxicity against cancer cells in which the target molecule of the antibody light chain is not present on the cell surface thereof. Consequently, the anticancer agent of the present invention is expected to be useful in distinguishing types of cancer.

EXAMPLES

Although the following provides a more detailed explanation of the present invention through examples thereof, the present invention is not limited by these examples.

Example 1

(1. Preparation of Human Peripheral Blood cDNA)

Lymphocytes were isolated using Ficoll-paque from peripheral blood acquired from volunteers hyperimmunized over a plurality of times using rabies virus vaccine. Total RNA was obtained from roughly 3.0×10^7 isolated lymphocytes using an RNA extraction kit (Stratagene Corp.). The target cDNA (cDNA library) was then prepared by reverse transcribing the total RNA with the ThermoScript RT-PCT System (Invitrogen Inc.) using oligo(dT) as primer.

(2. Acquisition of Human Antibody κ-Type Light Chain Genes)

PCR reactions were carried out in two stages using the cDNA acquired in step 1 above as template and using primers for amplifying antibody light chain gene having a Vκ gene belonging to subgroup II to obtain roughly 750 bp PCR products (κ-type light chain genes belonging to subgroup II). These PCR products were cloned and subjected to sequence analysis, and the Vκ gene in each germline gene was estimated by a homology search. As a result, all of the resulting 18 clones belonged to subgroup II. Among these, nine clones, namely, clone #1 (germline genotype: A18b), clone #2 (germline genotype: A3/A19), clone #4 (germline genotype: 011/o1), clone #7 (germline genotype: A3/A19), clone #8 (germline genotype: A18b), clone #9 (germline genotype: A18b), clone #11 (germline genotype: A18b), clone #13 (germline genotype: A3/A19) and clone #14 (germline genotype: A3/A19) were used in subsequent experimentation.

(3. Expression of Human Antibody κ-Type Light Chains)

Each of the clones acquired in step 2 above was respectively introduced into a plasmid vector having an His tag sequence site followed by introducing the plasmid vector into *Escherichia coli* to produce transformants. When each transformant was cultured and subjected to induction of expression with IPTG, the protein expressed in the *E. coli* was able to be identified as a human antibody light chain by SDS-PAGE analysis and Western blotting using anti-human $(Fab')_2$ antibody. The resulting human antibody light chains had M (initiating methionine) on the N-terminal and LEHHHHHH (SEQ ID NO: 23) derived from the plasmid vector on the C-terminal.

(4. Preparation of Human Peripheral Blood cDNA)

Subjects were hyperimmunized over a plurality of times using rabies virus vaccine followed by measurement of serum neutralizing activity. Peripheral blood was collected from the donor subject having the highest level of serum

neutralizing activity (7.21 U), and lymphocytes were isolated from the peripheral blood using Ficoll-paque. Total RNA was then obtained from roughly 3.0×10^7 isolated lymphocytes using an RNA extraction kit (Stratagene Corp.). cDNA to be used as template was prepared in a PCR reaction to be subsequently described by reverse transcribing the total RNA with the ThermoScript RT-PCR System (Invitrogen Inc.) using oligo(dT) as primer.

(5. Acquisition of Human Antibody κ-Type Light Chain Genes)

A PCR reaction was carried out using a primer set for comprehensively amplifying human antibody light chain gene and using the cDNA acquired in step 4 above as template to obtain a roughly 660 bp PCR product. This PCR product was purified and inserted into the *E. coli* expression vector pET101/D-TOPO® (Invitrogen Inc.) to construct an LCA library. Furthermore, protein in which an His tag was added to the C-terminal of the protein encoded by the PCR product was expressed from an expression vector in which the PCR product was inserted in the pET101/D-TOPO vector. PCR reactions were carried out using the cDNA of this LCA library as template and using primers for amplifying human antibody light chain gene having a Vκ gene belonging to subgroup II to obtain roughly 660 bp PCR products. These PCR products were cloned and subjected to sequence analysis and their amino acid sequences and light chain variable and constant regions were estimated using analytical software (Genetix® Ver. 8) followed by estimation of the Vκ gene in each germline gene. Among these clones, two clones, namely, clone 22F6 (germline genotype: A3/A19) and clone 23D4 (germline genotype: A3/A19) were used in subsequent experimentation. The resulting human antibody light chains had M (initiating methionine) on the N-terminal and LEHHHHHH (SEQ ID NO: 23) derived from the plasmid vector on the C-terminal.

As a result of sequencing each clone, the total length of the human antibody light chain pertaining to clone #1 (human antibody light chain (#1_WT)) was the base sequence indicated in SEQ ID NO: 27, the total length of the human antibody light chain pertaining to clone #8 (human antibody light chain (#8_WT)) was the base sequence indicated in SEQ ID NO: 28, the total length of the human antibody light chain pertaining to clone #9 (human antibody light chain (#9_WT)) was the base sequence indicated in SEQ ID NO: 29, the total length of the human antibody light chain pertaining to clone #11 (human antibody light chain (#11_WT)) was the base sequence indicated in SEQ ID NO: 30, the total length of the human antibody light chain pertaining to clone #4 (human antibody light chain (#4_WT)) was the base sequence indicated in SEQ ID NO: 31, the total length of the human antibody light chain pertaining to clone #2 (human antibody light chain (#2 WT)) was the base sequence indicated in SEQ ID NO: 32, the total length of the human antibody light chain pertaining to clone #7 (human antibody light chain (#7_WT)) was the base sequence indicated in SEQ ID NO: 33, the total length of the human antibody light chain pertaining to clone #13 (human antibody light chain (#13_WT)) was the base sequence indicated in SEQ ID NO: 34, the total length of the human antibody light chain pertaining to clone #14 (human antibody light chain (#14_WT)) was the base sequence indicated in SEQ ID NO: 35, the total length of the human antibody light chain pertaining to clone 22F6 (human antibody light chain (22F6_WT)) was the base sequence indicated in SEQ ID NO: 36, and the total length of the human antibody light chain pertaining to clone 23D4 (human antibody light chain (23D4 WT)) was the base sequence indicated in SEQ ID NO: 37.

The amino acid sequences estimated from each of the base sequences are shown in FIG. **1**. In addition, the locations of the variable regions, constant regions and CDR1 to CDR3 are also shown. The human antibody light chain pertaining to clone #1 (human antibody light chain (#1_WT)) was the amino acid sequence shown in SEQ ID NO: 2, the human antibody light chain pertaining to clone #8 (human antibody light chain (#8_WT)) was the amino acid sequence shown in SEQ ID NO: 4, the human antibody light chain pertaining to clone #9 (human antibody light chain (#9_WT)) was the amino acid sequence shown in SEQ ID NO: 6, the human antibody light chain pertaining to clone #11 (human antibody light chain (#11_WT)) was the amino acid sequence shown in SEQ ID NO: 8, the human antibody light chain pertaining to clone #4 (human antibody light chain (#4_WT)) was the amino acid sequence shown in SEQ ID NO: 10, the human antibody light chain pertaining to clone #2 (human antibody light chain (#2_WT)) was the amino acid sequence shown in SEQ ID NO: 12, the human antibody light chain pertaining to clone #7 (human antibody light chain (#7_WT)) was the amino acid sequence shown in SEQ ID NO: 14, the human antibody light chain pertaining to clone #13 (human antibody light chain (#13_WT)) was the amino acid sequence shown in SEQ ID NO: 16, the human antibody light chain pertaining to clone #14 (human antibody light chain (#14_WT)) was the amino acid sequence shown in SEQ ID NO: 18, the human antibody light chain pertaining to clone 22F6 (human antibody light chain (22F6_WT)) was the amino acid sequence shown in SEQ ID NO: 20, and the human antibody light chain pertaining to clone 23D4 (human antibody light chain (23D4_WT)) was the amino acid sequence shown in SEQ ID NO: 22.

Furthermore, the wild type human antibody light chains used in the present example were polypeptides in which methionine was added to the N-terminal of each amino acid sequence shown in FIG. **1** and LEHHHHHH (SEQ ID NO: 23) derived from the plasmid vector was added to the C-terminal.

(6. Production of Monomer Human Antibody Light Chains)

The human antibody κ-type light chains of the clones acquired in steps 2 and 5 above formed dimers due to the formation of disulfide (S—S) bonds by cysteine on the C-terminal. Then, cDNA was designed so as to form only monomer human antibody enzymes by introducing a mutation in which the cysteine involved in S—S bond formation (cysteine on the C-terminal of the amino acid sequences of FIG. **1**) is substituted with alanine. The details of this design with respect to the human antibody light chain having LEHHHHHH derived from the plasmid vector on the C-terminal thereof (#1_WT) are shown in FIGS. **2**A and **2**B. As shown in FIG. **2**A, TGT encoding cysteine at position 220 in the full-length human antibody enzyme gene is substituted with GCT. As a result, as shown in FIG. **2**B, although a dimer is formed in the original amino acid sequence due to the presence of cysteine at position 220, S—S bonds are not formed in the substituted amino acid sequence as a result of substituting alanine at position 220, thereby resulting in a monomer.

More specifically, TGT encoding the aforementioned cysteine in the wild-type full-length human antibody enzyme gene was substituted with GCTCTCGAGCACCACCACCACCACCACTGA (SEQ ID NO: 26) that encodes ALE-

HHHHHH (SEQ ID NO: 25) (having a stop codon). In other words, the monomer human antibody light chain used in the present example was a polypeptide in which methionine was added to the N-terminal of each amino acid sequence shown in FIG. **1** and ALEHHHHHH was added to the C-terminal instead of cysteine. Furthermore, among those mutants obtained in this manner, in which the cysteine involved in S—S bonding was substituted with alanine, the mutant of human antibody light chain (#1_WT) is referred to as the human antibody light chain(#1_C220A), the mutant of human antibody light chain (#8_WT) is referred to as the human antibody light chain(#8_C220A), the mutant of human antibody light chain (#9_WT) is referred to as the human antibody light chain(#9_C220A), the mutant of human antibody light chain (#11_WT) is referred to as the human antibody light chain(#11_C220A), the mutant of human antibody light chain (#4_WT) is referred to as the human antibody light chain(#4_C220A), the mutant of human antibody light chain (#2 WT) is referred to as the human antibody light chain(#2_C220A), the mutant of human antibody light chain (#7_WT) is referred to as the human antibody light chain(#7_C220A), the mutant of human antibody light chain (#13_WT) is referred to as the human antibody light chain(#13_C220A), the mutant of human antibody light chain (#14_WT) is referred to as the human antibody light chain(#14_C220A), the mutant of human antibody light chain (22F6_WT) is referred to as the human antibody light chain(22F6_C220A) and the mutant of human antibody light chain (23D4_WT) is referred to as the human antibody light chain(23D4_C220A).

(7. Purification of Human Antibody Light Chains)

Each of the human antibody light chains was subjected to primary purification and secondary purification in the manner described below. FIG. **3**A is a diagram indicating the results of Ni-NTA column chromatography and FIG. **3**B is a stained image of SDS-PAGE analysis during primary purification of human antibody light chain (#1_WT) and human antibody light chain (#1_C220A). FIG. **3**C is a diagram indicating the results of cation exchange chromatography and FIG. **3**D is a stained image of SDS-PAGE analysis during secondary purification.

As shown in FIG. **3**A, buffer A (25 mM Tris-HCl (pH 8.0), 0.25 M NaCl, 40 mM imidazole and 0.005% Tween 20) was passed through the column after applying the sample until all the flow-through fraction had passed through the column. As indicated by the broken line in the graph on the left side, the concentration of imidazole was increased gradually from 40 mM to 300 mM to elute a component bound to the gel. An Ni-NTA agarose column (diameter: 1 cm, 2 ml) was used for the column and the flow rate was maintained at 0.1 mL/min throughout purification. As shown in FIG. **3**B, a target band of roughly 31 kDa was detected in fractions 30 to 37. These samples were combined and subjected to the secondary purification indicated below.

As shown in FIG. **3**C, buffer A (50 mM sodium acetate (pH 5.4), 0.2 M NaCl and 0.005% Tween 20) was passed through the column after applying the sample until all the flow-through fraction had passed through the column. As indicated by the broken line in the graph on the left side, the concentration of NaCl was increased gradually from 0.2 M to 0.4 M to elute a component bound to the gel. The SP5PW column (Tosho Corp.) was used for the column and the flow rate was maintained at 0.1 ml/min throughout purification. Components contained in the sample prior to purification, the region "a" surrounded by broken lines in the graph (fraction numbers 10 to 15) and the region "c" surrounded by broken lines in the graph (fraction numbers 25 to 30) were analyzed by SDS-PAGE. As shown in FIG. **3**D, a target band of roughly 31 kDa was detected in regions "a" and "c" in the reduced sample. In addition, in the unreduced sample, a roughly 31 kDa band was detected only in region "a" while a roughly 51 kDa band was detected only in region "c". As has been described above, the monomer of the antibody light chain is roughly 31 kDa and the dimer is roughly 51 kDa. Sample a is the monomer fraction of the antibody light chain while sample c is the dimer fraction of the antibody light chain.

The other clones also contained dimers and monomers in the expression products of the wild-type human antibody light chains in the same manner as clone (#1), dimers were purified by two-stage purification utilizing Ni-NTA column chromatography and cation exchange chromatography, monomers were contained in the expression products of mutants in which cysteine involved in S—S bonding had been mutated to alanine, and the monomers were purified by the same two-stage purification.

(8. Cytotoxicity Against Cancer Cells)

A test was conducted of the cytotoxicity of various human antibody κ-type light chains against cancer cells. Human alveolar adenocarcinoma cell line A549 purchased from ATCC was used for the cancer cells, and the cells were cultured in accordance with routine methods using F-12K medium containing 10% fetal calf serum (FCS).

First, after thawing and recovering frozen A549 cells, 100 μl aliquots of the cells were disseminated in a 96-well plate to a concentration of 5×10^3 cells/well. After culturing for 24 hours at 37° C. and removing the medium added to the 96-well plate by decantation, each human antibody κ-type light chain adjusted to a concentration of about 1 mg/mL was added in 100 μL aliquots to each well. 10 μl aliquots of WST-1 reagent (Roche Diagnostics GmbH) were added to each well at 24 hours and 48 hours after adding the human antibody κ-type light chains (48 hours and 72 hours after disseminating the cells), followed by measurement of absorbance of the formasan pigment formed (Abs 450 nm) 1, 1.5 and 2 hours later. Cell viability was determined in each well based on the resulting absorbance results using a value of 100% for cell viability in a well to which a human antibody κ-type light chain was not added (N.C.) followed by evaluation of cytotoxicity of the added human antibody κ-type light chains.

Cell viability at 24 hours and 48 hours after adding human antibody κ-type light chain is shown in FIG. **4**, FIG. **5**, Table 1 and Table 2 for each of the human antibody κ-type light chains. The results for the clones having a germline genotype of A18b or 011/ol are shown in FIG. **4** and Table 1, and the results for the clones having a germline genotype of A3/A19 are shown in FIG. **5** and Table 2. In addition, Tables 1 and 2 also indicate the concentrations of the human antibody κ-type light chains in the wells.

TABLE 1

Clone	Concentration in well (μM)	Cell viability (%) After 24 hr	Cell viability (%) After 48 hr
#1_WT	44	60	60
#1 C220A	40	72	75
#8 WT	29	79	81
#8 C220A	38	96	93
#9 WT	20	78	75
#9 C220A	40	86	84
#11 WT	28	73	80
#11 C220A	44	95	94

TABLE 1-continued

Clone	Concentration in well (μM)	Cell viability (%) After 24 hr	Cell viability (%) After 48 hr
#4 WT	20	50	54
#4 C220A	44	96	93

TABLE 2

Clone	Concentration in well (μM)	Cell viability (%) After 24 hr	Cell viability (%) After 48 hr
#2 WT	27	81	86
#2 C220A	40	94	95
#7 WT	35	49	53
#7 C220A	40	92	93
#13 WT	40	101	101
#13 C220A	56	97	81
#14 WT	32	100	94
#14 C220A	40	89	88
22F6 WT	62	80	92
22F6 C220A	32	65	64
23D4 WT	28	83	85
23D4 C220A	44	96	92

As a result, the four clones consisting of clone (#1_WT), clone (#4_WT), clone (#7 WT) and clone (22F6_C220A) demonstrated cytotoxicity on the order of 40% to 50% against A549 cells. Other clones were observed to hardly demonstrate any cytotoxicity against A549 cells.

Among these four clones, clone (#4_WT) and clone (#7_WT) demonstrated particularly potent cytotoxicity. Among these, clone (#7_WT), namely, human antibody κ-type light chain (#7), was suggested to have an effect that suppresses proliferation of A549 cells since there were hardly any changes in the number of cells in the wells between prior to addition of the human antibody κ-type light chain (0 hours) and after addition of the human antibody κ-type light chain (48 hours).

In addition, on the basis of the results for the clones used in this test, potent cytotoxicity was suggested to be present in dimers since it was observed that dimers (WT) have a tendency to demonstrate more potent cytotoxicity than monomers.

In addition, cytotoxicity of human antibody κ-type light chain against various cell lines was evaluated in the same manner as described above while also including other clones. Those results are shown in Table 3.

TABLE 3

Cell type	Clone	Cell viability (%) 24 hr after addition	Cell viability (%) 48 hr after addition
A549	#1 H31Y C220A	72	53
	#7 VL(I)	77	82
	#7 RLI	74	90
	C51	78	87
	C87	75	65
MOLT-4	#1 H31Y C220A	57.1	60.2
	#4 wt	73.8	90.6
	#7 EI	87	80.2
	#7 TR	93.2	74.1
	#7 RLI	55	73
	#7 VL	77.3	84.2
	S13	75.3	108
	S21	78.2	91.3
	S38	77.3	85.5
	C51	59.4	63
ES-2	#1 H31Y C220A	59.9	72.7
	#4	83.9	93.3
	#7 wt	98.3	98.6
	#7 RLI	100	94.8
	#10	79.9	92.4
	#11	57	78.8
	22F6	63.1	89
	22F6 C220A	53.2	67.4
	C51	71.2	70.7
	C67	69.7	76.1
	C82	62.2	72.7
	C88	78.1	76.6
BxPC	#4	58	63.3
	#7 G	88.3	71.9
	#7 EI	80.5	69.9
	#7 RLI	87.9	77.3
	#7 VL	77.7	75.9
	#13	120.4	67.6
	#14	116.6	69.3
	22F6	115.2	65.5
B-16	#7 wt	85	92

As a result, clone (#1_H31Y C220A) demonstrated a high level of cytotoxicity against A549 cells, MOLT-4 cells and ES-2 cells. In addition, clone (#7 RLI) and clone (C51) demonstrated a high level of cytotoxicity against MOLT-4 cells. Moreover, clone (#4) demonstrated a high level of cytotoxicity against ES-2 cells.

Furthermore, the amino acid sequence of clone (#1_H31Y C220A) is shown in SEQ ID NO: 38, the amino acid sequence of clone (#7 VL(I)) is shown in SEQ ID NO: 39, the amino acid sequence of clone (#7 RLI) is shown in SEQ ID NO: 40, the amino acid sequence of clone (C51) is shown in SEQ ID NO: 41, the amino acid sequence of clone (C87) is shown in SEQ ID NO: 42, the amino acid sequence of clone (#7 EI) is shown in SEQ ID NO: 43, the amino acid sequence of clone (#7 TR) is shown in SEQ ID NO: 44, the amino acid sequence of clone (#7 VL) is shown in SEQ ID NO: 45, the amino acid sequence of clone (S13) is shown in SEQ ID NO: 46, the amino acid sequence of clone (S21) is shown in SEQ ID NO: 47, the amino acid sequence of clone (S38) is shown in SEQ ID NO: 48, the amino acid sequence of clone (#10) is shown in SEQ ID NO: 49, the amino acid sequence of clone (C67) is shown in SEQ ID NO: 50, the amino acid sequence of clone (C82) is shown in SEQ ID NO: 51, the amino acid sequence of clone (C88) is shown in SEQ ID NO: 52, and the amino acid sequence of clone (#7 G) is shown in SEQ ID NO: 53.

In addition, as shown in FIGS. **7** and **8**, the anticancer agent containing the human antibody κ-type light chain of the present application did not demonstrate any toxicity in animal studies. FIG. **7** and FIG. **8** show the results of administering human antibody κ-type light chain of the present invention to animals and mice. FIG. **7**A shows a condition of a single-dose oral administration study in animals. FIG. **7**B shows the body weight change in animals in the single-dose oral administration study. FIG. **7**C shows the macroscopic findings in animals in the single-dose oral administration study. FIG. **8**A shows the toxicity study

conducted in order to confirm the safety to human. FIG. **8**B shows the body weight change in mice in the 7-day repeat-dose toxicity study (caudal vein). FIG. **8**C shows the autopsy findings in mice in the 7-day repeat-dose toxicity study (caudal vein).

INDUSTRIAL APPLICABILITY

The present invention allows the development of a novel anticancer agent and the use thereof in the field of cancer treatment.

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Asp Gly Lys Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly His Ser
         35                  40                  45

Pro His Leu Leu Leu Tyr Glu Val Ser Ser Arg Phe Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
                 85                  90                  95

Leu His Leu Pro Gln Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
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Lys
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Asp Gly Lys Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly His Ser
         35                  40                  45

Pro His Leu Leu Leu Tyr Glu Val Ser Ser Arg Phe Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
                 85                  90                  95

Leu His Leu Pro Gln Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
            100                 105                 110

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
        115                 120                 125

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
    130                 135                 140

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
145                 150                 155                 160

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
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Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
            180                 185                 190

Glu Lys His Lys Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
        195                 200                 205

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
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<213> ORGANISM: human

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Gln Pro Ala Ser Leu Ser Cys Lys Ser Ser Gln Ser Leu Leu His Ser
             20                  25                  30

Asp Gly Lys Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Ser
         35                  40                  45

Pro Gln Leu Leu Ile Tyr Glu Val Ser Ser Arg Phe Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Glu Gly
                 85                  90                  95

Thr His Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


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Gln Pro Ala Ser Leu Ser Cys Lys Ser Ser Gln Ser Leu Leu His Ser
             20                  25                  30

Asp Gly Lys Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Ser
         35                  40                  45

Pro Gln Leu Leu Ile Tyr Glu Val Ser Ser Arg Phe Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Glu Gly
                 85                  90                  95

Thr His Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
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                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


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Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu His Ser
             20                  25                  30

Asp Gly Lys Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Ser
         35                  40                  45

Pro Gln Leu Leu Ile Tyr Glu Val Ser Ser Arg Phe Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
                 85                  90                  95

Ile His Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110


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Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu His Ser
             20                  25                  30

Asp Gly Lys Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Ser
         35                  40                  45

Pro Gln Leu Leu Ile Tyr Glu Val Ser Ser Arg Phe Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
                 85                  90                  95

Ile His Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
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Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
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<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 7

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Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu His Ser
             20                  25                  30

Asp Gly Lys Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Ser
         35                  40                  45

Pro Gln Leu Leu Leu Tyr Glu Val Ser Ser Arg Phe Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
                 85                  90                  95

Ile His Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110


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Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu His Ser
             20                  25                  30

Asp Gly Lys Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Ser
         35                  40                  45

Pro Gln Leu Leu Leu Tyr Glu Val Ser Ser Arg Phe Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
                 85                  90                  95

Ile His Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
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Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
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Lys His Lys Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
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Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
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             20                  25                  30

Asp Gly Val Asn Pro Ser Phe Asp Trp Tyr Val Gln Lys Pro Gly Gln
         35                  40                  45

Ser Pro Gln Leu Leu Ile His Arg Gly Phe Tyr Arg Ala Ser Gly Val
     50                  55                  60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg
 65                  70                  75                  80

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln
                 85                  90                  95

Arg Ile Glu Phe Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Leu
            100                 105                 110

Lys


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             20                  25                  30

Asp Gly Val Asn Pro Ser Phe Asp Trp Tyr Val Gln Lys Pro Gly Gln
         35                  40                  45

Ser Pro Gln Leu Leu Ile His Arg Gly Phe Tyr Arg Ala Ser Gly Val
     50                  55                  60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg
 65                  70                  75                  80

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln
                 85                  90                  95

Arg Ile Glu Phe Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Leu
            100                 105                 110

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
        115                 120                 125

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
    130                 135                 140

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
145                 150                 155                 160
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Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
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Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
            180                 185                 190

Glu Lys His Lys Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
        195                 200                 205

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
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         35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Ile Arg Ala Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Gln Leu Lys Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Asp Asp Val Gly Ile Tyr Tyr Cys Met Gln Ala
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Gln Gln Gly Pro Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
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Asn Gly Asn Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
         35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Ile Arg Ala Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Gln Leu Lys Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Asp Asp Val Gly Ile Tyr Tyr Cys Met Gln Ala
                 85                  90                  95

Gln Gln Gly Pro Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160
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Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
               165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
           180                 185                 190

Lys His Lys Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
       195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
   210                 215


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         35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65                  70                  75                  80

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         35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                 85                  90                  95

Leu Gln Thr Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
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Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160
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Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
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Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
           180                 185                 190

Lys His Lys Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
       195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> SEQ ID NO 15
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 15

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
  1               5                  10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
             20                  25                  30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
         35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                 85                  90                  95

Leu Gln Thr Pro Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
            100                 105                 110

Lys


<210> SEQ ID NO 16
<211> LENGTH: 220
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 16

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
  1               5                  10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
             20                  25                  30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
         35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                 85                  90                  95

Leu Gln Thr Pro Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
            100                 105                 110

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
        115                 120                 125

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
    130                 135                 140
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Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
145                 150                 155                 160

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
                165                 170                 175

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
            180                 185                 190

Glu Lys His Lys Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
        195                 200                 205

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215                 220


<210> SEQ ID NO 17
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 17

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
  1               5                  10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
             20                  25                  30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
         35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                 85                  90                  95

Leu Gln Thr Pro Arg Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110


<210> SEQ ID NO 18
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 18

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
  1               5                  10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
             20                  25                  30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
         35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                 85                  90                  95

Leu Gln Thr Pro Arg Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140
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Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> SEQ ID NO 19
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 19

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
  1               5                  10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
             20                  25                  30

Asn Gly Phe Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
         35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Thr Arg Ala Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Phe Cys Met Gln Ala
                 85                  90                  95

Val Gln Thr Pro Phe Thr Phe Gly Pro Gly Thr Arg Leu Asp Ile Lys
            100                 105                 110


<210> SEQ ID NO 20
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 20

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
  1               5                  10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
             20                  25                  30

Asn Gly Phe Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
         35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Thr Arg Ala Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Phe Cys Met Gln Ala
                 85                  90                  95

Val Gln Thr Pro Phe Thr Phe Gly Pro Gly Thr Arg Leu Asp Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140
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Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> SEQ ID NO 21
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 21

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
  1               5                  10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
             20                  25                  30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
         35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                 85                  90                  95

Leu Gln Thr Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


<210> SEQ ID NO 22
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 22

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
  1               5                  10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
             20                  25                  30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
         35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                 85                  90                  95

Leu Gln Thr Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140
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```
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> SEQ ID NO 23
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:Artificially
      Synthesized Sequence

<400> SEQUENCE: 23

Leu Glu His His His His His His
  1               5


<210> SEQ ID NO 24
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:Artificially
      Synthesized Seqence

<400> SEQUENCE: 24

ctcgagcacc accaccacca ccactga                                          27


<210> SEQ ID NO 25
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:Artificially
      Synthesized Sequence

<400> SEQUENCE: 25

Ala Leu Glu His His His His His His
  1               5


<210> SEQ ID NO 26
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:Artificially
      Synthesized Seqence

<400> SEQUENCE: 26

gctctcgagc accaccacca ccaccactga                                       30


<210> SEQ ID NO 27
<211> LENGTH: 660
<212> TYPE: DNA
<213> ORGANISM: human

<400> SEQUENCE: 27

gatattgtga tgacccagac tccactctct ctgtccgtca cccctggaca gccggcctcc      60
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atctcctgca agtctagtca gagcctcctg catagtgatg gaaagaccta tttgtattgg 120

tacctgcaga agccaggcca ctctccacat ctcctaatct atgaggtttc cagccggttc 180

tctggagtgc cagataggtt cagtggcagc gggtcaggga cagatttcac actgaaaatc 240

agccgggtgg aggctgagga tgttggggtt tattactgca tgcaaggttt acaccttcct 300

cagtacactt ttggccaggg gaccaagctg gagatcaaac gaactgtggc tgcaccatct 360

gtcttcatct tcccgccatc tgatgagcag ttgaaatctg gaactgcctc tgttgtgtgc 420

ctgctgaata acttctatcc cagagaggcc aaagtacagt ggaaggtgga taacgccctc 480

caatcgggta actcccagga gagtgtcaca gagcaggaca gcaaggacag cacctacagc 540

ctcagcagca ccctgacgct gagcaaagca gactacgaga aacacaaact ctacgcctgc 600

gaagtcaccc atcagggcct gagctcgccc gtcacaaaga gcttcaacag gggagagtgt 660

<210> SEQ ID NO 28
<211> LENGTH: 657
<212> TYPE: DNA
<213> ORGANISM: human

<400> SEQUENCE: 28

gatgttgtga tgacccagac tccactctct ctgtccgtca cccctgggca gccggcctcc 60

ctctcctgca agtctagtca gagcctcctg catagtgatg gaaagaccta tttgtattgg 120

tacctgcaga agccaggcca gtctccacaa ctcctaatct atgaagtttc cagccggttc 180

tctggagtgc cagataggtt cagtggcagc gggtcaggga cagatttcac actgaaaatc 240

agccgcgtgg aggctgagga tgttggagtt tattactgta tggaaggtac acaccttccg 300

tggacgttcg gccaagggac caaggtggaa atcaaacgaa ctgtggctgc accatctgtc 360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaactcta cgcctgcgaa 600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt 657

<210> SEQ ID NO 29
<211> LENGTH: 657
<212> TYPE: DNA
<213> ORGANISM: human

<400> SEQUENCE: 29

gatgttgtga tgacccagac tccactctct ctgtccgtca cccctggaca gccggcctcc 60

atctcctgca agtctagtca gagcctcctg catagtgatg gaaagaccta tttgtattgg 120

tacctgcaga agccaggcca gtctccacag ctcctaatct atgaagtttc cagccggttc 180

tctggagtgc cagataggtt cagtggcagc gggtcaggga cagatttcac actgaaaatc 240

agccgggtgg aggctgagga tgttggggtt tattactgca tgcaaggtat acaccttccg 300

tacacttttg gccaggggac caagctggag atcaaacgaa ctgtggctgc accatctgtc 360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaactcta cgcctgcgaa 600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt 657

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<210> SEQ ID NO 30
<211> LENGTH: 657
<212> TYPE: DNA
<213> ORGANISM: human

<400> SEQUENCE: 30

gatattgtga tgacccagac tccactctct ctgtccgtca cccctggaca gccggcctcc 60

atctcctgca agtctagtca gagcctcctg catagtgatg gaaagaccta tttgtattgg 120

tacctgcaga agccaggcca gtctccacag ctcctaatct atgaagtttc cagccggttc 180

tctggagtgc cagataggtt cagtggcagc gggtcaggga cagatttcac actgaaaatc 240

agccgggtgg aggctgagga tgttggggtt tattactgca tgcaaggtat acaccttccg 300

tacacttttg gccaggggac caagctggag atcaaacgaa ctgtggctgc accatctgtc 360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaactcta cgcctgcgaa 600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt 657

<210> SEQ ID NO 31
<211> LENGTH: 660
<212> TYPE: DNA
<213> ORGANISM: human

<400> SEQUENCE: 31

gatgttgtga tgacccagac tccactctcc ctgtccgtca cccctggaga gccggcctcc 60

atctcctgca ggtctactca gagcctcttg gatagtgatg gtgtaaaccc ctctttcgac 120

tggtatgtac agaagccagg gcagtctcca caactcctga ttcatagagg tttctatcgg 180

gcctctggag tcccagacag gttcagtggc agtgggtcag gcactgattt cacactgagg 240

atcagcaggg tggaggctga ggatgttgga gtctattact gcatgcaacg catagagttt 300

cctctcactt tcggcggagg gaccaaggtg gagatcaagc gaactgtggc tgcaccatct 360

gtcttcatct tcccgccatc tgatgagcag ttgaaatctg gaactgcctc tgttgtgtgc 420

ctgctgaata acttctatcc cagagaggcc aaagtacagt ggaaggtgga taacgccctc 480

caatcgggta actcccagga gagtgtcaca gagcaggaca gcaaggacag cacctacagc 540

ctcagcagca ccctgacgct gagcaaagca gactacgaga aacacaaact ctacgcctgc 600

gaagtcaccc atcagggcct gagctcgccc gtcacaaaga gcttcaacag gggagagtgt 660

<210> SEQ ID NO 32
<211> LENGTH: 657
<212> TYPE: DNA
<213> ORGANISM: human

<400> SEQUENCE: 32

gatgttgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60

atctcctgca ggtctagtca gagcctcctg tatgggaatg gaaacaacta tttggattgg 120

tacctgcaga agccaggaca gtctccacag ctcctgatct atttgggttc tattcgggcc 180

tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagatttcca actgaaaatc 240

agcagagtgg aggctgacga tgttgggatt tattactgca tgcaagctca acaaggtccg 300

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cccactttcg gcggagggac caaggtggag atcaaacgaa ctgtggctgc accatctgtc 360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaactcta cgcctgcgaa 600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt 657

<210> SEQ ID NO 33
<211> LENGTH: 657
<212> TYPE: DNA
<213> ORGANISM: human

<400> SEQUENCE: 33

gatgttgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60

atctcctgca ggtctagtca gagcctcctg catagtaatg gatacaacta tttggattgg 120

tacctgcaga agccagggca gtctccacag ctcctgatct atttgggttc taatcgggcc 180

tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240

agcagagtgg aggctgagga tgttggggtt tattactgca tgcaagctct acaaactcct 300

cgtacgttcg gccaagggac caaggtggaa atcaaacgaa ctgtggctgc accatctgtc 360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaactcta cgcctgcgaa 600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt 657

<210> SEQ ID NO 34
<211> LENGTH: 660
<212> TYPE: DNA
<213> ORGANISM: human

<400> SEQUENCE: 34

gatgttgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60

atctcctgca ggtctagtca gagcctcctg catagtaatg gatacaacta tttggattgg 120

tacctgcaga agccagggca gtctccacag ctcctgatct atttgggttc taatcgggcc 180

tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240

agcagagtgg aggctgagga tgttggggtt tattactgca tgcaagctct acaaactcct 300

ccgtggacgt tcggccaagg gaccaaggtg gaaatcaaac gaactgtggc tgcaccatct 360

gtcttcatct tcccgccatc tgatgagcag ttgaaatctg gaactgcctc tgttgtgtgc 420

ctgctgaata acttctatcc cagagaggcc aaagtacagt ggaaggtgga taacgccctc 480

caatcgggta actcccagga gagtgtcaca gagcaggaca gcaaggacag cacctacagc 540

ctcagcagca ccctgacgct gagcaaagca gactacgaga aacacaaact ctacgcctgc 600

gaagtcaccc atcagggcct gagctcgccc gtcacaaaga gcttcaacag gggagagtgt 660

<210> SEQ ID NO 35
<211> LENGTH: 657
<212> TYPE: DNA
<213> ORGANISM: human

<400> SEQUENCE: 35

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gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60

atctcctgca ggtctagtca gagcctcctg catagtaatg gatacaacta tttggattgg 120

tacctgcaga agccagggca gtctccacag ctcctgatct atttgggttc taatcgggcc 180

tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240

agcagagtgg aggctgagga tgttggggtt tattactgca tgcaagctct acaaactcct 300

cggacttttg gccaggggac caagctggag atcaaacgaa ctgtggctgc accatctgtc 360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaactcta cgcctgcgaa 600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt 657

<210> SEQ ID NO 36
<211> LENGTH: 657
<212> TYPE: DNA
<213> ORGANISM: human

<400> SEQUENCE: 36

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60

atctcctgca ggtctagtca gagcctcctg catagtaatg gattcaacta tttggattgg 120

tatctgcaga agccagggca gtctccacag ctcctgatct atttgggttc tactcgggcc 180

tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgagaatc 240

agcagagtgg aggctgagga tgttggggtt tatttctgca tgcaagctgt ccaaactcct 300

ttcactttcg gccctgggac cagactggat atcaaacgaa ctgtggctgc accatctgtc 360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt 657

<210> SEQ ID NO 37
<211> LENGTH: 657
<212> TYPE: DNA
<213> ORGANISM: human

<400> SEQUENCE: 37

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60

atctcctgca ggtctagtca gagcctcctg catagtaatg gatacaacta tttggattgg 120

tacctgcaga agccagggca gtctccacag ctcctgatct atttgggttc taatcgggcc 180

tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240

agcagagtgg aggctgagga tgttggggtt tattactgca tgcaagctct acaaactccc 300

tggacgttcg gccaagggac caaggtggaa atcaaacgaa ctgtggctgc accatctgtc 360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

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agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt 657

<210> SEQ ID NO 38
<211> LENGTH: 220
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 38

Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
20 25 30

Asp Gly Lys Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly His Ser
35 40 45

Pro His Leu Leu Ile Tyr Glu Val Ser Ser Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
85 90 95

Leu His Leu Pro Gln Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
100 105 110

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
115 120 125

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
130 135 140

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
145 150 155 160

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
165 170 175

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
180 185 190

Glu Lys His Lys Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
195 200 205

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Ala
210 215 220

<210> SEQ ID NO 39
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 39

Glu Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Thr Arg Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
85 90 95

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Leu Gln Thr Pro Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> SEQ ID NO 40
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 40

Glu Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
  1               5                  10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
             20                  25                  30

Asn Thr Arg Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
         35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
                 85                  90                  95

Leu Gln Thr Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> SEQ ID NO 41
<211> LENGTH: 214
<212> TYPE: PRT
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<213> ORGANISM: human

<400> SEQUENCE: 41

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asp Trp Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> SEQ ID NO 42
<211> LENGTH: 213
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 42

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Phe Ser Cys Arg Ala Ser Gln Ser Leu Ser Ser Tyr
20 25 30

Val Ala Trp Tyr Gln Lys Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Thr Ser Thr Arg Ala Ala Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Gly Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Cys Ala Val Tyr Tyr Cys Gln Arg Arg Ala Thr Pro Tyr Thr
85 90 95

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg Thr Val Ala Ala Pro
100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys

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    130                 135                 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165                 170                 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Arg Val Tyr Ala
            180                 185                 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
        195                 200                 205

Asn Arg Gly Glu Cys
    210


<210> SEQ ID NO 43
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 43

Glu Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
  1               5                  10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
             20                  25                  30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
         35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                 85                  90                  95

Leu Gln Thr Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> SEQ ID NO 44
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 44

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
  1               5                  10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
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            20                  25                  30

Asn Thr Arg Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

Leu Gln Thr Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> SEQ ID NO 45
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 45

Glu Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
  1               5                  10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30

Asn Thr Arg Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
                85                  90                  95

Leu Gln Thr Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175
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Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> SEQ ID NO 46
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 46

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
  1               5                  10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
             20                  25                  30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
         35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Asp Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65                  70                  75                  80

Ser Ser Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                 85                  90                  95

Leu Glu Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> SEQ ID NO 47
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 47

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
  1               5                  10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
             20                  25                  30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
         35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
     50                  55                  60
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Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                 85                  90                  95

Leu Gln Thr Pro Arg Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> SEQ ID NO 48
<211> LENGTH: 218
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 48

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
  1               5                  10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
             20                  25                  30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
         35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                 85                  90                  95

Leu Gln Thr Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
            100                 105                 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
        115                 120                 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
    130                 135                 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145                 150                 155                 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
            180                 185                 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
        195                 200                 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215
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<210> SEQ ID NO 49
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 49

Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asp Gly Lys Thr Tyr Phe Tyr Trp Tyr Leu Gln Arg Pro Gly Arg Ser
35 40 45

Pro Gln Leu Leu Ile Gln Glu Val Ser Arg Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Ser Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
85 90 95

Thr Tyr Val Pro His Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> SEQ ID NO 50
<211> LENGTH: 215
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 50

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Asn Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Leu Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Leu
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

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Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
        115                 120                 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
                165                 170                 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
            180                 185                 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
        195                 200                 205

Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> SEQ ID NO 51
<211> LENGTH: 215
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 51

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
  1               5                  10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Gly Pro Phe
             20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
         35                  40                  45

Tyr Asp Thr Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
     50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
 65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Tyr Thr Trp Pro Gly
                 85                  90                  95

Asn Ser Phe Gly Gly Gly Ala Lys Val Glu Ile Lys Arg Thr Val Ala
            100                 105                 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
        115                 120                 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
                165                 170                 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
            180                 185                 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
        195                 200                 205

Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> SEQ ID NO 52
<211> LENGTH: 216
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 52
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Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
  1               5                  10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val Ser Gly Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
         35                  40                  45

Tyr Glu Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
     50                  55                  60

Ser Gly Ser Gly Pro Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
 65                  70                  75                  80

Glu Asp Phe Ala Phe Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85                  90                  95

Arg Ser Thr Phe Gly Gln Gly Thr Arg Leu Glu Met Lys Arg Thr Val
            100                 105                 110

Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
        115                 120                 125

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
    130                 135                 140

Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
145                 150                 155                 160

Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
                165                 170                 175

Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
            180                 185                 190

Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
        195                 200                 205

Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> SEQ ID NO 53
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 53

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
  1               5                  10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
         35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
                85                  90                  95

Leu Gln Thr Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
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145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> SEQ ID NO 54
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 54

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
  1               5                  10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
             20                  25                  30

Asn Gly Phe Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
         35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Thr Arg Ala Ser Gly Val Pro
     50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile
 65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Phe Cys Met Gln Ala
                 85                  90                  95

Val Gln Thr Pro Phe Thr Phe Gly Pro Gly Thr Arg Leu Asp Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Ala
    210                 215


<210> SEQ ID NO 55
<211> LENGTH: 66
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description: Artificially Synthesized Seqence

<400> SEQUENCE: 55

gtcacaaaga gcttcaacag gggagagtgt ctcgagcacc accaccacca ccactgagat     60

ccggct                                                                66
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<210> SEQ ID NO 56
<211> LENGTH: 66
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description: Artificially Synthesized Seqence

<400> SEQUENCE: 56

gtcacaaaga gcttcaacag gggagaggct ctcgagcacc accaccacca ccactgagat 60

ccggct 66

The invention claimed is:

1. A method of eradicating cancer cells or suppressing or inhibiting a proliferation of the cancer cells, comprising:

administering a therapeutically effective amount of an anticancer composition to an object requiring an administration, the anticancer composition comprising:

(5) a human antibody κ-type light chain in the form of a monomer in which a variable region is composed of a polypeptide of

an amino acid sequence of SEQ ID NO: 19,

an amino acid sequence having homology of 95% or more with the amino acid sequence of SEQ ID NO: 19 and having the same CDRs of the amino acid sequence of SEQ ID NO: 19,

wherein the CDRs in the amino acid sequence of SEQ ID NO: 19 are the first 24 to 39 amino acid residues, the first 55 to 61 amino acid residues, and the first 94 to 101 amino acid residues.

2. A method of eradicating cancer cells or suppressing or inhibiting a proliferation of the cancer cells according to claim **1**, wherein

the human antibody κ-type light chain of (5) above is a human antibody κ-type light chain in the form of a monomer composed of a polypeptide of

an amino acid sequence in which cysteine at position 219 has been deleted or substituted by an amino acid other than cysteine in the amino acid sequence of SEQ ID NO: 20,

an amino acid sequence having homology of 95% or more with the amino acid sequence of SEQ ID NO: 20 and having the same CDRs of the amino acid sequence of SEQ ID NO: 20,

wherein the CDRs in the amino acid sequence of SEQ ID NO: 20 are the first 24 to 39 amino acid residues, the first 55 to 61 amino acid residues, and the first 94 to 101 amino acid residues.

3. A method of eradicating cancer cells or suppressing or inhibiting a proliferation of the cancer cells according to claim **1**, wherein the object requiring the administration has already developed lung cancer.

4. A method of eradicating cancer cells or suppressing or inhibiting a proliferation of the cancer cells according to claim **1**, comprising: administrating the anticancer composition in a form which enables the anticancer composition to be delivered to pneumocytes from a nose or bronchi.

5. A method of eradicating cancer cells or suppressing or inhibiting a proliferation of the cancer cells according to claim **1**, wherein protein contained in the anticancer composition is administered at a dose of 0.01 mg/kg to 30 mg/kg of body weight.

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